Photocycloadditions and photorearrangements

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Organic synthesis using light as reagent and producing complex molecules from simple starting materials is realized in exemplary fashion in natural photosynthesis. Mankind still struggles for an efficient molecular system that mimics this natural process. In order to harvest light energy and to transform it into chemical energy, photochemical reactions must be studied and optimized for synthetic applications. Two major reaction paths that use electronic excitation are photocycloadditions and photochemical rearrangements. These reactions have been intensively investigated in recent decades in terms of regio-, stereo-, spin- and (electronic) configurational selectivities.

Prior to every photochemical reaction, an electronically excited state is generated either by direct light absorption or by energy transfer sensitization. This excited state has to be sufficiently well characterized in order to understand its chemical and physical behaviour. Organic molecules can react either as triplet or singlet excited states, often showing spin-specific reactivities and selectivities. Additionally, the nature of the excited state, as characterized by the state configuration, is crucial for the reactivity of the molecule, for example, nπ* states favour hydrogen abstraction and addition modes whereas ππ* states favour addition and electron transfer modes.

Photocycloaddition reactions can be performed in numerous ways using unsaturated substrates such as carbonyl compounds, Michael acceptors, monoalkenes, polyenes, or aromatic substrates leading to complex products that can be used in subsequent transformations. The carbonyl-ene photocycloaddition, for example, is an important route to oxetanes, products that have recently gained increasing attention as building blocks in organic synthesis as well as in materials science [1]. Photochemical rearrangements are impressive reactions with regard to the generation of complexity: 1,2- and 1,3-acyl shifts are known from carbonyl photochemistry, di-π-methane and oxa-di-π-methane rearrangements are processes that can occur with a remarkable increase in molecular and stereochemical complexity, as can meta arene photocycloadditions.

It was a great pleasure to act as the editor of this Thematic Series on photochemical reactions and I would like to thank all authors for their excellent contributions and the staff of the Beilstein-Institut for their support.

Axel G. Griesbeck

Cologne, January 2011
Reference

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Synthesis of 2a,8b-Dihydrocyclobuta[a]naphthalene-3,4-diones

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Full Research Paper

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Abstract

On irradiation ($\lambda = 350 \text{ nm}$) in neat hex-1-yne, naphthalene-1,2-dione monoacetals 1 afford mixtures of pentacyclic photodimers and up to 25% (isolated yield) of mixed photocycloadducts 2. Careful acidic hydrolysis of the acetal function of 2 gives the title compounds 3, the overall sequence representing a first approach to a (formal) [2 + 2] photocycloadduct of a 1,2-naphthoquinone to an alkyne.

Introduction

The behaviour of excited 1,2- and 1,4-quinones towards ground-state molecules differs greatly. Whereas the former typically react via H-abstraction by an excited carbonyl group [1], the latter smoothly undergo [2 + 2] cycloaddition to alkenes to afford cyclobutane-type products [2]. Very recently we reported the use of 1,2-dihydro-1,1-dimethoxynaphthalen-2-ones 1 as protected precursors for the synthesis of both photocycldimers and ketene-photocycloadducts of 1,2-naphthoquinones [3,4]. Here we report the preparation of – novel – 2a,8b-dihydrocyclobuta[a]naphthalene-3,4-diones, i.e. (formal) 1,2-naphthoquinone + alkyne [2 + 2] cycloadducts.

Results

Irradiation of 1 in the presence of alkynes affords the – known [3] – pentacyclic dimers and variable amounts (0–33%) of enone + alkyne cycloadducts as indicated by $^1\text{H}$ NMR spectroscopy. The yields of mixed cycloadducts with many alkynes (3,3-dimethylbut-1-yn, trimethylsilylacetylene, 3-[(trimethylsilyloxy)prop-1-yn or hex-3-yn) were invariably low (<5%). Moderately higher yields (15–25%) were obtained using hex-1-yn in either benzene or acetonitrile as solvent. Best results were obtained using hex-1-yn, both as reaction partner and as solvent. Thus, irradiation of either 1a or 1b in neat hex-1-yn affords a mixture of the corresponding dimeric dibenzophenylenediones (two regioisomers [3], 67–70%) and up to 30–33% of cycloadducts 2a or 2b, respectively. Compounds 2 can easily be isolated by chromatography (25% isolated yield) as they exhibit much higher $R_f$-values than the corresponding dimers. In contrast, naphthalenone 1c under the same conditions only affords <5% of 2c. Hydrolysis of cycloadducts 2 in a
two phase mixture (CH₂Cl₂, aq HCl) at r.t. [5] leads to quantitative deprotection of the acetal function as indicated by ¹H NMR spectroscopy to afford compounds 3a or 3b, respectively (Scheme 1). Compounds 3 are also easy to purify by chromatography (83–85% isolated yield) which is greatly assisted by the fact that they are easily detectable on account of their yellow colour.

Scheme 1: Synthesis of 2a,8b-dihydrocyclobuta[a]naphthalene-3,4-diones.

Discussion

At first glance, the (relatively) low yield of mixed cycloadduct formation from excited 1 and alkynes seems disappointing. Nevertheless, one should bear in mind that a) dimer formation on irradiation of phenyl-conjugated enones, e.g., 3-phenylcyclohex-2-enone, is not suppressed even in neat alkenes as solvent [6], as these compounds tend to associate via π–π-stacking, and b) radical additions to alkynes usually proceed with significantly lower relative rates (30–50%) than those to the corresponding alkenes [7]. Taking these findings and the observed regioselectivity of the cycloaddition into consideration, the maximum relative yield (33%) of compounds 2a or 2b at total conversion of starting material is acceptable. Moreover, the fact that hydrolysis of the cycloadducts proceeds quantitatively, then the overall yields in the preparation of the – novel – 1,2-naphthoquinone + alkyne cycloadducts even becomes satisfactory. In the same experiment with 1c, the MeO-group apparently tends to increase the efficiency in photodimerization vs mixed photocycloaddition, otherwise there is no obvious explanation for this result.

Experimental

1. General. Acetals 1 were synthesized according to [8]. Both 1b, m.p. 60–62 °C, and 1c, m.p. 76–78 °C, originally described as oils, solidified on standing. Hex-1-yne was commercially available. Photolyses were conducted in a Rayonet RPR-100 photoreactor equipped with (16) 350 nm lamps. Column chromatography (CC) was carried out with silica gel 60 (Merck; 230–400 mesh). ¹H and ¹³C NMR spectra (including 2D plots) were recorded with a Bruker WM-500 instrument at 500.13 and 125.8 MHz, resp., in CDCl₃, δ in ppm, J in Hz.

2. Photolyses. Ar-Degassed solns. of 1 (1 mmol) in hex-1-yne (10 ml) were irradiated for 15 h up to total conversion (monitoring by TLC). After evaporation of the excess alkylene, the crude mixtures were analyzed by ¹H NMR in order to determine the crude yield. CC (SiO₂, pentane/Et₂O 6:1) gave the photocycloadducts 2. 1-Butyl-3,4-dihydro-4,4-dimethoxy-2H,8H-cyclo-buta[a]naphthalene-3-one (2a): 72 mg (25%), colourless oil, Rs = 0.65. ¹H NMR: 7.70 (d, J = 8.4, 1H); 7.36 (t, J = 8.4, 1H); 7.30 (m, 2H); 5.97 (s, 1H); 4.52 (d, J = 4.6, 1H); 4.00 (bs, 1H); 3.53 & 3.00 (s, 3H); 2.16 (t, J = 7.0, 2H); 1.52 (m, 2H); 1.38 (m, 2H); 0.92 (t, J = 6.9, 3H). ¹³C NMR: 203.1 (s); 156.2 (s); 137.3 (s); 134.5 (s); 129.1 (d); 128.6 (d); 128.4 (d); 127.8 (d); 125.2 (d); 99.1 (s); 51.0 (q); 50.1 (d); 49.2 (q); 48.3 (d); 30.2 (t); 28.6 (t); 22.5 (t); 14.2 (q). Anal. Calcd for C₁₈H₂₁O₂: C, 75.50; H, 7.74. Found: C, 75.43; H, 7.78.

3. Hydrolyses. A soln. of the acetals 2 (0.2 mmol) in CH₂Cl₂ (2 ml), was added 8N HCl (1.5 ml) and the mixture stirred for 5 h at room temperature. The org. phase was washed with sat. aq NaCl, dried (MgSO₄) and the residue (100% conversion to product from ¹H NMR) purified by CC (SiO₂, pentane/Et₂O 6:1) to afford the diketones 3. 1-Butyl-3,4-dihydrocyclobuta[a]naphthalene-3,4-dione (3a): 37 mg (85%), viscous yellow oil, Rs = 0.45. ¹H NMR: 8.06 (d, J = 8.5, 1H); 7.62 (t, J = 8.5, 1H); 7.42 (t, J = 8.5, 1H); 7.37 (d, J = 8.5, 1H); 5.72 (s, 1H); 4.25 (d, J = 3.2, 1H); 4.16 (bs, 1H); 1.97 (m, 2H); 1.40 (m, 2H); 1.26 (m, 2H); 0.83 (t, J = 6.9, 3H). ¹³C NMR: 196.2 (s); 184.5 (s); 164.1 (s); 137.1 (s); 134.5 (d); 130.1 (d); 128.4 (d); 127.8 (d); 51.1 (q); 50.2 (d); 49.1 (q); 48.2 (d); 30.2 (t); 28.6 (t); 22.5 (t); 14.2 (q). Anal. Calcd for C₁₈H₂₁BrO₃: C, 59.19; H, 5.79. Found: C, 59.22; H, 5.82.
0.84 (t, J = 6.9, 3H). $^{13}$C NMR: 196.1 (s); 184.6 (s); 164.2 (s);
144.2 (s); 137.1 (s); 134.5 (d); 130.1 (s); 128.4 (d); 127.8 (d);
122.5 (d); 48.6 (d); 46.3 (d); 28.8 (t); 28.0 (t); 27.4 (t); 22.4 (q).
Anal. Calcd for C$_{16}$H$_{15}$BrO$_2$: C, 60.21; H, 4.71. Found: C,
60.13; H, 4.77.

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Heavy atom effects in the Paternò–Büchi reaction of pyrimidine derivatives with 4,4’-disubstituted benzophenones

Feng-Feng Kong, Jian-Bo Wang and Qin-Hua Song*

Abstract

The regioselectivity and the photochemical efficiency were investigated in the Paternò–Büchi reaction of 1,3-dimethylthymine (DMT) and 1,3-dimethyluracil (DMU) with benzophenone (1b) and some 4,4’-disubstituted derivatives (dimethoxy (1a), difluoro (1c), dichloro (1d), dibromo (1e) and dicyano benzophenone (1f)) that gives rise to two regioisomeric oxetanes, 2 and 3. The regioselectivity (the ratio of 2/3) decreased gradually for both DMT/DMU photochemical systems from 1a to 1f. That is, a halogen atom as an electron-withdrawing group (EWG) has a pronounced effect on the regioselectivity. However, the photochemical efficiency of the 1e systems did not show the expected increase, but decreased relative to systems with 1b. Temperature effects on the regioselectivity of 1b–e systems showed some interesting features for systems with heavy atoms (including the 1d and 1e systems), such as higher inversion temperatures, and an entropy-controlled regioselectively whereas the regioselectivity for two other systems (1b and 1c) is enthalpy–entropy controlled. A heavy atom effect is suggested to be responsible for these unusual phenomena based on the triplet-diradical mechanism of the Paternò–Büchi reaction.

Introduction

The regio- and stereoselectivity in the Paternò–Büchi reaction, which is a photochemical [2 + 2] cycloaddition of a carbonyl compound with an olefin, has been extensively studied [1-4]. The ene–carbonyl photocycloaddition generally proceeds through attack of the excited carbonyl state (singlet or triplet or both) on a ground-state olefin. For aromatic carbonyl compounds, the reaction is a triplet cycloaddition, that is, a triplet-excited carbonyl compound adding to an olefin to yield a triplet 1,4-diradical intermediate, which undergoes intersystem crossing (ISC) to produce a singlet 1,4-diradical. Ring-close of the latter gives an oxetane. The higher selectivity observed for the triplet reaction is rationalized by the optional conformation
of the intermediate 2-oxabutane-1,4-diy for ISC to the singlet diradical, which is preferentially controlled by spin-orbit coupling, thus leading to substantial control of regio- and stereoselectivity [5-13].

The “heavy atom effect” is a term which has been used to describe the influence of “heavy atom” substitution on a spin-forbidden transition such as various intersystem crossings. If heavy atoms are present in a Paternò–Büchi reaction, spin-transition processes would be affected, and this may lead to interesting results.

Abe et al. [14] investigated the effect of a sulfur atom on the stereoselective formation of oxetanes in Paternò–Büchi reaction of aromatic aldehydes with silyl $O,S$-ketene acetals to give trans-3-siloxyoxetanes and found that this was ca. 70/30 to 90/10. The trans-selectivity is explained by the sulfur atom effect in the silyl $O,S$-ketene acetal which controls the approach direction of the electrophilic oxygen of triplet $n,\pi^*$ aldehyde to the nucleophilic alkene. A fast ISC process of the triplet 1-alkylthio-1-siloxy-2-oxatetramethylene 1,4-diradical in competition with the bond rotation was proposed [14]. Griesbeck et al. [15] observed substantial $^2$H-magnetic isotope effects on the diastereoselectivity of triplet photocycloaddition reactions. Weaker isotope effects on the diastereoselectivity were detected for the reaction of $\alpha$-deuterated propionaldehyde [15].

In this work, we have investigated the Paternò–Büchi reaction of 1,3-dimethylthymine (DMT) and 1,3-dimethyluracil (DMU) with benzophenone (1b) and its 4,4’-disubstituted derivatives 1a–1f with the formation of the regioisomeric oxetanes 2 and 3 (Scheme 1). By changing the halogen at para positions in the benzophenones, the photochemical efficiency and the regioselectivity were significantly affected, and the effects cannot be considered as a pure electronic effect (of the electron-withdrawing groups, EWGs), by comparing the observations with those of systems of 1a (with electron-donating groups, EDGs), and 1b and 1f (also with EWGs). However, as a heavy atom effect, observations above can be rationalized based on the triplet mechanism of the Paternò–Büchi reaction.

### Results and Discussion

#### Substituent effects

To investigate substituent effects of benzophenones in the Paternò–Büchi reaction, photochemical reactions of DMT/DMU with 1a–1f in acetonitrile-$d_3$ were performed in Pyrex NMR tubes. The regioselectivity (the ratio of 2/3) and the yield were measured directly from the $^1$H NMR spectra of crude product mixtures and are listed in Table 1. The substituent effect of benzophenones on the regioselectivity (2/3) is similar to our previous observations [10], a gradual decrease according to their electronic effect from 1a to 1e.

<table>
<thead>
<tr>
<th>Y</th>
<th>DMT/Yield%</th>
<th>2/3</th>
<th>DMU/Yield%</th>
<th>2/3</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH$_3$O</td>
<td>25</td>
<td>52:48</td>
<td>19</td>
<td>&gt; 95:5$^d$</td>
</tr>
<tr>
<td>H</td>
<td>52</td>
<td>55:45</td>
<td>51</td>
<td>64:36</td>
</tr>
<tr>
<td>F</td>
<td>53</td>
<td>56:44</td>
<td>64</td>
<td>63:37</td>
</tr>
<tr>
<td>Cl</td>
<td>77</td>
<td>38:62</td>
<td>70</td>
<td>56:44</td>
</tr>
<tr>
<td>Br</td>
<td>46</td>
<td>33:67</td>
<td>28</td>
<td>53:47</td>
</tr>
<tr>
<td>CN</td>
<td>82</td>
<td>14:86</td>
<td>75</td>
<td>39:61</td>
</tr>
</tbody>
</table>

$^a$Average of two parallel determinations, DMT (DMU)/benzophenones = 10 mM:10 mM, in acetonitrile, irradiation at 10 °C with 125 W high-pressure Hg lamp, values determined by $^1$H NMR of the crude product mixture, the experimental error < 5%.

$^b$Irradiation for 30 min.

$^c$Irradiation for 90 min.

$^d$Oxetane 3a$_2$ was not detected, see Experimental section.

#### Scheme 1: The Paternò–Büchi reaction of DMT/DMU with benzophenones to generate two regioisomeric photoproducts.
In our previous papers [10,13], the photochemical [2 + 2] cycloadditions of DMT and DMU with benzophenones generate two series of regioisomeric oxetanes, 2 and 3, via 1,4-diradical intermediates, and reveal notable substituent effects on the regioselectivity and the photochemical efficiency. The reactions initiated by triplet benzophenones with EDGs give a higher proportion of 2 and a lower photochemical efficiency, whilst benzophenones with EWGs yield a lower proportion of 2 and have a higher efficiency.

The data in Table 1 show that the regioselectivity (2/3) and the photochemical efficiency correlates clearly with electronic property of substituents. The benzophenones with EWGs give more efficient Paternò–Büchi reactions (except 1e systems) and lower ratios of 2/3, and the benzophenones with EDGs undergo less efficient Paternò–Büchi reactions and have higher ratios of 2/3, in accord with our previous observations [10,13]. However, the photochemical efficiency of the 1e systems decreased significantly. According to our understanding of these oxetanes [10], this low efficiency was considered to be due to poor stability of the photoproducts, in particular oxetanes 3.

To verify this speculation, the yield and the regioselectivity were tracked over an irradiation time of 15 min for the DMT-1e (5 mM/5 mM) system (Figure 1). Figure 1 clearly shows that the yield increases with irradiation time and the ratio of 2/3 is slightly higher (37:63) during the initial irradiation period (1–3 min), and then becomes constant (33:67) on further irradiation (> 3 min). However, this change is within the experimental error of 5%. According to our understanding of the stability of oxetanes, 3 are less stable than 2. The constant ratio of 2/3 implies that no significant decomposition of the photoproduct oxetanes occurs in the photochemical reaction. In other words, the stability of photoproducts in the systems is not responsible for the low yields. Therefore, the effect of halo-substituted benzophenones on the Paternò–Büchi reaction is not a “pure” substituent effect.

Temperature effects
In our previous papers [9,11], the photochemical [2 + 2] cycloadditions of DMT/DMU with benzophenones revealed notable temperature effects on the regioselectivity and the photochemical efficiency. We have demonstrated that the temperature-dependent regioselectivity is derived from the conformational properties of the intermediate triplet 1,4-diradicals. The observations show that the reaction temperature influences the regioselectivity by changing the populations of two regioisomeric diradicals as a result of differences in the potential energies of two stable conformers, the productive conformation of the triplet diradical and the unproductive conformation of the triplet diradical, for each regioisomeric diradical [9,11].

To investigate further the temperature effects in four systems with 4,4′-dihalo-substituted benzophenones, we carried out the Paternò–Büchi reactions of DMT with 1b–1e over a temperature range of −30 to 70 °C. Notable temperature effects were observed. Both the photochemical efficiency and the regioselectivity (2/3) decreased with increasing temperature from the general trend (Table 2).

Table 2 shows clearly that efficiencies of the 1b system are lower than those of the 1c and 1d systems except for the values at the initial three temperatures, i.e., the efficiency of 1b system is the most sensitive to reaction temperature, and the efficiency of 1e system is the lowest among the four systems studied. In addition, the data show that a higher reaction temperature is unfavorable for Paternò–Büchi reactions.

The regioselectivity (2/3) data in Table 2 have been plotted in Figure 2 against the inverse absolute temperature according to the Eyring formalism [16].

\[
\ln \left( \frac{k_2}{k_3} \right) = \ln \left( \frac{2}{3} \right) = \frac{\Delta \Delta H^\ddagger}{RT} + \frac{\Delta \Delta S^\ddagger}{R} \tag{1}
\]

Where \( k_2 \) and \( k_3 \) are the overall rate constants of the reactions leading to the two regioisomers 2 and 3, respectively.

The Eyring plots obtained are nonlinear across the whole temperature range. The nonlinear Eyring plot is indicative of a change of the selectivity-determining step during the change in the reaction temperature [1,17-19].
Although the Eyring plots obtained were nonlinear over whole temperature range, strict linearity (correlation coefficients R > 0.99) on both sides of inversion points were found. The temperature at the point of inversion is called the inversion temperature, \( T_{\text{inv}} \), of the system. The temperatures increase gradually from H- to Br-substituted Paternò–Büchi systems (Table 2). In our previous paper [11], the temperature effect of the Paternò–Büchi reaction DMU with three benzophenones, 1b, 1c and 1f, was investigated, and similar inversion temperatures could be obtained from the Eyring plots, 295 K for 1b, 294 K for 1c and 291 K for 1f. Although CN is a strong EWG, 1f-DMU system did not give a high inversion temperature. Hence, this result indicates that the halogen (Cl or Br) acts not as a pure EWG but as a heavy atom and induces a higher inversion temperature.

According to the Eyring theory, when this relationship is plotted, the slope corresponds to the difference in the overall activation enthalpies (\( \Delta \Delta H^\ddagger \)) and the intercept represents the difference in the overall activation entropies (\( \Delta \Delta S^\ddagger \)) (Figure 2).

The inversion temperature reveals two sets of activation parameters (\( \Delta \Delta H_{1,2}^\ddagger \) and \( \Delta \Delta S_{1,2}^\ddagger \) \((T > T_{\text{inv}})\), \( \Delta \Delta H_{2}^\ddagger \) and \( \Delta \Delta S_{2}^\ddagger \) \((T < T_{\text{inv}})\), which were obtained from the slope and the intercept of the linear plot for each system. Table 3 presents the parameters of activation \( \Delta \Delta H_{1,2}^\ddagger \) and \( \Delta \Delta S_{1,2}^\ddagger \) values. These large parameters of activation are unprecedented, \( \Delta \Delta H_{1}^\ddagger \) values range from ~19.9 to ~27.5 kJ mol\(^{-1}\) and are much higher than the published values ~4.2 kJ mol\(^{-1}\) [1], 4.3 kJ mol\(^{-1}\) [8] and ~4.8 kJ mol\(^{-1}\) [7]. Therefore, the regioselectivity in the Paternò–Büchi reaction is strongly temperature-dependent. Moreover, these activation parameters (\( \Delta \Delta H^\ddagger \) and \( \Delta \Delta S^\ddagger \)) increase gradually from the F- to Br-benzophenones systems, with the exception of \( \Delta \Delta H_{1}^\ddagger \) for 1d.

In addition, the values of \( \Delta \Delta H^\ddagger \) are similar to \( T_{\text{inv}}/\Delta \Delta S^\ddagger \) for the 1b and 1c systems since the ratio of 2/3 is ~50:50. However, the values of \( \Delta \Delta H^\ddagger \) are less than \( T_{\text{inv}}/\Delta \Delta S^\ddagger \) for two other systems (~2.1 J/mol for 1d, ~3.2 kJ/mol for 1e). In other words, this is an entropy-determined selection for the regioselectivity over the whole temperature range investigated.

**Interception of heavy atom effects**

Based on the triplet mechanism of the Paternò–Büchi reaction, it is possible to have a more detailed discussion on a heavy atom effect on the Paternò–Büchi reaction based on the phenomena noted above. The formation of two regioisomers in the Paternò–Büchi reaction is detailed in Scheme 2.

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**Table 2**: Temperature dependence on the regioselectivity (2/3) and the yields in the Paternò–Büchi reactions of DMT with compounds 1b–e.

<table>
<thead>
<tr>
<th>Temp./°C</th>
<th>1b (yield %)</th>
<th>1c (yield %)</th>
<th>1d (yield %)</th>
<th>1e (yield %)</th>
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<tr>
<td>-27.4</td>
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<td>(62.2)</td>
<td>(56.4)</td>
<td>(68.5)</td>
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<td>(64.0)</td>
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<td>(62.3)</td>
<td>(69.6)</td>
</tr>
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<td>(64.5)</td>
<td>(52.3)</td>
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<td>(50.4)</td>
<td>(58.2)</td>
<td>(51.9)</td>
<td>(31.9)</td>
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<td>(56.4)</td>
<td>(34.6)</td>
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<td>(41.5)</td>
<td>(26.7)</td>
<td>(23.7)</td>
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<td>69.1</td>
<td>(36.3)</td>
<td>(43.0)</td>
<td>(67.4)</td>
<td>(26.7)</td>
</tr>
</tbody>
</table>

*See Table 1.

**Table 3**: Inversion temperature, \( T_{\text{inv}} \) and parameters of activation, \( \Delta \Delta H_{1,2}^\ddagger \), \( \Delta \Delta S_{1,2}^\ddagger \) \((T > T_{\text{inv}})\), \( \Delta \Delta H_2^\ddagger \), \( \Delta \Delta S_2^\ddagger \) \((T < T_{\text{inv}})\).

<table>
<thead>
<tr>
<th>( \Delta \Delta H_{1,2}^\ddagger ) /kJ mol(^{-1})</th>
<th>( \delta \Delta \Delta H^\ddagger ) /kJ mol(^{-1})</th>
<th>( \Delta \Delta S_{1,2}^\ddagger ) /J mol(^{-1})K(^{-1})</th>
<th>( T_{\text{inv}} ) /K</th>
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</thead>
<tbody>
<tr>
<td>1b</td>
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<td>10.9</td>
<td>-66.4</td>
</tr>
<tr>
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<td>-24.4</td>
<td>14.1</td>
<td>-80.7</td>
</tr>
<tr>
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<td>-22.6</td>
<td>11.8</td>
<td>-81.3</td>
</tr>
<tr>
<td>1e</td>
<td>-27.5</td>
<td>16.1</td>
<td>-97.9</td>
</tr>
</tbody>
</table>

**Figure 2**: Eyring plots for the photoreaction of DMT with compounds 1b–e.
Among these processes, there are four factors that determine the regioselectivity [7]. (i) Initial O-attacked site selection at the double bond by \( ^3 \text{benzophenones} \), \( k_{2a} + k_{2a}' \) versus \( k_{3a} + k_{3a}' \), (ii) equilibrium constants, \( K_2 ( = [C5-^3 \text{DR2}]/[C5-^3 \text{DR1}] ) \) versus \( K_3 ( = [C6-^3 \text{DR2}]/[C6-^3 \text{DR1}] ) \): This factor only operates when the conformational change is faster than the ISC process, (iii) the relative rate constants of the ISC processes in the triplet 1,4-diradicals, \( k_{2I}/k_{2I}' \) versus \( k_{3I}/k_{3I}' \) and (iv) the relative rate constants of the bond-forming and bond-breaking step from the singlet 1,4-diradical C5-1DR1 and C6-1DR1, \( k_{2b}/k_{2c} \) versus \( k_{3b}/k_{3c} \).

According to the Curtin–Hammett principle [20], the ratios of the productive conformers of singlet diradicals C5-1DR1 and C6-1DR1 are determined not only by the populations of C5-1DR1 and C6-1DR1 but also by the relative rate constants of ISC processes, the \( k_{2I}/k_{2I}' \) and \( k_{3I}/k_{3I}' \). The former is determined by the equilibrium constants, \( K_2 \) and \( K_3 \), whilst the latter processes (\( k_{2I}, k_{3I}, k_{2I}' \) and \( k_{3I}' \)) would be accelerated by heavy atoms. Thus, the equilibrium between the productive conformers and the unproductive conformers, of the triplet 1,4-diradicals, would be achieved at a higher temperature for the system with heavy atoms than that without heavy atoms. Due to the energy barriers between the two stable conformers [9], the equilibrium is more favorable for the formation of oxetanes 3 rather than oxetanes 2 at a higher temperature. This would lead to a higher inversion temperature and a higher ratio of 2/3. In addition, the ISC process from singlet excited state to triplet excited state is very fast, \( 10^{11} \) s\(^{-1} \) for benzophenones, and not affected by heavy atoms, but the ISC process of triplet benzophenones to singlet ground state would be accelerated, reducing lifetime of triplet benzophenones. Finally, triplet benzophenones with a short lifetime would give rise to a less efficient Paternò–Büchi reaction.

**Experimental Materials**

1,3-Dimethylthymine (DMT) and 1,3-dimethyluracil (DMU) were prepared from thymine and uracil, respectively. 4,4’-Dimethoxybenzophenone, 4,4’-dichlorobenzophenone, 4,4’-dibromobenzophenone and 4,4’-dicyanobenzophenone were prepared. Benzophenone, 4,4’-difluorobenzophenone, acetonitrile-\( d_3 \) and other materials were obtained from commercial suppliers and used as received without further purification. \(^1\)H and \(^13\)C NMR spectra were measured with a Bruker AV 300 spectrometer operating at 300 MHz and 75 MHz, respectively.
The Paternó–Büchi reaction of DMT/DMU with benzophenones generates two regioisomers 2 and 3. The oxetanes were numbered by using subscript “1” for DMT and “2” for DMU, e.g., oxetanes from DMT-1a system are denoted as 2a1 and 3a1. For oxetanes mentioned in this work, most were reported in our previous papers [9,10] except for the following oxetanes. 3a2 has not been detected by 1H NMR. 3d1, 3d2, 3e1, 2e2 and 3e2 could be detected by 1H NMR, but could not be isolated because of their poor stability towards acid and silica gel. 2e1 was isolated and the characterization data of 2e1 was as follows:

8,8-Bis-(4-bromo-phenyl)-2,4,6-trimethyl-7-oxa-2,4-diaza-bicyclo[4.2.0]octane-3,5-dione (2e1). 1H NMR (300 MHz, CDCl3) δ = 1.73 (s, 3H, CH3), 2.91 (s, 3H, NCH3), 3.11 (s, 3H, NCH3), 3.40 (s, 1H, NH), 7.13–5.54 (m, 8H, HAr), 1068 ppm; 13C NMR (75 MHz, CDCl3) δ = 24.1, 27.6, 35.9, 66.8, 91.0, 122.5, 122.8, 126.8, 127.4, 131.8, 132.1, 137.6, 142.8, 151.6, 169.6 ppm; IR (KBr) 3435 (s), 2933 (w), 1704 (m), 1675 (s), 1484 (s), 1282 (s), 1068 (s), 1008 (m), 818 (m), 746 (m) cm⁻¹; TOFMS (Cl) m/z calculated for (M+H)⁺ C20H18N2O2Br2: 494.9742, found 494.9731.

Photoprodut assay

The Paternó–Büchi reactions of DMT/DMU with benzophenones were performed in acetonitrile-d₃. A solution of the reactants was placed in a Pyrex NMR tube (transmitted light > 290 nm), purged with high purity N₂ for 10 min and then irradiated with a 125 W high-pressure Hg lamp at 10 °C. The sample tubes were placed on a merry-go-round equipment moving around the Hg lamp. Photoproducts 2 and 3 have no significant absorption for light at above 290 nm. Hence, a secondary photolysis of the oxetane products (2 or 3) should not occur unless there is prolonged irradiation. Compositions in photoreaction mixture were quantified by 1H NMR spectroscopy (300 MHz) directly on the crude product mixture, using the sum of 5-methyl (5-H) and 6-H signals as internal standards. The yields and the ratios of the two regioisomeric oxetanes were obtained from the peak areas of 5-methyl and 6-H for DMT system and those of 5-H and 6-H for DMU system in the 1H NMR spectra. The experimental error was within 5%.

Acknowledgements

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References


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Synthesis of cationic dibenzosemibullvalene-based phase-transfer catalysts by di-π-methane rearrangements of pyrrolinium-annelated dibenzobarrelene derivatives

Heiko Ihmels* and Jia Luo

Abstract
Dibenzoarrelene derivatives, that are annelated with a pyrrolinium unit [N,N-dialkyl-3,4-(9',10'-dihydro-9',10'-anthraceno-3-pyrrolinium) derivatives], undergo a photo-induced di-π-methane rearrangement upon triplet sensitization to give the corresponding cationic dibenzosemibullvalene derivatives [N,N-dialkyl-3,4-(8c,8e-(4b,8b-dihydrodibenz[a,f]cyclopenta[cd]pentaleno)pyrrolidinium derivatives]. Whereas the covalent attachment of a benzophenone functionality to the pyrrolinium nitrogen atom did not result in an internal triplet sensitization, the introduction of a benzophenone unit as part of the counter ion enables the di-π-methane rearrangement of the dibenzobarrelene derivative in the solid-state. Preliminary experiments indicate that a cationic pyrrolidinium-annelated dibenzosemibullvalene may act as phase-transfer catalyst in alkylation reactions.

Introduction
The di-π-methane (DPM) rearrangement is among the most thoroughly investigated organic photoreactions [1,2]. Since the discovery of the DPM rearrangement of dibenzobarrelene [3], extensive studies have been carried out to assess the mechanistic aspects of this reaction and to explore their application in synthetic organic chemistry [1-5]. Along these lines, the DPM rearrangement of dibenzobarrelene (DBB), also termed dibenzobicyclo[2.2.2]octatetraene, and its derivatives has been investigated in detail and has provided significant insights into the mechanism of the DPM rearrangement [6,7]. The DPM rearrangement of DBB proceeds according to the mechanism shown in Scheme 1 through biradical intermediates BR1 and...
BR2 and leads to the formation of the corresponding dibenzosemibullvalene (DBS) [6,7]. Notably, the photoreactivity of the dibenzobarrelene system is multiplicity-dependent: Upon photoinduced triplet sensitization in the presence of an appropriate sensitizer, such as acetone or benzophenone, dibenzobarrelene (DBB) rearranges to dibenzosemibullvalene (DBS), whereas the direct excitation leads to dibenzocyclooctene (DBC) through the singlet excited-state (Scheme 1) [4,5,7]. The DPM photorearrangement of dibenzobarrelene and its derivatives is a synthetically useful reaction, because it allows the preparation of polycyclic structures which are relatively difficult to obtain by ground-state transformations [8].

During our attempts to develop novel ammonium-based phase-transfer catalysts [9-11] that are embedded within a rigid structure, we noticed that the complex dibenzosemibullvalene structure may constitute a reasonable starting point. We proposed that the general structure pyDBS (Figure 1), as established by the annelation of a pyrrolidinium unit to the dibenzosemibullvalene structure [12], represents an amphiphilic tetraalkylammonium derivative that exhibits three different benzene-containing concave sites to which an organic substrate may associate by attractive van der Waals interactions or \( \pi \)-stacking. Moreover, additional functionalities, e.g., hydroxy or amino groups, may be attached to the benzene rings of the semibullvalene structure to enable additional hydrogen bonding with the substrate. Also, the benzene rings may be further annelated with additional aromatic units to increase the potential \( \pi \)-stacking area [13]. Most notably, dibenzosemibullvalenes are chiral compounds, so that the propensity of an enantiopure pyDBS derivative to act as phase-transfer catalyst in stereoselective reactions may be considered in long-term studies. Herein we demonstrate that the pyrrolidinium-annelated dibenzosemibullvalene structure is indeed available via the DPM rearrangement of appropriately substituted dibenzobarrelene derivatives and that such a compound may act as phase-transfer catalyst in alkylation reactions.

Note that according to the IUPAC rules the compounds presented in the following should be classified as pyrrolidinium or pyrrolinium derivatives because of the higher priority of the cationic heterocycles; however, for clarity and to keep the focus on the photochemical reaction we chose to name these compounds dibenzobarrelene and dibenzosemibullvalene derivatives throughout the text.

Results and Discussion

The cationic dibenzobarrelene derivatives 2a–g were synthesized by the base-catalyzed reaction between the dibromomethyl-substituted dibenzobarrelene derivative 1 [14] with selected secondary amines (Scheme 2). The reaction was initially performed with a slight excess of the amine and DBU as a base in dichloromethane at room temperature, but under these conditions the products could not be completely separated from the remaining amine or the DBU catalyst, even by column chromatography. Nevertheless, the products were available in reasonable yields (47–85%) when the reaction was performed with polymer-bound DBU as catalyst (2a–f: 0.1 equiv; 2g: 0.5 equiv) or when the quaternary ammonium derivatives were precipitated from aqueous solutions by the addition of perchloric acid to the reaction mixture and, if necessary, subsequent column chromatography. All products were identified and fully characterized by NMR spectroscopy, mass spec-
Scheme 2: Synthesis of dibenzoabarrelene derivatives 2a–g.

Scheme 3: Di-π-methane rearrangements of dibenzoabarrelene derivatives 2a–f (counter ions omitted for clarity).
of the dibenzosemibullvalene ring (3eI: 4.30, 4.75; 3eII: 4.17, 4.91; 3fI: 4.31, 5.05 ppm; 3fII: 4.20, 5.02, in CDCl3). After column chromatography and subsequent recrystallization, the major photoproducts 3eI and 3fI were isolated in low yields (15% and 18%). The relative configuration of the ammonium functionality was deduced from NOE experiments. Specifically, the close proximity between the methyl group and the methine proton (8b'-H) of the cyclopropane ring gave rise to an NOE in 3eI and 3fI (Scheme 3). The structure of the minor products 3eII and 3fII, although not isolated, were determined by 1H NMR spectroscopic analyses of the photolysates. In these cases, the dibenzosemibullvalene structure was indicated by the characteristic 1H NMR spectroscopic shifts of the 4b-H and 8b-H protons.

It has been demonstrated with several examples that solid-state photoreactions are an excellent tool to induce highly selective di-π-methane rearrangements of dibenzobarrelene derivatives [17], because the constrained medium within the crystal lattice allows only limited molecular movement, so that the reaction pathway with the least required molecular motion is preferred. Accordingly, the solid-state photoreactivity of the dibenzobarrelene derivatives 2a–f was investigated; but unfortunately, all tested derivatives, either as chloride or as perchlorate salts, were photoinert in the crystalline state. Since one of the possible reasons for this photoinertness may be the lack of proper sensitization, the dibenzobarrelene derivative 2g was prepared with a triplet-sensitizing functionality attached, namely the benzophenone unit. Although in acetone the dibenzobarrelene 2g underwent a DPM rearrangement with full conversion (Scheme 4), the irradiation of 2g in water or acetonitrile solution in the absence of an external sensitizer only induced a relatively low conversion of 2g. Thus, irradiation of 2g in acetonitrile for 12 h led to ca. 10% conversion with ca. 60% dibenzosemibullvalenes formed. At the same time, several unidentified byproducts were formed in significant amounts.

The analysis of the photolysate by 1H NMR spectroscopy revealed that independent of the solvent, the two semibullvalenes 3gI and 3gII were formed in a 45:55 ratio; however, attempts to separate the two regioisomers by chromatography were unsuccessful (Scheme 4). Derivative 2g was also photoinert in the solid-state.

The lack of internal photosensitization of derivative 2g resembles the behavior of the hydrochloride salt of a cationic ammoniummethyl-substituted dibenzobarrelene derivative [18] which is also photoinert in the presence of benzophenone and even acetone. It may be assumed that attachment of the benzophenone unit to the cationic dibenzobarrelene structure has an influence on the intersystem-crossing (ISC) rate or the triplet energy of the carbonyl functionality leading to insufficient sensitization. In addition, competing deactivation pathways of the excited ketone may be considered, such as rotation about the Car–CH2 group or reaction with the chloride counter ion. However, further attempts to clarify this aspect or to optimize the conditions for sensitization were not made, because the photoreaction of 2g upon external sensitization by acetone showed that the products of the DPM rearrangement of 2g are formed only slowly in relatively low yield and cannot be separated.

Since the covalent attachment of a sensitizer unit to the dibenzobarrelene chromophore did not induce the desired triplet sensitization, the ionic auxiliary strategy [19] was applied to achieve triplet-sensitization in the solid-state, i.e., the sensitizer was introduced as counter anion. For this purpose, an anionic derivative of benzophenone was prepared and associated with the ammonium functionality of the dibenzobarrelene 2b by anion metathesis (Scheme 5). The known sulfonic acid 4 [20] was transformed to the corresponding silver salt Ag-4 by reaction with Ag2O, and subsequent ion metathesis upon treatment with 2b-Cl in acetonitrile gave the salt 2b-4 in 73% yield.

Scheme 4: Di-π-methane rearrangement of dibenzobarrelene derivative 2g.
Scheme 5: Synthesis and solid-state photoreactivity of the sulfonate salt 2b-4.

Irradiation of ground crystals of the salt 2b-4 for 2 h induced a DPM rearrangement to the dibenzosemibullvalene derivative 3b with full conversion and without any detectable byproducts as determined by $^1$H NMR spectroscopy. A solid-state photoreaction was also performed by the irradiation of a suspension of crystalline 2b-4 in diethyl ether. The solid products were dissolved and precipitated as perchlorate salts. Although the dibenzosemibullvalene 3b was formed (68%), $^1$H NMR spectroscopic analysis of the photolysate indicated the additional formation of significant amounts of byproducts (ca. 15%). These results indicate that, in principle, the internal sensitization of the DPM rearrangement of the cationic dibenzobarrelene derivatives may be achieved in a solid-state reaction with a sensitizing counter ion; however, the sensitization by acetone solvent appears to be more practical as it allows the handling of larger scales.

The general catalytic ability of the dibenzosemibullvalene salt 3d in phase-transfer catalyzed nucleophilic substitution reactions was investigated. Compounds 5 [21], 7, 9, and 11 were chosen as substrates in alkylation reactions under phase-transfer conditions, and the catalytic activity of 3d was compared with a tetrabutyrammonium salt (Scheme 6, Table 1; TBAB = tetrabutyrammonium bromide; TBAC = tetrabutyrammonium chloride.). All four reactions under investigation were significantly accelerated in the presence of substoichiometric amounts of the quaternary ammonium catalysts. Notably, under identical conditions the dibenzosemibullvalene salt 3d induced higher conversions in the phase-transfer reactions than the tetrabutyrammonium salts, except for the alkylation of compound 5, in which

![Scheme 6: Phase-transfer catalyzed alkylation reactions (see Table 1 for details).](image-url)

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Catalyst</th>
<th>Conv. / %</th>
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<tr>
<td>5</td>
<td>–</td>
<td>5&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>TBAB</td>
<td>92&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>3d</td>
<td>32&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>7</td>
<td>–</td>
<td>2</td>
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<td>49</td>
</tr>
<tr>
<td>11</td>
<td>3d</td>
<td>&gt;97</td>
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</table>

<sup>a</sup>TBAB = tetrabutyrammonium bromide; TBAC = tetrabutyrammonium chloride. <sup>b</sup>Conversion determined by $^1$H NMR spectroscopic analysis of the reaction mixture, relative to 2,7-dimethyl naphthalene as internal standard; estimated error: ±3% of the given value. <sup>c</sup>Determined by GC analysis, relative to ethyl acetate as internal standard.
92% conversion was achieved using TBAB, whereas under identical conditions a conversion of only 32% was obtained with dibenzosemibullvalene 3d as the catalyst. In contrast, the alkylation of the β-oxoester 7 in the presence of 3d gave the product in 82% conversion after 2 h at room temperature, whereas with TBAC as catalyst the conversion was only 36% under identical conditions. The dibenzosemibullvalene salt 3d was also found to be more efficient in the alkylation of cyclic β-oxoesters 9 and 11, as compared with the TBAC catalyst (Table 1). Interestingly, the alkylation of the indanone derivative 11 is less efficient in the presence of TBAC as compared with the non-aromatic cyclopentanone derivative 9, whereas in the presence of dibenzosemibullvalene 3d both substrates are alkylated with comparable efficiency.

Conclusion
In summary, it was shown that cationic pyrrolinium-annelated dibenzosemibullvalene derivatives are accessible by the photoinduced di-π-methane rearrangement of appropriately substituted dibenzobarrelene substrates. With one representative example, it was demonstrated that these compounds may act as phase-transfer catalysts in alkylation reactions with comparable or even better performance than the commonly employed tetrabutylammonium salts. It is therefore concluded that this class of chiral compounds may be used as a promising platform for the development of versatile phase-transfer catalysts.

Experimental
General remarks: NMR spectra were recorded on a Bruker Avance 400 (1H NMR: 400 MHz; 13C NMR: 100 MHz) and a Varian NMR system 600 (1H NMR: 600 MHz; 13C NMR: 150 MHz). 1H NMR chemical shifts are given relative to δTMS = 0.00 ppm, and 13C NMR chemical shifts refer to either the TMS signal (δTMS = 0.00 ppm) or the solvent signals [CDCl3: 77.0 ppm; CD2OD: 49.0 ppm; (CD3)2CO: 29.8 ppm, CD3CN: 118.2 ppm, (CD3)2SO: 39.5 ppm]. Melting points were determined with a Büchi 510K and are uncorrected. Mass spectra were recorded on a Hewlett-Packard HP 5968 (EI) and a Finnigan LCQ Deca instrument (ESI). Elemental analyses were performed on a KEKA-tech EuroEA combustion analyzer by Mr. H. Bodenstedt, Organic Chemistry I, University of Siegen. TLC analyses were performed on silica-gel sheets (Macherey-Nagel Polygram Sil G/UV254). Unless otherwise noted, commercially available chemicals were reagent grade and used without further purification. Polymer-bound DBU (polystyrene cross-linked with 1% divinylbenzene; loading: 1.15 mmol/g) was obtained from Aldrich. Anhydrous THF and diethyl ether were obtained by distillation from sodium wire, and anhydrous CH2Cl2 was distilled from calcium hydride. Distilled water was used for all the synthetic reactions performed. Preparative column chromatography was performed on MN Silica Gel 60 M (particle size 0.04–0.063 mm, 230–440 mesh).

Synthesis of dibenzobarrelene derivatives
General procedure for the preparation of N,N-diaryl-3,4-(9',10'-dihydro-9,10'-anthraceno-3-pyrrrolinium derivatives (GP-1): A mixture of 11,12-bis(bromomethyl)-9,10-dihydro-9,10-ethanoanthracene (I, 1.0–5.0 mmol), the corresponding secondary amine (1.2 equiv) and catalytic amount of DBU (0.1 equiv or otherwise explicitly specified) in dichloromethane (10 ml/mmol of I) was stirred at room temperature for 3–6 days until TLC analysis indicated the full conversion of I. The solvent was removed in vacuo and the residue re-dissolved in methanol (10–25 ml depending on the scale and solubility); if necessary, gentle heating was applied to dissolve the residue. Aqueous perchloric acid (60%, 1–3 ml) was added to the mixture. The perchlorate salt of the ammonium-dibenzobarrelene derivative precipitated spontaneously, or upon subsequent addition of a few drops of water. The solid was collected by filtration, washed with cold methanol and recrystallized from acetone. In those cases when no solid product precipitated from the methanol solution, water was added and the mixture extracted with dichloromethane. The organic layer was concentrated and the product purified by column chromatography (SiO2; 3–5% MeOH in dichloromethane).

The corresponding chloride salts were prepared by dissolving the perchlorate salt in MeCN and passing the solution through an ion-exchange column (DOWEX 1 x 8, Cl- form). After removal of the solvent in vacuo, the residue was crystallized from Et2O/MeOH.

N,N-Di-n-butyl-3,4-(9',10'-dihydro-9,10'-anthraceno-3-pyrrrolinium perchlorate (2d): Prepared from dibenzo-barrelene 1 (1.60 g, 4.08 mmol) according to GP-1, yield 1.46 g (3.18 mmol, 78%), colorless prisms, mp 173–174 °C. 1H NMR [400 MHz, (CD3)2CO]: δ = 0.75 (t, J = 7 Hz, 6H, CH3), 1.20–1.26 (m, 4H, CH2CH2), 1.42–1.46 (m, 4H, CH2CH2CH2), 3.52–3.56 (m, 4H, NCH2CH2), 4.72 (s, 4H, C=CH2N), 5.39 (s, 2H, CH), 6.99, 7.39 (3.18 mmol, 78%), colorless prisms, mp 173–174 °C. 13C NMR [100 MHz, (CD3)2CO]: δ = 14.1 (CH3), 20.7 (CH2), 26.5 (CH2), 49.8 (CH2), 65.6 (CH), 69.0 (CH), 124.8 (CH), 126.1 (CH), 144.6 (Cq), 146.9 (Cq). UV (CH2Cl2): λmax (log e) = 273 (4.00), 280 (4.17). MS (ESI+): m/z (%) = 358 (100). Anal. Calcd for C26H28ClN2O4 (458.0): C, 68.18; H, 7.04; N, 3.06. Found: C, 68.22; H, 7.12; N, 3.05.

N,N-Di-n-butyl-3,4-(9',10'-dihydro-9,10'-anthraceno-3-pyrrrolinium chloride (2d-Cl): Obtained quantitatively (1.37 g, 3.47 mmol) as a white powder by ion exchange of the perchlorate 2d (1.59 g, 3.47 mmol; eluent: acetonitrile; DOWEX resin).
mp 194–195 °C. \(^1^H\) NMR (400 MHz, CD$_3$CN): \(\delta = 0.78\) (t, \(J = 7\) Hz, 6H, CH$_3$), 1.16–1.34 (m, 8H, CH$_2$CH$_2$CH$_3$), 3.28–3.30 (m, 4H, NCH$_2$CH$_3$), overlapped with the solvent signal), 4.48 (s, 4H, C=CCH$_2$N), 5.12 (s, 2H, CH), 6.99, 7.35 (AA‘BB’-system, 8H, CH$_2$). \(^1^3^C\) NMR (100 MHz, CD$_3$CN): \(\delta = 13.9\) (CH$_3$), 20.8 (CH$_2$), 26.5 (CH$_2$), 50.0 (CH$_2$), 65.7 (CH$_2$), 68.7 (CH), 126.2 (CH$_{ar}$), 126.7 (CH$_{ar}$), 144.6 (C$_{q}$), 147.0 (C$_p$).

Synthesis of dibenzosemibullvalene derivatives

**General procedure for the photolysis in solution (GP-2):** Solutions of the substrates (10$^{-2}$ to 10$^{-3}$ mol/l) were placed in a 200 ml Duran flask (acetonitrile) or a quartz test tube (other solvents), and argon gas was bubbled through the solution for at least 20 min. The solution was stirred and irradiated for 4–15 h until the starting material was fully converted, as determined by TLC or \(^1^H\) NMR spectroscopic analysis. After evaporation of the solvent in vacuo, the photolysate was analyzed by \(^1^H\) NMR spectroscopy, or, in preparative experiments, isolated by recrystallization or column chromatography to obtain the photo-product.

rac-N,N-di-n-butyl-4b',8b',8c',8e'-dibenzo[a,f]cycclopenta[cd]pentaleno-pyrrolidinium perchlorate (3d): Prepared from 2d (50.0 mg, 0.11 mmol) according to GP-2 in acetone solution as colorless prisms (42.0 mg, 0.09 mmol, 85%), mp 176–178 °C. \(^1^H\) NMR (400 MHz, CD$_3$CN): \(\delta = 0.61\) (t, \(J = 7\) Hz, 3H, CH$_3$), 0.74 (t, \(J = 7\) Hz, 3H, CH$_3$), 0.85–0.94 (m, 1H, CH$_2$), 0.99–1.07 (m, 1H, CH$_2$), 1.16–1.33 (m, 4H, CH$_2$), 1.33–1.39 (m, 2H, CH$_2$), 2.74–2.82 (m, 1H, CH$_2$), 2.88–2.95 (m, 2H, CH$_2$), 3.48 (d, \(J = 13\) Hz, 1H, NCH$_{HC}$), 3.73 (d, \(J = 13\) Hz, 1H, NCH$_{HC}$), 4.04 (s, 1H, CH), 4.24 (d, \(J = 13\) Hz, 1H, NCH$_{HC}$), 4.57 (d, \(J = 13\) Hz, 1H, NCH$_{HC}$), 4.91 (s, 1H, CH), 6.97–7.01 (m, 2H, CH$_{ar}$), 7.09–7.17 (m, 4H, CH$_{ar}$), 7.34–7.37 (m, 1H, CH$_{ar}$), 7.39–7.41 (m, 1H, CH$_{ar}$), 7.38–7.40 (m, 1H, CH$_{ar}$). \(^1^3^C\) NMR (100 MHz, CD$_3$CN): \(\delta = 13.0\) (CH$_3$), 13.6 (CH$_3$), 20.1 (CH$_2$), 20.3 (CH$_2$), 24.8 (CH$_2$), 25.8 (CH$_2$), 55.5 (CH$_2$), 55.7 (CH$_2$), 59.2 (CH$_2$), 60.0 (CH$_2$), 61.9 (C$_q$), 67.3 (CH), 69.4 (C$_q$), 70.1 (CH), 122.5 (CH$_{ar}$), 123.3 (CH$_{ar}$), 125.8 (CH$_{ar}$), 125.9 (CH$_{ar}$), 127.7 (CH$_{ar}$), 128.3 (CH$_{ar}$), 128.4 (CH$_{ar}$), 128.9 (CH$_{ar}$), 137.0 (C$_q$), 137.1 (C$_q$), 152.0 (C$_q$), 154.5 (C$_q$). MS (ESI$^-$): m/z (%) = 358 (100).

Three PTC reactions were run in parallel with a) no catalyst, b) TBAB as the catalyst, or c) 3d as the catalyst.

### Supporting Information

**Supporting Information File 1**

Experimental procedures, characterization data and copies of \(^1^H\) NMR and \(^1^3^C\) NMR spectra of compounds 2a–g and 3a–f.

[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-17-S1.pdf](http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-17-S1.pdf)

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### References


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Photocycloaddition of aromatic and aliphatic aldehydes to isoxazoles: Cycloaddition reactivity and stability studies

Axel G. Griesbeck*, Marco Franke, Jörg Neudörfl and Hidehiro Kotaka

Abstract
The first photocycloadditions of aromatic and aliphatic aldehydes to methylated isoxazoles are reported. The reactions lead solely to the \( \text{exo} \)-adducts with high regio- and diastereoselectivities. Ring methylation of the isoxazole substrates is crucial for high conversions and product stability. The 6-arylated bicyclic oxetanes \( \text{9a-9c} \) were characterized by X-ray structure analyses and showed the highest thermal stabilities. All oxetanes formed from isoxazoles were highly acid-sensitive and also thermally unstable. Cleavage to the original substrates is dominant and the isoxazole derived oxetanes show type T photochromism.

Introduction
Photochemical \( [2 + 2] \) cycloadditions are among the most efficient photoreactions and are used in numerous synthetic applications due to the generation of highly reactive four-membered rings. An important example is the photocycloaddition of electronically excited carbonyl compounds to alkenes (Paternö–Büchi reaction). This reaction is a superior route to oxetanes, which can be subsequently transformed into polyfunctionalized products [1]. With regards to the regio- and diastereoselectivity of the Paternö–Büchi reaction, recent experimental and computational studies have brought about a remarkable increase in our understanding of this reaction. Especially the role of intermediary triplet 1,4-biradicals – their stability, lifetimes and intersystem crossing geometries – was crucial for a more sophisticated description [2-5], which also improved the synthetic significance of this reaction [6].

Previous publications have clearly demonstrated the versatility of the Paternö–Büchi reaction in various synthetic applications which gives rise to a multiplicity of different products. The photocycloaddition of furans to carbonyl compounds affords the corresponding \( \beta \)-hydroxy-1,4-diketones after hydrolysis of the primary photochemical products (photo aldol reaction) [7].
whilst the reaction of oxazoles with carbonyl compounds is a convenient protocol for the stereoselective synthesis of α-amino β-hydroxy ketones [8,9] as well as highly substituted α-amino β-hydroxy acids [10,11].

The results on five-membered aromatic heterocycles published so far, however, has not included a study of isoxazoles as substrates in the Paternò–Büchi reaction. This class of heterocyclic compounds can be considered as masked β-amino ketones [12], and subsequently hydrolysed to the corresponding 1,3-diketones [13] or deaminated to yield Michael systems [14]. Thus, isoxazoles also appear to be important substrates for carbonyl–ene photocycloaddition due to possible applications in ring-opening transformations.

Results and Discussion

Synthesis of the isoxazole substrates

The substrates isoxazole (7a), 5-methylisoxazole (7b), 3,5-dimethylisoxazole (7d) and 3,4,5-trimethylisoxazole (7e) were synthesized by reaction of the corresponding carbonyl compounds with hydroxylamine, while 3-methylisoxazole (7c) was obtained by the [3 + 2]-cycloaddition of acrylonitrile with the trimethylsilyl ester of aci-nitroethane (Scheme 1). The reaction of acetylacetalddehyde with hydroxylamine gave 7b, exclusively.

3,5-Diphenylisoxazole (7f) was prepared from acetophenone and methyl benzoate, followed by cyclization of the resulting diketone 4 with hydroxylamine. 5-Methoxy-3-phenylisoxazole (7g) and 5-(trimethylsilyloxy)-3-phenylisoxazole (7h) were synthesized from 3-phenylisoxazol-5-one (5) which was obtained by the [3 + 2]-cycloaddition of acrylonitrile with the trimethylsilyl ester of aci-nitroethane (Scheme 1). The reaction of acetylacetalddehyde with hydroxylamine gave 7b, exclusively.

Photochemistry of the isoxazoles 7a–h: test reactions

The isoxazoles 7a–e were irradiated in the presence of benzaldehyde or propionaldehyde as model compounds for aromatic and aliphatic carbonyl compounds, respectively, at λ = 300 nm in perdeuterated acetonitrile. 1H NMR studies showed that the expected photoadducts were formed only from isoxazoles 7d and 7e with benzaldehyde (Scheme 3 and Table 1). In the presence of propionaldehyde no reaction was observed.

The use of a tenfold excess of aldehyde had no significant influence on the reaction. The use of a tenfold excess of the isoxazole, however, led to a considerable change in the reaction conversions (Table 2).
The isoxazoles 7f-h were treated similarly to 7a-e. However, in these experiments, the formation of the corresponding Paternò–Büchi products were not observed, neither in the presence of propionaldehyde nor in the presence of benzaldehyde. Instead, a reaction could be observed which also occurred both in the presence of a tenfold excess of aldehyde or without any aldehyde. This reaction was identified as the intramolecular ring contraction of 7f-h to yield the corresponding azirines 8a–c (Scheme 4) [16].

The conversion is highly dependent on the degree of substitution of the isoxazole used. In terms of frontier orbital interactions, the reason is the decreasing energy difference between the HOMO of the isoxazole and the SOMO of the excited aldehyde with increasing degree of substitution. Indirect proof of the increasing energy levels of the isoxazole-HOMO is provided from the corresponding ionization energies (Table 3) [15] which decrease with increasing substitution.

Surprisingly, in the absence of aldehydes as the potential reaction partners, the conversions of 7f-h were significantly lower, suggesting the possibility of an energy transfer from the excited singlet or triplet aldehyde to the isoxazole.

Since the photolysis of 7d and 7e in presence of benzaldehyde showed the highest conversions, further irradiations were conducted in order to examine the effect of other aryl substituted aldehydes on reaction conversions (Scheme 5, Table 4).

The reactions of 7e with p- and m-tolualdehyde showed no change in the reaction conversions compared with benzaldehyde, whilst the conversions of 7d with these two aldehydes were considerably decreased. Irradiation of 7d and 7e with p- and m-anisaldehyde showed in all cases lower reaction conversions.

### Table 1: Irradiation of isoxazoles 7a–e with benzaldehyde.

<table>
<thead>
<tr>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>R&lt;sup&gt;3&lt;/sup&gt;</th>
<th>conversion [%]&lt;sup&gt;a&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>7a</td>
<td>H</td>
<td>H</td>
<td>0</td>
</tr>
<tr>
<td>7b</td>
<td>H</td>
<td>Me</td>
<td>0</td>
</tr>
<tr>
<td>7c</td>
<td>Me</td>
<td>H</td>
<td>0</td>
</tr>
<tr>
<td>7d</td>
<td>Me</td>
<td>Me</td>
<td>13</td>
</tr>
<tr>
<td>7e</td>
<td>Me</td>
<td>Me</td>
<td>41</td>
</tr>
</tbody>
</table>

<sup>a</sup>based on the formation of the photoproduct, by NMR (benzaldehyde - isoxazole ratio = 1:1, irradiation time: 6 h).

### Table 2: Irradiations of 7a–e with a tenfold excess of isoxazoles.

<table>
<thead>
<tr>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>R&lt;sup&gt;3&lt;/sup&gt;</th>
<th>conversion [%]&lt;sup&gt;a&lt;/sup&gt;</th>
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<td>7a</td>
<td>H</td>
<td>H</td>
<td>&lt;5</td>
</tr>
<tr>
<td>7b</td>
<td>H</td>
<td>Me</td>
<td>15</td>
</tr>
<tr>
<td>7c</td>
<td>Me</td>
<td>H</td>
<td>10</td>
</tr>
<tr>
<td>7d</td>
<td>Me</td>
<td>Me</td>
<td>40</td>
</tr>
<tr>
<td>7e</td>
<td>Me</td>
<td>Me</td>
<td>98</td>
</tr>
</tbody>
</table>

<sup>a</sup>based on the formation of the photoproduct, by NMR (benzaldehyde - isoxazole ratio = 1:10, irradiation time: 6 h).

### Table 3: Vertical ionization energies (E<sub>I</sub>) of isoxazoles 7a, 7b and 7d.

<table>
<thead>
<tr>
<th></th>
<th>E&lt;sub&gt;I&lt;/sub&gt; [eV]</th>
</tr>
</thead>
<tbody>
<tr>
<td>7a</td>
<td>10.15</td>
</tr>
<tr>
<td>7b</td>
<td>9.61</td>
</tr>
<tr>
<td>7d</td>
<td>9.34</td>
</tr>
</tbody>
</table>

In contrast, the use of a tenfold excess of isoxazole in presence of propionaldehyde did not lead to an increased formation of the corresponding photoproducts. Only in the case of 7e could traces of the expected photoproduct be detected (<5%). Since the LUMO energy of propionaldehyde is larger than that of benzaldehyde, it can be assumed that the energy difference between the isoxazole-HOMO and the aldehyde-LUMO is too large to promote an efficient reaction.
Table 4: Photocycloadditions of 7d and 7e with aromatic aldehydes.

<table>
<thead>
<tr>
<th></th>
<th>conversion [%]a</th>
</tr>
</thead>
<tbody>
<tr>
<td>7d</td>
<td>H</td>
</tr>
<tr>
<td></td>
<td>p-Me</td>
</tr>
<tr>
<td></td>
<td>m-Me</td>
</tr>
<tr>
<td></td>
<td>p-OMe</td>
</tr>
<tr>
<td></td>
<td>m-OMe</td>
</tr>
<tr>
<td>7e</td>
<td>H</td>
</tr>
<tr>
<td></td>
<td>p-Me</td>
</tr>
<tr>
<td></td>
<td>m-Me</td>
</tr>
<tr>
<td></td>
<td>p-OMe</td>
</tr>
<tr>
<td></td>
<td>m-OMe</td>
</tr>
</tbody>
</table>

a based on the formation of the photoproduct (aldehyde - isoxazole = 1:10, irradiation time: 6 h).

Synthesis of oxetanes from 7e and aryl substituted aldehydes

The preparative photoreactions of 7e together with aryl substituted aldehydes were carried out in acetonitrile at −10 ºC in presence of 10 mol % potassium carbonate (in order to neutralize traces of acid). In all cases, the regioisomers 9a–c were formed with excellent (ex) diastereoselectivity (> 99:1, by 1H NMR spectroscopy) in moderate yields and high purities (Scheme 6).

Scheme 6: Preparative photocycloadditions of 7e with aromatic aldehydes.

The chemical structures of these bicyclic oxetanes were established on the basis of the NMR- and X-ray data (Figure 1) [17].

Both regio- and diastereoselectivity are in accord with the rules previously reported for the carbonyl-furan photocycloaddition [3]: High regiocontrol due to the FMO-controlled formation of the corresponding triplet 1,4-biradical and high stereocontrol due to SOC-controlled crossing from the triplet to the singlet surface [4,5].

Reaction behavior of the photoproducts 9a–c

All bicyclic oxetanes obtained in the analytical photochemical experiments as well as in preparative studies (i.e., 9a–c) were acid labile and decomposed already in the presence of catalytic amounts of acid to give solely the starting materials. The photo-products are also thermally labile and decompose at temperatures above approximately 100 ºC, again to give solely the starting materials. Thus, isoxazole-carbonyl photocycloaddition products constitute another class of photochromic T-type systems (Scheme 7) [18].

Hydrogenation of 9a by palladium/charcoal did not lead to the expected aminoketone 10, but to the enamino ketone 11 and benzyl alcohol, indicating decomposition of 9a back to the starting materials, followed by hydrogenation of these substrates (Scheme 8). Variations of reaction temperature (−10 ºC), reaction time (6 h, 1 h) and solvent (ethanol, ethyl acetate) led to the same results.

Hydrogenation of 9a by Raney-nickel led to partial decomposition without any further reaction, whilst treatment with lithium aluminium hydride (3 equiv) yielded complex mixtures with benzyl alcohol as one of the main components. By contrast, no reaction could be observed in presence of sodium borohydride or sodium cyanoborohydride. Attempted reduction with sodium triacetoxyborohydride led to decomposition, probably due to
class of T-type chromophoric systems.

are acid-labile and thermally unstable and thus constitute a new
detected. Apparently, the bicyclic oxetanes isolated in this study
mally labile cycloadducts which thus have not yet been
are also reactive in Paternò–Büchi chemistry resulting in ther-
cannot be excluded at the current stage, that other combinations
addition and give adducts with sufficient thermal stability. It
aromatic aldehydes is sufficient to allow photochemical

traces of acetic acid contained in the hydride reagent. Reduc-
tive treatment with sodium or samarium diiodide also led to de-
composition of the photoproduct. Treatment of 9a with ethyl-
magnesium bromide did not lead to the alkylated photoproduct,
but to partial decomposition into isoxazole 7e and benzalde-
hyde, while at −78 °C, no reaction could be observed. In
contrast, the use of an excess of Grignard reagent (3 equiv) at
−78 °C again led to decomposition. The application of boron
trifluoride at −78 °C also led to decomposition, followed by a
normal nucleophilic attack of the Grignard reagent on the liber-
ated benzaldehyde.

Conclusion
The photocycloaddition of electronically excited carbonyl com-
pounds to isoxazoles is clearly less effective than with other
five-membered aromatic or non-aromatic heterocycles (furans,
thiophenes, pyroles, oxazoles, dihydrofurans, dihydropyrroles)
[1]. Only the combination of methylated isoxazoles and
aromatic aldehydes is sufficient to allow photochemical
addition and give adducts with sufficient thermal stability. It
cannot be excluded at the current stage, that other combinations
are also reactive in Paternò–Büchi chemistry resulting in ther-
mally labile cycloadducts which thus have not yet been
detected. Apparently, the bicyclic oxetanes isolated in this study
are acid-labile and thermally unstable and thus constitute a new
class of T-type chromophoric systems.

Experimental
General methods. All solvents were dried before use. Benzene,
toluene and chloroform were distilled from CaH$_2$. $^1$H NMR and
$^{13}$C NMR spectra were recorded on a Bruker AV 300 or a
Bruker DRX 500 spectrometer. Melting points were deter-
mimed with a Büchi melting apparatus (type Nr. 535) and are
uncorrected. X-ray data collections were performed on a Nonius
Kappa-CCD-diffractometer, using a monochromatic Mo K$_\alpha$
(0.71073 Å) radiation. Combustion analyses were measured
using an Elemental Vario EL Instrument. All irradiations were
carried out in quartz vessels. Photochemical reactors LZ-C4
(14 × 3000 Å lamps, $\lambda = 300 \pm 10$ nm) and RPR-208 (8 × 3000
Å lamps, $\lambda = 300 \pm 10$ nm) were used for irradiations.

Trimethylsilyl ester of aci-nitroethane (1) [19]. Chloroti-
methylsilane (43.20 g, 0.4 mol, 50.5 mL) was added to
nitroethane (30.0 g, 0.4 mol, 28.7 mL) and triethylamine
(40.40 g, 0.4 mol, 55.6 mL) in benzene (200 mL). The mixture
was stirred vigorously for 18 h at rt, filtered and evaporated.
The crude product was obtained as a yellow oil and used imme-
diately without further purification.

3-Methyl-5-trimethylsilyloxy-2-isoxazoline (2) [19]. A mixture
of acrylonitrile (10.61 g, 0.2 mol, 13.2 mL), triethylamine
(10.12 g, 0.1 mol, 13.9 mL) and 1 (28.73 g, 0.2 mol) in toluene
(90 mL) was heated at 85 °C for 1 h. The solvent was removed
and the crude product fractionated (105−110 °C, 20 mbar) to
give 22.50 g (65%) of 2 as a colorless oil. $^{13}$C NMR
(75.5 MHz, CDC$_3$): 155.2 (1C, C$_q$), 97.4 (1C, CH), 47.4 (1C, CH$_2$), 12.9 (1C, CH$_3$), 0.0 (3C, 3 × CH$_3$). $^1$H NMR (300 MHz, CDC$_3$):
5.80–5.77 (dd, 1H, 3$^J$ = 5.8 Hz, 0.9 Hz, CH$_2$), 3.04–2.96 (dq, 1H, 3$^J$ = 5.5 Hz, 0.8 Hz, CH$_2$), 2.71–2.65 (dq, 1H, 3$^J$ = 1.8 Hz, 0.8 Hz, CH$_2$), 2.01 (s, 3H, CH$_3$), 0.15 (s, 9H, 3 × CH$_3$).

3-Methylpentane-2,4-dione (3) [20]. A mixture of freshly
distilled 2,4-pentanediene (28.03 g, 0.28 mol, 28.8 mL), anhy-
drous potassium carbonate (38.70 g, 0.28 mol) and methyl
iodide (49.68 g, 0.35 mol, 21.8 mL) was heated at 85 °C for 1 h. The solvent was removed
and the crude product fractionated (105−110 °C, 20 mbar) to
give 22.50 g (65%) of 3 as a colorless oil. $^{13}$C NMR
(75.5 MHz, CDC$_3$): 204.8 (2C, C$_q$), 190.1 (1C, C$_q$), 104.5 (1C, C$_q$), 61.4 (1C, CH), 28.4 (2C, CH$_3$), 23.0 (1C, CH$_3$), 20.9 (1C, CH$_3$), 12.2 (1C, CH$_3$). $^1$H NMR (300 MHz, CDC$_3$): 3.59 (q, 1H, 3$^J$ = 7.2 Hz, CH$_2$), 2.06 (s, 6H, 2 × CH$_3$), 1.97 (s, 3H, CH$_3$), 1.70 (s, 1.5H, CH$_3$), 1.19–1.16 (d, 3H, 3$^J$ = 6.9 Hz, CH$_3$).

$^1$H NMR (300 MHz, CDCl$_3$).

$^13$C NMR (75.5 MHz, CDCl$_3$).
1,3-Diphenylpropane-1,3-dione (4). A mixture of acetophenone (30.04 g, 0.25 mol, 29.2 mL), methyl benzoate (34.04 g, 0.25 mol, 31.5 mL), sodium methoxide (16.21 g, 0.3 mol) and toluene (300 mL) was refluxed for 3 h. The resulting solution was concentrated, cooled to rt, poured into hydrochloric acid (300 mL, 6 N) and stirred for 30 min. The azeotropic mixture was extracted twice with toluene and the combined organic layers were neutralized with aqueous sodium hydroxide. The organic solution was then washed two times with water, dried over magnesium sulfate, filtered and evaporated. The resulting solid was recrystallized twice from ethanol to yield 6.34 g (41%) of 4 as colorless crystals. $^{13}$C NMR (75.5 MHz, CDCl$_3$): 185.6 (2C, C$_q$), 135.4 (2C, C$_q$), 132.4 (2C, CH), 128.6 (4C, CH), 127.1 (4C, CH), 93.0 (1C, CH). $^1$H NMR (300 MHz, CDCl$_3$): 8.03–7.99 (m, 4H, CH), 7.59–7.47 (m, 6H, CH), 6.87 (s, 1H, CH).

3-Phenylisoxazol-5-one (5) [21]. A mixture of ethyl benzoylecetate (15.38 g, 80 mmol), hydroxylamine hydrochloride (5.56 g, 80 mmol), potassium carbonate (5.53 g, 40 mmol), ethanol (40 mL) and water (40 mL) was stirred at rt for 15 h. The solid was filtered, washed with water and extracted three times with ether. The combined organic layers were dried over magnesium sulfate, filtered and the solvent was evaporated. The residue was recrystallized from ethanol to give 9.21 g (71%) of 5 as colorless crystals. $^1$H NMR (300 MHz, CDCl$_3$): 7.69–7.67 (m, 2H, CH), 7.54–7.47 (m, 3H, CH), 3.80 (s, 1H, CH), 2.19 (s, 3H, CH) and 2.317 (s, 3H, CH) ppm.

3-Phenyl-5-chloroisoxazole (6) [22]. A mixture of 5 (4.84 g, 30 mmol) and phosphorous oxychloride (16.3 mL, 175 mmol) was stirred at 0 °C and triethylamine (3.37 g, 33 mmol, 4.6 mL) added slowly ($T < 25$ °C). The solution was then heated at 120 °C for 2.5 h and the excess phosphorous oxychloride removed in vacuo. The brown residue was triturated with 100 mL iced water and extracted two times with ethyl acetate. The combined organic layers were dried over magnesium sulfate, filtered and the solvent was evaporated. The resulting residue was mixed with chloroform and the remaining solid removed by filtration. The solvent was again removed and the last step repeated with cyclohexane. After evaporation of the solvent, 3.18 g (59%) of 6 was obtained as a yellow solid. $^{13}$C NMR (75.5 MHz, CDCl$_3$): 164.1 (1C, C$_q$), 155.0 (1C, C$_q$), 130.5 (1C, CH), 128.9 (2C, CH), 128.1 (1C, C$_q$), 126.5 (2C, CH), 99.5 (1C, CH). $^1$H NMR: 7.77–7.74 (m, 2H, CH), 7.47–7.45 (m, 3H, CH), 6.47 (s, 1H, CH).

Isoxazole (7a) [23]. Malonaldehyde tetraethyl acetal (22.03 g, 0.1 mol) was added over a 30 min period to hydroxylamine hydrochloride (7.64 g, 0.11 mol) in water (50 mL) at 70 °C. Heating was continued for 3 h and the resulting mixture distilled at 95 °C and a mixture of isoxazole, alcohol and water collected. The distillate was added dropwise to a solution of cadmium chloride (18.30 g) in water (15 mL). The resulting precipitate was filtered, washed with a little cold water and dried. The resulting solid was then suspended in water, heated to boiling and a mixture of isoxazole and water was obtained on distillation. The distillate (two phases) was extracted with ether, dried over magnesium sulfate and filtered. After evaporation of the solvent, 2.97 g (43%) of 7a was obtained as a colorless liquid. $^{13}$C NMR (75.5 MHz, CDCl$_3$): 157.4 (1C, CH), 148.7 (1C, CH), 103.2 (1C, CH). $^1$H NMR (300 MHz, CDCl$_3$): 8.36 (s, 1H, CH), 8.19 (s, 1H, CH), 6.26 (s, 1H, CH).

5-Methylisoxazole (7b). A mixture of acetylacetaldelyde (30.0 g, 0.227 mol), diethyamine (17.40 g, 0.238 mol, 24.6 mL) and methanol (70 mL) was heated at 65 °C for 1 h. Hydroxylamine hydrochloride (16.50 g, 0.238 mol) of in water (50 mL) was then added dropwise and heating was continued for 2 h. The solution was cooled to rt, extracted with ether, dried over magnesium sulfate and filtered. The solvent was evaporated and the residue fractionated (78–80 °C, 270 mbar) to yield 4.94 g (26%) of 7b as a colorless liquid. $^{13}$C NMR (75.5 MHz, CDCl$_3$): 168.4 (1C, C$_q$), 150.1 (1C, CH), 100.5 (1C, CH), 11.6 (1C, CH$_2$). $^1$H NMR (300 MHz, CDCl$_3$): 8.02 (s, 1H, CH), 5.88 (s, 1H, CH), 2.33 (s, 3H, CH$_3$).

3-Methylisoxazole (7c) [24]. A solution of 2 (20.80 g, 0.12 mol) and p-toluenesulfonic acid (2.0 g) in chloroform (200 mL) was refluxed for 2 h. The resulting mixture was cooled to rt, washed with aqueous sodium bicarbonate and extracted several times with chloroform. The combined organic phases were washed several times with water, dried over magnesium sulfate, filtered and evaporated to give 3.89 g (39%) of 7c as a colorless liquid. $^{13}$C NMR (75.5 MHz, CDCl$_3$): 158.4 (1C, C$_q$), 157.9 (1C, CH), 104.8 (1C, CH), 10.9 (1C, CH$_2$). $^1$H NMR (300 MHz, CDCl$_3$): 8.22 (s, 1H, CH), 6.11–6.10 (d, 1H, $^3$J = 0.9 Hz, CH), 2.24 (s, 3H, CH$_3$).

3,5-Dimethylisoxazole (7d) [25]. A solution of 2,4-pentanedione (100.10 g, 1 mol, 103.2 mL) and hydroxylamine hydrochloride (74.70 g, 1.075 mol) in water (150 mL) and ethanol (100 mL) was refluxed for 90 min. The mixture was cooled to rt, poured onto ice (200 mL) and extracted four times with dichloromethane. The combined organic phases were dried over magnesium sulfate, filtered and evaporated. The resulting dark mixture was fractionated (141 °C) to yield 77.5 g (80%) of 7d as a colorless liquid. $^{13}$C NMR (75.5 MHz, CDCl$_3$): 168.2 (1C, C$_q$), 159.0 (1C, C$_q$), 101.6 (1C, CH), 11.1 (1C, CH$_2$), 10.4 (1C, CH$_2$). $^1$H NMR (300 MHz, CDCl$_3$): 5.76 (s, 1H, CH), 2.317 (s, 3H, CH$_3$), 2.19 (s, 3H, CH$_3$).
3,4,5-Trimethylisoxazole (7e) [26]. A mixture of 3 (20.55 g, 0.18 mol), hydroxylamine hydrochloride (12.50 g, 0.18 mol) and water (80 mL) was stirred at rt for 24 h. The solution was then extracted three times with chloroform and the combined organic layers were dried over magnesium sulfate and filtered. After removal of the solvent, the residue was distilled (165 °C) to yield 13.0 g (65%) of 7e as a colorless liquid. $^{13}$C NMR (75.5 MHz, CDCl$_3$): 163.4 (1C, C q), 139.3 (1C, Ar-C), 129.7 (1C, Ar-C), 126.4 (2C, Ar-C), 115.6 (1C, OCO), 86.4 (1C, CO), 63.8 (1C, C q), 21.1 (1C, CH$_3$), 19.2 (1C, CH$_3$), 11.1 (1C, CH$_3$), 10.2 (1C, CH$_3$). $^1$H NMR (500 MHz, CD$_2$CN): 7.45–7.35 (m, 5H, Ar-CH), 5.59 (s, J$_3$ = 7.0 Hz, Ar-CH), 2.05 (s, 3H, CH$_3$), 1.60 (s, 3H, CH$_3$), 0.79 (s, 3H, CH$_3$). Anal. calcd. for C$_{13}$H$_{17}$N$_2$: C 71.67, H 6.98, N 6.40. Colorless needles, unit cell parameters: a = 9.3804(6), b = 14.8345(10), c = 9.080(6), $\beta$ = 109.944(4), space group $\text{P2}_1$/$\text{c}$. Yield: 50%.

Photocycloaddition reactions of 7e with aryl substituted aldehydes: General procedure. A solution of 7e (2.22 g, 20 mmol) and the corresponding aldehyde (20 mmol) in acetonitrile (200 mL) was transferred to a quartz NMR tube, degassed with argon and irradiated in a photo reactor (LZ-C4, 300 nm) for 6 h. The mixture was examined before and after irradiation by $^1$H NMR spectroscopy.

Photocycloaddition reactions of 7e with aryl substituted aldehydes: General procedure. A solution of 7e (2.22 g, 20 mmol) and the corresponding aldehyde (20 mmol) in acetonitrile (200 mL) was transferred to a quartz vessel, mixed with potassium carbonate (0.28 g, 10 mol %) and degassed with nitrogen. The mixture was stirred and irradiated in a Rayonet photochemical reactor (RPR 208, lamps centered 300 nm) at −10 °C for 48–72 h. The resulting yellow solution was concentrated (35 °C) and extracted three times with ether. The combined organic layers were dried over magnesium sulfate and the solvent was evaporated. The solid residue was mixed with a little ethanol, stirred for 30 min, filtered and recrystallized at −10 °C from ethanol.

$^{ex}	ext{o-1,4,5-trimethyl-6-phenyl-2,7-dioxa-3-aza-bicyclo[3.2.0]hept-3-en (9a).}$ Yield: 35%. $^{13}$C NMR (500 MHz, CD$_2$CN): 163.7 (1C, CN), 139.3 (1C, Ar-C), 129.3 (2C, Ar-C), 128.9 (1C, Ar-C), 126.2 (2C, Ar-C), 115.6 (1C, OCO), 86.4 (1C, CO), 63.8 (1C, C q), 21.1 (1C, CH$_3$), 19.2 (1C, CH$_3$), 11.1 (1C, CH$_3$). $^1$H NMR (500 MHz, CD$_2$CN): 7.45–7.24 (m, 4H, Ar-CH), 5.55 (s, 3H, J = 7.6 Hz, J = 7.0 Hz, Ar-CH), 2.05 (s, 3H, CH$_3$), 1.60 (s, 3H, CH$_3$), 0.78 (s, 3H, CH$_3$). Anal. calcd. for C$_{13}$H$_{17}$N$_2$: C 71.67, H 6.98, N 6.45. Found: C 71.67, H 6.98, N 6.40. Colorless needles, unit cell parameters: a = 9.3804(6), b = 14.8345(10), c = 9.080(6), $\beta$ = 109.944(4), space group $\text{P2}_1$/$\text{c}$.
Ar-CH, 5.54 (s, 1H, CH), 2.37 (s, 3H, Ar-CH3), 2.04 (s, 3H, CH3CN), 1.60 (s, 3H, CH3), 0.79 (s, 3H, CH3). Anal. calcd. for C14H17NO2: C 72.70, H 7.41, N 6.06. Found: C 72.55, H 7.39, N 6.09. Colorless needles, unit cell parameters: a = 13.3045(8), b = 6.9356(6), c = 17.5348(10), β = 129.284(3), space group P21/c.

References
17. The crystallographic data for the isoxazole photoadducts 9a, 9b, and 9c have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications no. CCDC-795107 (9a), CCDC-795108 (9b), CCDC-795109 (9c).
Abstract
The asymmetric synthesis of gymnastatin H has been achieved by using the photoisomerisation of a conjugated ester to its \(\beta,\gamma\)-unsaturated isomer through the protonation of an in situ generated dienol as key step. Thanks to diacetone D-glucose used as a chiral alkoxy group, the protonation occurred well onto one of the two diastereotopic faces with very high yields and selectivities. Moreover, by this way the configuration of the C-6 centre of the target molecule was controlled.

Introduction
The photodeconjugation of \(\alpha,\beta\)-unsaturated esters 1 – which bear at least one hydrogen atom on \(\gamma\)-position – allows a straightforward access to \(\beta,\gamma\)-unsaturated isomers 2 [1]. This reaction was first reported by Jorgenson [2,3] and has been extensively studied by different groups in a mechanistical point of view. For example, Weedon et al. were able to trap an intermediate species identified as a photodienol (its formation resulting from a [1,5]-sigmatropic rearrangement). It was shown that the efficiency of the isomerisation process is highly dependent on the nature of the solvent and on the presence of various additives (e.g., amines) which could catalyse the reketonisation of the transient dienol [4] (Scheme 1). Despite the potential interest in \(\beta,\gamma\)-unsaturated acid derivatives, until recently only a few applications of this photochemical transformation in total synthesis appeared in the literature. However, the scope of the photochemical isomerisation has been greatly enhanced thanks to the development of diastereo- and enantioselective versions. Starting from \(\alpha\)-substituted esters 3 in the presence of a catalytic amount of an enantiomERICally pure bicyclic amino alcohol 4 – derived from camphor –, the protonation of the prochiral photodienol can be achieved with an ee up to 91% [5]. This value is one of the highest values observed for an enantioselective protonation transformation.
reaction. However, as the selectivities were highly dependent on the substrate, an alternative diastereoselective version has been developed. By using cheap and commercially available diacetone D-glucose (DAG-OH) as chiral alkoxy group and dimethylamino alcohol as additive, a selective protonation of one of the two diastereotopic faces of the transient dienol was achieved which lead to esters 7 with a d.r. better than 97.5:2.5 [6] (Scheme 2). This transformation allowed the formation of a new allylic stereogenic centre and found already a direct application to the asymmetric synthesis of different natural products including (R)-lavandulol (8), (R)-arundic acid (9) and 2-fluoroacids or lactones [7-9] (Figure 1).

Filamentous fungi are the source of a wide range of secondary metabolites which possess very promising biological activities. Among them, gymnastatins 10 constitute a family of compounds isolated from Gymnascella dankaliensis which grows in symbiosis with the marine sponge Halichondria japonica [10] (Figure 2). Gymnastatins 10 possess a common unsaturated fatty acid residue connected to a tyrosine subunit. These compounds have been reported to exhibit antibacterial activity and cytotoxities against cultured P388 cancer cells. Interestingly, the same acid chain with an R-configuration has been identified in other structures like dankastatins [11] isolated from the same source, aranorosin (11) isolated from Pseudoarachniotus roseus [12] and manumycin C (12) isolated from Streptomyces parvulus [13]. Different groups have investigated the synthesis of gymnastatins 10a–c [14-16], compounds 11 [17] and 12 [18]. In most cases, the lateral acid chain was prepared starting from (R)-2-methyloctanal by iterative Wittig reactions to build the
dienoate chain. The configuration at the C-2 carbon atom of this precursor was controlled by using a diastereoselective alkylation of an acyl oxazolidinone. In some cases, a Claisen condensation took place and afforded a \( \beta \)-ketoamide in noticeable amounts diminishing the overall yield of the sequence [15]. In this context, we have considered an alternative synthetic route to the fatty acid common to all gymnastatins according to a photoisomerisation–diastereoselective protonation sequence involving catalytic amounts of an achiral organocatalyst (e.g., amino alcohol \( 4b \)). Our goal was to describe the first de novo total synthesis of gymnastatin H (\( 10c \)).

**Results and Discussion**

Ethyl ester \( 14 \), readily prepared from hexanal by a Wittig–Horner reaction, was saponified and esterified under DCC activation with commercially available diacetone D-glucose (Scheme 3). Irradiation of \( 16 \) at 254 nm in methylene chloride at \(-60^\circ C\) delivered the \( \beta,\gamma \)-unsaturated ester \( 17 \) in 90% yield as an inseparable mixture of \( E \)- and \( Z \)-isomers. Hydrogenation of the double bond lead to the saturated ester \( 18 \) for which a 95:5 diastereomeric ratio was measured by \( ^1H \) NMR spectroscopy. Next, a two-step sequence delivered 2-methyloctanal (\( 20 \)) in 58% overall yield. The configuration of the newly created centre was first assigned as \( R \) by applying a model we disclosed earlier and was confirmed by comparison with optical rotation values published in the literature [19]. Aldehyde \( 20 \) was submitted to a Wittig condensation with phosphorane \( 13b \) at reflux of toluene to deliver ester \( 21 \) only as the \( E \)-isomer. It should be pointed out that the Wadsworth–Emmons variant using 2-phosphonatoester \( 13a \) led mainly to the \( Z \)-isomer, a phenomenon which was already observed with \( \alpha \)-substituted aldehydes [20]. The reduction of the ethyl ester into the corresponding allylic alcohol \( 22 \) followed by the oxidation with Dess–Martin periodinane (DMP) [21] afforded aldehyde \( 23 \) which was converted into the known ethyl ester (\( E,E \)-\( 24 \)) by a subsequent Wittig–Horner reaction. The comparison of the optical rotation with literature data confirmed the (\( R \)) configuration at the C-6 carbon. By saponification under mild conditions, \( 24 \) was converted into carboxylic acid \( 25 \) which was implicated into a free-epimerising amidation procedure with HOBt [22] and the readily available \( O \)-protected tyrosine derivative \( 26 \). Finally, the TBS group of the amino ester moiety was removed under standard conditions to deliver compound \( 10c \). The measured spectroscopic data were identical to those reported for gymnastatin H [10]. Interestingly, the optical rotation of the synthetic product showed a higher value ([\( \alpha \]D\( _{25} \) = +104 (0.3, CHCl\( _3 \))) than those measured for the isolated natural product ([\( \alpha \]D\( _{25} \) = +42.3 (0.76, CHCl\( _3 \))). Similar discordances have been already observed in the case of gymnastatin N and were shown to be a consequence of a partial epimerisation at the C-2’ carbon of the natural compound’s amino ester subunit [15].

**Conclusion**

In conclusion, we have achieved the total synthesis of (6R)-gymnastatin H in 14 steps and 4.3% overall yield by using a highly diastereoselective photodeconjugation of a diacetone D-glucose ester as key step (de >95%). Now, work is underway to prepare parent structures that either possess an opposite configuration on the stereogenic centre or a modified geometry of the two double bonds. Furthermore, the biological activities of these novel structures are going to be studied.
Scheme 3: Reagents and conditions: (a) $\text{NaH}$, 13a, THF, 25 °C, 83%. (b) $\text{KOH}$, $\text{EtOH/H}_2\text{O}$ (95/5), $\Delta$, 97% ($E/Z$: 90/10). (c) $\text{DAG-OH}$, $\text{DCC}$, $\text{DMAP}$, $\text{CH}_2\text{Cl}_2$, 0 °C then rt, 76%. (d) hv (254 nm), 4b (0.3 equiv), $\text{CH}_2\text{Cl}_2$, -60 °C, 90%. (e) $\text{H}_2$ (1 atm), $\text{PtO}_2$ (cat.), $\text{Et}_2\text{O}$, 99%. (f) LiAlH$_4$, $\text{Et}_2\text{O}$, 0 °C, 83%. (g) $\text{DMP}$, $\text{CH}_2\text{Cl}_2$, 0 °C, 70%. (h) 13b, PhMe, 80 °C, 80% (E-only). (i) Dibal-H (2 equiv), THF, 0 °C, 99%. (j) $\text{DMP}$, $\text{CH}_2\text{Cl}_2$, 0 °C, 75%. (k) 13c, NaH, THF, rt, 60%. (l) LiOH, MeOH, THF, $\text{H}_2\text{O}$, 70%. (m) 26, $\text{DCC}$, $\text{HOBt}$, $\text{CH}_2\text{Cl}_2$, 57%. (n) TBAF, THF, 0 °C, 96%.

Supporting Information

Supporting Information File 1
Full experimental and spectral data for compounds 10c, 14–27.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-21-S1.pdf]

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References

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Formation of macrocyclic lactones in the Paternò–Büchi dimerization reaction

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Abstract
Furan-2-ylmethyl 2-oxoacetates 1a,b, in which the furan ring and the carbonyl moiety were embedded intramolecularly, were synthesized from commercially available furan-2-ylmethanol and their photochemical reaction (hν > 290 nm) was investigated. Twelve-membered macrocyclic lactones 2a,b with C₁₀ symmetry including two oxetane-rings, which are the Paternò–Büchi dimerization products, were isolated in ca. 20% yield. The intramolecular cyclization products, such as 3-alkoxyoxetane and 2,7-dioxabicyclo[2.2.1]hept-5-ene derivatives, were not detected in the photolysate.

Findings
Photochemical [2 + 2] cycloaddition reaction of alkenes with carbonyls, so-called Paternò–Büchi reaction [1-13], is one of the most efficient methods for preparing synthetically useful four-membered heterocyclic compounds, i.e., oxetanes. The Paternò–Büchi reaction of furan with a triplet carbonyl, such as n,π* triplet benzophenone, produces regioselectively 2-alkoxyoxetanes 2OX (Scheme 1). The regioselective formation is rationalized by the relative stability of the intermediary triplet biradicals, BR versus BR', and also by the relative nucleophilicity of the furan-ring carbons, i.e., C₁ versus C₂ (Scheme 1) [14-18].

Biradical BR, in principle, possess two resonance forms, i.e., 1,4-biradical form and 1,6-biradical form. The 1,4-biradical form affords oxetane 2OX after the intersystem crossing (ISC). Alternatively, 2,7-dioxabicyclo[2.2.1]hept-5-ene OBH would be formed from the 1,6-biradical form. The regioisomeric oxetane 3OX should be formed via the regioisomeric biradical
BR'. Biradical BR is energetically more stable than BR', because BR can undergo radical delocalization. The electrophilic oxygen of the excited carbonyl should preferably interact with more nucleophilic C1 carbon to give selectively the biradical BR. Thus, only the 2-alkoxyoxetane 2OX has been observed in the Paternò–Büchi reactions reported so far [19-27]. Thus, in this study, furan-2-ylmethyl 2-oxoacetates 1a, b and 2-(furan-2-yl)methyl 2-oxo-2-phenylacetate 1c [28] were synthesized, in which the furan ring and the carbonyl moiety are connected intramolecularly, and their photochemical reactions were investigated to see whether the reaction proceeds intramolecularly to produce the 3-alkoxyoxetane derivative A and/or the dioxabicyclo[2.2.1]hept-5-ene derivative B, or intermolecularly to give the 2-alkoxyoxetane derivative C (Scheme 2).

Compounds 1a–c [28] were synthesized from furan-2-ylmethanol or furan-2-ylethanol [29] (Scheme 3). Compound 1a (R = Ph) was irradiated in degassed benzene with a high-pressure Hg lamp with a Pyrex filter (Scheme 3). Interestingly, the Paternò–Büchi dimer product 2a (R = Ph), which possesses C₁ symmetry, was obtained as the major product and contains the biologically important macrocyclic lactone structure [30-33]. The structure of 2a was unequivocally determined by the X-ray crystallographic analysis (Figure 1). The one-step preparation of the highly functionalized twelve-membered macrocyclic lactone is synthetically attractive. Intramolecular products, such as compounds A and B, were not detected in the photolysate, although intramolecular cyclization products are known to be products in the photoreaction of 3-substituted furan derivatives [11, 21]. Furan-2-carbaldehyde (3) was the only assignable product during the photochemical reaction, which was monitored by ¹H NMR spectroscopy (Figure 2). The intermolecular Paternò–Büchi reaction product, i.e., C in Scheme 2, was also not observed in the photolysate. This result suggests that the
intra- and intermolecular Paternò–Büchi reaction of 1 is faster than the first intermolecular Paternò–Büchi reaction of 1a. The photoreaction of 1b (R = Me) gave 2b and 3 in 25% and 18%, respectively (Scheme 3). The dimerization product 2c was not observed in the reaction of 1c. Only polymeric products were present in the photolysate. Although the dimerization is sensitive to the chain-length, the Paternò–Büchi dimerization reaction could in future be applicable to the synthesis of a variety of macrocyclic lactones.

To investigate the effects of concentration, solvent, and temperature on the formation of 2a, the photochemical reaction of 1a was conducted under the variety of conditions (Table 1). The yield of intermolecular product 2a was expected to be improved when the concentration of 1a was increased; however, no concentration effect was observed (entry 2). Under the reaction conditions, the formation of polymeric products increased as evidenced by $^1$H NMR analysis of the photolysate. Even with low concentrations of 1a (entry 3), the intramolecular photoproducts A and B were not detected by $^1$H NMR (500 MHz).

To investigate the medium effect on the formation of 2a, the photochemical reaction of 1a was performed in several solvents (entries 4–6). The yield of 2a decreased with increasing solvent polarity; 16% in toluene (entry 4) and 10% in CH$_3$CN (entry 6). Temperature had no effect on the yield of 2a (entries 7–9).

In summary, the intramolecular products such as A and B were not observed in the photochemical reaction of furan derivatives 1a,b, but interestingly the Paternò–Büchi dimers 2a,b with the $C_3$ symmetry, i.e., macrocyclic lactones, were isolated in ca. 20% yield. The results indicate that the intramolecular reactions, which produce 3-alkoxyoxetanes and 2,7-dioxabicyclo[2.2.1]hept-5-ene (Scheme 1 and Scheme 2), are slower than the intermolecular reaction which leads to the preferential formation of 2-alkoxyoxetane C which is followed by a second Paternò–Büchi reaction to give the observed macrocyclic lactones 2. This finding should stimulate future experimental investigations.

![Figure 2: $^1$H NMR spectra (500 MHz) for (a) the photolysate of 1a after 4 h irradiation in degassed and dried C$_6$D$_6$ solution, (b) for isolated macrocyclic lactone 2a, and (c) for furan-2-carbaldehyde (3).](image)
and computational studies on the mechanistically and synthetically fascinating formation of macrocyclic lactone derivatives.

Experimental

NMR and MS measurements were made using JEOL JMN-LA500 and Thermo Fisher Scientific LTD Orbitrap XL spectrometers, respectively, at the Natural Science Center for Basic Research and Development (N-BARD), Hiroshima University.

The furan derivatives 1a–c (129 mg, 0.561 mmol) were dissolved in benzene (7.0 ml) and the degassed reaction mixture was irradiated with a high-pressure Hg lamp (300 W, hv > 290 nm) with a Pyrex filter. After 13 h, the solvent was removed in vacuo and dimethyl fumarate added as an internal standard. $^1$H NMR (500 MHz, CDCl$_3$) was measured to determine the ratio of products. After the photoreaction, the residue was purified by repeated column chromatography and PTLC (hexane–EtOAc = 2:1) to give 2a,b as colorless crystals.

2a: $^1$H NMR (500 MHz, CDCl$_3$) δ 7.55–7.51 (m, 4H), 7.40–7.31 (m, 6H), 6.35 (dd, J = 3.1, 1.1 Hz, 2H), 5.28 (dd, J = 12.5, 0.9 Hz, 2H), 4.82 (dt, J = 3.0, 0.9 Hz, 2H), 4.67 (dd, J = 3.0, 1.1 Hz, 2H), 3.71 (d, J = 12.5 Hz, 2H), 4.27 (dd, J = 12.5, 0.9 Hz, 2H), 3.77 (d, J = 12.5 Hz, 2H), 1.57 (s, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 171.6 (C), 148.7 (CH), 136.0 (CH), 128.6 (CH), 128.4 (CH), 125.7 (CH), 112.6 (C), 102.1 (CH), 90.7 (C), 61.4 (CH2), 55.2 (CH); HRMS (ESI) m/z calcd for C$_{26}$H$_{32}$O$_8$Na (M + Na)$^+$ 483.10504, found 483.10526.

2b: $^1$H NMR (500 MHz, CDCl$_3$): δ 6.66 (dd, J = 3.0, 1.2 Hz, 2H), 5.23 (dt, J = 3.0, 0.8 Hz, 2H), 5.14 (dd, J = 12.5, 0.8 Hz, 2H), 4.27 (dd, J = 3.0, 1.2 Hz, 2H), 3.77 (d, J = 12.5 Hz, 2H), 1.57 (s, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 134.7 (C), 127.9 (CH), 112.7 (C), 101.3 (CH), 88.1 (C), 61.5 (CH$_2$), 53.1 (CH), 21.2 (CH$_3$); HRMS (ESI) m/z calcd for C$_{16}$H$_{16}$O$_8$Na (M + Na)$^+$ 359.07374, found 359.07391.

Supporting Information

Supporting Information File 1
Experimental section for preparation of compounds 1a–c, the detail of the X-ray structure of compound 2a, and $^1$H NMR and $^{13}$C NMR spectra for compounds 2a,b.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-35-S1.pdf]

Supporting Information File 2
X-Ray crystallographic data for compound 2a.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-35-S2.cif]

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References


Photoinduced homolytic C–H activation in N-(4-homoadamantyl)phthalimide

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Abstract

N-(4-homoadamantyl)phthalimide (5) on excitation and population of the triplet excited state underwent intramolecular H-abstractions and gave products 6 and 7. The major product, exo-alcohol 6 was a result of the regioselective δ H-abstraction and the stereoselective cyclization of the 1,5-biradical. Minor products 7 were formed by photoinduced γ H-abstractions, followed by ring closure to azetidinols and ring enlargement to azepinediones. The observed selectivity to exo-alcohol 6 was explained by the conformation of 5 and the best orientation and the availability of the δ-H for the abstraction.

Introduction

Since the pioneering work of Ciamican and Paterno [1,2], the photochemistry of ketones has been intensively studied [3-6]. One important chemical pathway for the deactivation of ketones from the electronically excited states is photoinduced H-abstraction [7]. Intermolecular photoinduced H-abstraction leads principally to the reduction of the ketone [8-12], whereas intramolecular H-abstraction [13,14] leads to cyclization [15-17] or fragmentation, the so called Norish type II reaction [18-20]. The photochemistry of phthalimide derivatives is often similar to that of simple ketones [21-33]. For example, phthalimide derivatives in the electronically excited state abstract H-atoms from alcohols to give reduction products [34]. Furthermore, suitably substituted phthalimides deactivate from the excited state by intramolecular H-abstractions to yield cyclization products, often benzazepinone derivatives [35-37]. Therefore, photoinduced homolytic C–H activation by phthalimide derivatives can, in principle, be used in organic synthesis for the preparation of benzazepinones [21,25,33].

In continuation of our interest in the Majerski’s laboratory in the functionalization and transformation of cage molecules [38-48] as well as the preparation of biologically active compounds...
[49], we turned our attention to adamantylphthalimides [50-52]. Recently, in cooperation with the group of Griesbeck we discovered a photoinduced domino reaction of adamantyl-phthalimide that involves two consecutive γ H-abstractions and leads to a complex methanoadamantane benzazepinone 2 (Scheme 1) [51]. The mechanism of the photoinduced domino reaction was investigated and it was found that it probably takes place from a higher excited triplet state or the singlet state [52]. Herein, we report the synthesis and photochemistry of a phthalimide derivative of homoadamantane 5. The research was conducted to investigate the availability of different C–H bonds in the homoadamantane skeleton for the homolytic activation, that is, abstraction by the phthalimide. The research was, furthermore, sparked by the discovery that numerous polyazaheterocyclic adamantane derivatives show antiviral activity [53-55]. Thus, photoproducts derived from 5 may also exhibit antiviral activity, although that is yet to be substantiated.

![Scheme 1: Photoinduced domino reaction of adamantylphthalimide.](image1)

**Results and Discussion**

The synthesis of homoadamantylphthalimide 5 started from homoadamantanone 3 which is easily prepared by the ring enlargement of adamantanone with diazomethane, generated in situ from N-methyl-N-nitroso-p-toluenesulfonamide (Diazald®) [56]. Homoadamantanone 3 was first reduced to the alcohol 4 [57-59] and subsequently converted to homoadamantyl phthalimide 5 in moderate yield via the Mitsunobu protocol [60] (Scheme 2).

To get more insight into the availability of H-atoms in the homoadamantane skeleton for the abstraction by the phthalimide, molecular modeling was performed. The geometry of 5 was optimized by DFT B3LYP/6-31G method (Figure 1) [61].

Investigation of the distances between the carbonyl groups of the phthalimide moiety and the H-atoms of the homoadamantane skeleton revealed that there are principally two γ H-atoms (with respect to the carbonyl of the phthalimide) and one δ H-atom available for the abstraction (see Scheme 4 and the Experimental for the notation of atoms). The distances between the carbonyl and γ H-atoms at the positions 3 and 5 of the homoadamantane skeleton are 3.52 and 2.52 Å, respectively, whereas distance to the δ H-atom at the position 2 is 2.37 Å. The calculated distances suggest that phthalimide 5 in the excited state should primarily give rise to products derived from the abstraction of the γ H-atom from position 5 and the δ H-atom from position 2 in the homoadamantane skeleton.

![Figure 1: Molecular structure of 5, the geometry optimization was performed by use of DFT B3LYP/6-31G.](image2)

Irradiation of 5 was performed in CH₃CN, CH₃CN–H₂O (3:1), acetone and acetone–H₂O (3:1) and gave three products, i.e., the exo-alcohol 6, and the azepinediones syn-7 and anti-7 (Scheme 3). In all investigated solvents, exo-alcohol 6 was the major product. For example, when the irradiation was performed in acetone–H₂O for 4 h (see the Experimental), the ratio of the isolated starting phthalimide 5 and the photoproducts 6 and 7 was 10:8:6. However, prolonged irradiation in acetone–H₂O (18 h) gave only alcohol 6 which was isolated in 53% yield. Products 7 decomposed on prolonged irradiation. The photochemical reaction was more efficient in solvent system containing acetone rather than CH₃CN. After 18 h irradiation in acetone–H₂O, complete conversion of 5 was achieved, whereas under the same photolysis conditions in

![Scheme 2: Synthesis of homoadamantylphthalimide 5.](image3)
CH$_3$CN–H$_2$O, 72% of unreacted 5 was recovered. This finding is in accordance with acetone acting as a triplet sensitizer and the anticipated triplet state reactivity of the phthalimide in the H-abstraction reactions. Furthermore, the addition of H$_2$O as a protic solvent also increased the reactivity of the phthalimide, based on the conversion of the starting material under the same irradiation conditions. Thus, after 1 h photolysis of 5 in acetone, only 5% of 5 was converted to products, whereas after photolysis in acetone–H$_2$O, a 60% conversion was achieved. This suggests that phthalimide in the triplet excited state, in a protic solvent, undergoes H-abstraction to give products with ten times higher quantum yields than in an aprotic solvent. Such a finding is in accordance with previous reports for phthalimides and is probably due to a switching of the relative order of the singlet and the triplet excited states of the phthalimide [54,62,63].

The structures of photoproducts was determined by spectroscopic methods. In the $^1$H NMR spectrum of 6, in the aromatic region, 4 well-resolved signals are present, indicating the loss of symmetry of the aromatic part of the molecule (compared to the symmetry in 5). Similarly, in the aromatic part of the $^{13}$C NMR spectrum, 4 doublets are present. In the aliphatic part of the $^{13}$C spectrum, 6 doublets and 5 triplets are observed and one quaternary C at δ 98.13 ppm. All of these features are in agreement with the molecular structure of 6. The structure is further supported by 2D NMR wherein all the observed interactions are in agreement with the structure (for HMBC see the Experimental). The exo-stereochemistry of the product was established from the NOESY spectrum where an NOE interaction between the H-7 and H-10, and the H-7 and H-15 were present (for the notation of atoms see the Experimental). Assignment of the structure to azepinone products 7 was straightforward from the corresponding NMR spectra. In the $^1$H NMR spectra they display the characteristic broad N–H singlets at 6.4 and 6.0 ppm. Furthermore, in the aliphatic part of the $^{13}$C NMR spectra, 6 doublets and 5 triplets are present, in accord with the proposed structures. However, from their spectra we were unable to assign the syn- or the anti-stereochemistry to the isolated products 7. In the NOESY spectra of both isolated compounds, an NOE interaction was observed between the H-atoms at the position 1 and 11 (for the notation of atoms see the Experimental), which precluded unambiguous assignment of the stereochemistry to the isomers 7.

According to the above product study, a mechanism for the photochemical transformation of 5 can be proposed. On excitation (direct or sensitized) the triplet state of 5 is populated and undergoes intramolecular H-abstraction. The abstraction of the δ H-atom of the homoadamantane (Scheme 4) is probably the fastest since this H-atom is closest to the carbonyl of the phthalimide moiety. Although two γ H-atoms are available for the abstraction, and it is generally known that γ H-atoms are more readily abstracted [7,13,14], the conformation of the molecule is probably the most important factor that directs the selective δ-abstraction. The δ-abstraction gives rise to a 1,5-biradical (1,5BR) that undergoes stereoselective cyclization to furnish the major product, exo-alcohol 6. The observed selectivity of the 1,5-cyclization is in line with the stability of the product formed. According to B3LYP calculations [61], exo-6 is 15 kJ/mol more stable than endo-6. However, the reason for the observed selectivity is probably due to the preferred motion in which the half-filled orbitals of 1,5BR overlap after ISC, and induce ring-closure.

Two γ H-atoms in 5 are in the proximity to the carbonyl and, in principle, available for abstraction. However, the H-atom at the ethylene bridge of the homoadamantane skeleton (position 5) is closer to the carbonyl, and therefore, more readily abstracted. Abstraction gives a 1,4-biradical (1,4BR) that cyclizes to azetidinol intermediates AZT1 and AZT2. Azetidinols undergo subsequent ring enlargement to furnish products anti-7 and syn-7, respectively. The ratio of the isolated compounds 7 is 5:1. However, no assignment of their stereochemistry was made from their spectra. Nevertheless, the cyclization of 1,4BR is probably selective giving more AZT2, and product syn-7 from the subsequent ring enlargement. The reason for the suspected selectivity becomes evident from the inspection of the structure of 1,4BR where ring closure to the azetidinol probably takes place preferably from the upper side giving AZT2. The other approach (rear side) is sterically more demanding and results in a less stable trans-configuration on the azetidinol intermediate.

Scheme 3: Products after irradiation of 5.
AZT1. Consequently, we suspect that the major isomer 7 has the syn-configuration, whereas the minor isomer has the anti-configuration.

Conclusion

*N-(4-homoadamantyl)phthalimide (5)* was synthesized and its photochemistry investigated. On excitation and population of the triplet state, 5 undergoes intramolecular homolytic C–H activation and gives products 6 and 7. The major product of the photochemical reaction is exo-alcohol 6 formed via regioselective $\delta$ H-abstraction and stereocontrolled cyclization of the 1,5-biradical. The observed selectivity is due to the conformation of 5 where the $\delta$ H-atom is closest to the carbonyl of the phthalimide moiety. Minor products 7 are formed by photoinduced $\gamma$ H-abstraction, followed by ring closure to azetidinols and ring enlargement to azepinediones. High selectivity and high isolable yield of 6 in the photo-reaction of 5 makes this photoinduced C–H activation useful in the synthesis of very complex derivatives with the homoadamantane skeleton with potential antiviral activity for which otherwise tedious multi-step synthesis would be required.

Experimental

General

$^1$H and $^{13}$C NMR spectra were recorded on a Bruker Spectrometer at 300 or 600 MHz. All NMR spectra were measured in CDCl$_3$ using tetramethylsilane as a reference. High-resolution mass spectra (HRMS) were measured on an Applied Biosystems 4800 Plus MALDI TOF/TOF instrument. Melting points were obtained using an Original Kofler apparatus and are uncorrected. IR spectra were recorded on Perkin Elmer M-297 and ABB Bomem M-102 spectrophotometers. Solvents were purified by distillation. 4-Homoadamantanone (3) was prepared in the laboratory according to a known procedure [56]. Phthalimide, triphenylphosphine, lithium aluminum hydride (LAH) and diethyl azodicarboxylate (DEAD) were obtained from commercial sources. All photochemical experiments were performed in a Rayonet photochemical reactor equipped with 300 nm lamps.

4-Homoadamantanone (3)

To a suspension of LAH (3.00 g, 78.95 mmol) in dry THF (100 mL), was added a solution of 4-homoadamantanone (3, 1.00 g, 6.08 mmol) in THF (50 mL). The suspension was heated under reflux for 24 h. After the reaction was complete and cooled (ice bath), LAH was carefully destroyed by the slow addition of H$_2$O. The resulting precipitate was removed by filtration and washed with diethyl ether (3 × 30 mL). The combined organic solution was dried over anhydrous MgSO$_4$. After filtration and removal of the solvent under vacuum, compound 4 [57-59] was isolated in 99% yield (998 mg) and used in the next step without further purification.

*N-(4-homoadamantyl)phthalimide (5)*

4-Homoadamantanol (4)

To a suspension of LAH (3.00 g, 78.95 mmol) in dry THF (100 mL), was added a solution of 4-homoadamantanone (3, 1.00 g, 6.08 mmol) in THF (50 mL). The suspension was heated under reflux for 24 h. After the reaction was complete and cooled (ice bath), LAH was carefully destroyed by the slow addition of H$_2$O. The resulting precipitate was removed by filtration and washed with diethyl ether (3 × 30 mL). The combined organic solution was dried over anhydrous MgSO$_4$. After filtration and removal of the solvent under vacuum, compound 4 [57-59] was isolated in 99% yield (998 mg) and used in the next step without further purification.

4-Homoadamantanol (4)

N-(4-homoadamantyl)phthalimide (5)

4-Homoadamantanol (4, 1.00 g, 6.06 mmol), phthalimide (1.23 g, 8.35 mmol) and DEAD (2.00 mL, 12.64 mmol) were dissolved in dry THF (60 mL) in a three necked round bottomed flask. To the resulting mixture, a solution of triphenylphosphine (2.00 g, 7.63 mmol) in THF (60 mL) was added over a
raphy with the use of the following solvent mixtures: 2% CHCl₃ with 5% MeOH-CH₂Cl₂, 30% diethyl ether-CH₂Cl₂, ethyl acetate-diethyl ether-CH₂Cl₂ (1:1:3) and hexane-ethyl acetate-diethyl ether-CH₂Cl₂ (1:2:2:5).

Colorless crystals, mp 110–111 °C; ¹H NMR (CDCl₃, 300 MHz, δ/ppm) 7.84–7.77 (m, 2H), 7.72–7.66 (m, 2H), 4.61 (t, 1H, J = 9.5 Hz, H-4), 2.60–2.50 (m, 1H), 2.45 (d, 1H, J = 14.1 Hz), 2.22–2.03 (m, 3H), 1.98–1.85 (m, 5H), 1.80–1.62 (m, 3H), 1.60–1.52 (m, 3H); ¹³C NMR (CDCl₃, 75 MHz, δ/ppm) 170.00 (s, 2C, C-14 and C-14'), 131.96 (s, 2C, C-13 and C-13'), 133.60 (d, 2C, C-15 and C-15' or C-16 and C-16'), 131.96 (s, 2C, C-14 and C-14'), 122.82 (d, 2C, C-15 and C-15' or C-16 and C-16') 56.97 (d, C-4), 40.38 (t, C-2 or C-10), 39.56 (d, C-3), 36.64 (t, C-2 or C-10), 39.74 (t, C-2 or C-10), 39.56 (d, C-3), 36.64 (t, C-5), 35.58 (t, C-11), 33.99 (t, C-7 or C-9), 31.53 (t, C-7 or C-9), 29.44 (d, C-1), 27.18 (d, C-6), 27.17 (d, C-8); IR (KBr) ν/cm⁻¹ 2910, 2850, 1765, 1707, 1375, 1350, 1323, 1114, 1084, 1070, 710; HRMS (MALDI), calculated for C₁₉H₂₂NO₂ 296.1645, observed 296.1644.

General procedure for semi-preparative photolysis of N-(4-homoadamantyl)phthalimide (5)

Phthalimide 5 (10 mg, 0.034 mmol) was dissolved in 20 mL of the appropriate solvent, CH₂CN, CH₃CN-H₂O (3:1), acetone or acetone-H₂O (3:1) in a quartz cuvette. The solutions were purged with N₂ for 20 min and irradiated in a Rayonet at 300 nm for 1 h. The solvent was removed on a rotary evaporator and ¹H NMR spectrum of the crude photolysis mixture recorded to determine the ratio of the products.

Preparative photolysis of N-(4-homoadamantyl)-phthalimide (5)

A Pyrex vessel was filled with a solution of N-(4-homoadamantyl)phthalimide (5) (100 mg, 0.338 mmol) in acetone-H₂O (3:1, 200 mL). The solution was irradiated in a Rayonet photoreactor at 300 mm for 4 h. During irradiation the reaction mixture was continuously purged with argon and cooled with a finger-condenser with tap water. After irradiation, the solvent was removed on a rotary evaporator. Unreacted 5 (42%) was recovered by column chromatography on silica gel with 5% MeOH-CH₂Cl₂ as eluent. The photoproducts were isolated by repeated preparative thin layer chromatography with the use of the following solvent mixtures: 33 mg (33%); Colorless crystals; mp 183–185 °C; ¹H NMR (CDCl₃, 300 MHz, δ/ppm) 7.71 (td, 1H, J = 1.0 7.5 Hz, H-4), 7.61 (dt, 1H, J = 1.0, 7.5 Hz, H-6), 7.54 (td, 1H, J = 1.0, 7.5 Hz, H-7), 7.46 (dt, 1H, J = 1.0, 7.5 Hz, H-5), 4.35 (t(dd), 1H, J = 7.3 Hz, H-19), 2.70 (t(dd), 1H, J = 5.8 Hz, H-10), 2.60 (d, 1H, J = 14 Hz, H-16), 2.38 (br s, 1H, H-15), 2.11–2.22 (m, 3H, 2H-18, H-13), 2.03 (q, 1H, J = 6.9 Hz, H-11), 1.88–1.98 (m, 2H, H-17 and H-20), 1.70–1.88 (m, 3H, H-16, H-14 and H-12), 1.55–1.62 (m, 3H, H-14 and H-12), 1.43 (d, J = 13 Hz, H-20); ¹³C NMR (CDCl₃, 75 MHz, δ/ppm) 177.27 (s, c-2), 151.77 (s, C-8), 133.65 (d, C-6), 131.38 (s, C-3), 129.52 (d, C-5), 123.95 (d, C-4), 122.24 (d, C-7), 98.13 (s, C-9), 64.31 (d, C-19), 48.19 (d, C-10), 42.21 (d, C-11), 40.94 (t, C-18), 40.38 (t, C-20), 35.62 (t, C-14), 32.69 (t, C-16), 31.17 (d, C-13), 30.62 (t, C-12), 27.93 (d, C-15), 26.89 (d, C-17); IR (KBr) ν/cm⁻¹ 3300, 2980, 2902, 1694, 1605, 1464, 1433, 1338, 1320, 1297, 1231, 1125, 1053; HRMS (MALDI), calculated for C₁₉H₂₂NO₂ 296.1645, observed 296.1649.

Important HMBC interactions: H-19 and C-6, C-2, C-9, C-10; Important NOE interactions: H-7 and C-19; H-17 and C-19; H-16 and C-14, C-20; H-15 and C-9; H-12 and C-19; H-10 and C-19, C-8; H-4 and C-2, C-8; H-6 and C-8; H-7 and C-9; Important NOE interactions: H-7 and H-15; H-17 and H-10.

rel-(1R,11S)-2-azapentacyclo
[9.7.0.1⁴.⁷]eicosa-4,6,8-trien-2-dione (syn-7) and rel-(1S,11S)-2-azapentacyclo
[9.7.0.1⁴.⁷]eicosa-4,6,8-trien-3,10-dione (anti-7)
21 mg (21%); colorless crystals, mp 244–245 °C; 1H NMR (CDCl3, 300 MHz, δ/ppm) 7.90–7.85 (m, 1H), 7.62–7.54 (m, 2H), 7.33–7.28 (m, 1H), 6.02 (br s, 1H, NH), 4.43 (m, H-1), 3.09 (d, 1H, J = 8.0 Hz, H-11), 3.04 (m, 1H, H-12), 2.44 (m (add), 1H, H-18), 2.18 (s, 1H, H-13), 2.08–1.93 (m, 4H, H-14, H-15, H-19 and H-20), 1.89–1.83 (m, 2H, H-17 and H-20), 1.75 (d, 1H, H-13), 1.68–1.57 (m, 5H, 3H, 2H-15 and H-20 or H-17), 1.38 (d, J = 12 Hz, H-19); 13C NMR (CDCl3, 75 MHz, δ/ppm) 133.01 (d, 1C), 132.30 (d, 1C), 130.38 (d, 1C), 128.71 (d, 1C), 125.40 (d, 1C), 67.21 (d, C-11), 54.32 (d, C-1), 41.42 (t, C-19), 35.50 (t, C-15), 34.72 (t, C-18), 32.75 (t, C-17 or C-20), 32.69 (t, C-17 or C-20), 30.78 (t, C-13), 28.61 (d, C-12), 27.09 (d, C-16 or C-14), 27.05 (d, C-16 or C-14), quarternary C-signals were not detected; IR (KBr) ν/cm−1 3424, 2922, 2856, 1703, 1658, 1561, 1384, 1275, 1096, 801; HRMS (MALDI), calculated for C19H22NO2 296.1645, observed 296.1646.

Important COSY interactions: NH and H-1, H-1 and H-11, H-1 and H-18. Important NOE interaction: H-1 and H-11, H-1 and H-18, NH and H-17, H-11 and H-19 [64].

4 mg (4%); colorless crystals, mp 229–231 °C; 1H NMR (CDCl3, 300 MHz, δ/ppm) 8.12 (dd, 1H, J = 1.2, 7.6 Hz, H-5 or H-8), 8.06 (dd, 1H, J = 1.2, 7.6 Hz, H-5 or H-8), 7.72–7.60 (m, 2H, H-6 and H-7), 6.49 (br s, 1H, NH), 3.92 (t, 1H, J = 7.5 Hz, H-1), 3.00 (t, 1H, J = 5.4 Hz, H-12), 2.95 (d, 1H, J = 8.8 Hz, H-11), 2.17–1.82 (m, 7H, H-18, 2 H-13, H-14, H-17, H-16, H-19), 1.63–1.40 (m, 6H, 2 H-15, H-17, 2 H-20, H-19); 13C NMR (CDCl3, 75 MHz, δ/ppm) 133.01 (d, C-5 or C-8), 131.66 (d, C-5 or C-8), 130.81 (d, C-6 or C-7), 129.48 (d, C-6 or C-17), 67.33 (d, C-11), 58.49 (d, C-1), 40.43 (t, C-17 or C-19), 38.73 (t, C-17 or C-19), 36.00 (d, C-18), 35.78 (t, C-20), 32.06 (t, C-15), 30.36 (d, C-12), 30.18 (t, C-13), 26.48 (d, C-14 or C-16), 26.17 (d, C-14 or C-16), quarternary C-signals were not detected due to small quantity of the sample; IR (KBr) ν/cm−1 3159, 3057, 2899, 2851, 1681, 1658, 1595, 1441, 1403, 1275, 1266, 786, 756; HRMS (MALDI), calculated for C19H22NO2 296.1645, observed 296.1646. Important NOE interaction: H-1 and H-11, H-1 and H-18, NH and H-20 [64].

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References
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Effects of anion complexation on the photoreactivity of bisureido- and bisthioureido-substituted dibenzobarrelene derivatives

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Full Research Paper

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Abstract

Bisureido- and bisthioureido-substituted dibenzobarrelene derivative were synthesized and the photoreactivity of two representative examples were studied. Direct irradiation of the ureido-substituted derivative induces a di-π-methane rearrangement to the corresponding dibenzosemibullvalene derivative, whereas the thiourea-substituted derivative is almost photoinert. Complexes of the latter derivative with chloride, carboxylates, or sulfonate anions, however, are efficiently transformed to the dibenzosemibullvalene product upon irradiation, presumably by suppressing the self-quenching of the thiourea unit in the complex. The association of the ureido-substituted dibenzobarrelene derivative with (S)-mandelate and irradiation of this complex led to the formation of the dibenzosemibullvalene with moderate stereoselectivity (68:32 er). In contrast, the thiourea derivative showed no such effect upon complexation of chiral anions.

Introduction

The control of the selectivity of a photoreaction by supramolecular interactions has recently received much attention [1-3]. For example, chiral receptors have been employed that associate with photoreactive substrates, leading to a distinct preferential conformation of the latter and/or to a limited exposure of the substrate to other reagents due to the shielding effect of the receptor. Because of the restricted freedom of movement or availability of reactive sites within this assembly, mono- and bimolecular photoreactions may proceed through one preferential pathway resulting in regio- or stereoselective product formation. Indeed, this approach has been employed to carry out stereoselective photoreactions, for example [2 + 2] cycloaddition [4], [4 + 4] photocycloaddition [5], Norrish–Yang cyclization [6], and [6π] photocycloyzation [7]. Asymmetric photoreactions have also been carried out with very good stereoselectivities in organized or constrained media [8-10]. For
example, photoactive substrates may be accommodated as guest molecules in chiral host systems, such as suitably modified cucurbiturils [11-15], self-assembled cages [16] and bowls [17], liquid crystals [18], chiral crystals [19-23], or cyclodextrins (CDs) [24-26] in such a way that the chiral environment within the binding site has an influence on preferential reaction pathways, thus inducing stereoselective photoreactions.

Along these lines, the di-π-methane (DPM) rearrangement [27,28] of dibenzobarrelene (dibenzo[2.2]octatriene) (1a) and its derivatives has been shown to be an appropriate model reaction for the assessment of substituent effects on the selectivity of organic photoreactions (Scheme 1) [29,30]. The photoreactivity of dibenzobarrelene derivatives is multiplicity-dependent: The direct irradiation of 1a leads to the dibenzoclooctatetraene 3a in a singlet reaction that occurs via an initial [2 + 2] cycloaddition followed by a [4 + 2] retro-Diels–Alder reaction [27-30]. In the presence of a triplet sensitizer, e.g., acetone or benzophenone, a triplet-state di-π-methane rearrangement is induced. Thus, in the initial reaction step connection between one vinyl and one benzo carbon atom takes place, i.e., a so called vinyl–benzo bridging, that leads to the intermediate biradical BR1a [29]. Subsequent rearomatization with the formation of the intermediate BR2a and intramolecular radical recombination gives the dibenzosemibullvalene 2a as the reaction product. Notably, the DPM rearrangement of dibenzobarrelene derivatives such as 1b, that carry substituents other than hydrogen atoms at the vinyl positions, leads to the formation of two enantiomeric dibenzosemibullvalenes 2b and ent-2b. As indicated in Scheme 1, the two enantiomers originate from different vinyl–benzo bridging pathways in the first reaction step (path a or b). Note that the same two enantiomers are formed upon initial vinyl–benzo bridging with the other benzene unit.

Stereoselective DPM rearrangements of dibenzobarrelene derivatives have been reported in special media, such as chiral mesoporous silica [31] or ionic-liquids [32]; however, most examples for stereoselective DPM rearrangements of dibenzobarrelene derivatives have been observed in the solid-state. For example, the achiral derivative 1b crystallizes in the chiral space group $P2_12_12_1$, and irradiation of the chiral crystals gives dibenzosemibullvalene 2b with a high enantiomeric excess, >95% ee [33]. Since achiral molecules crystallize only very rarely in chiral space groups, the ionic chiral auxiliary strategy was developed by Scheffer et al. which allows to influence the stereoselectivity of solid-state photoreactions by chiral counter ions [34]. This is accomplished by providing the chromophore

\[
\begin{align*}
\text{Scheme 1: Photorearrangements of dibenzobarrelenes 1a and 1b.}
\end{align*}
\]
under investigation with a carboxylic acid functionality and then by attaching a chiral, enantiomerically pure amine by salt formation. An optically active salt is obtained, which consequently crystallizes in a chiral space group. The irradiation of these salts in the solid-state leads to enantiomerically enriched photoproducts. This approach has been successfully applied to the carboxy-substituted dibenzobarrelene derivative 1c which forms the chiral ammonium carboxylate 1c-P with (S)-proline (Scheme 2). After irradiation, acidic workup and subsequent esterification with diazomethane, the dibenzosemibullvalene 2c was obtained with high enantiomeric excess (>95% ee) [35,36].

Interestingly, several asymmetric photoreactions have been conducted with enantiomeric selectivity in homogeneous solution, whereas reports of asymmetric di-π-methane rearrangements in solutions are relatively rare. Chiral auxiliaries attached as ester or amide functionalities at the vinylic positions of dibenzobarrelene induce only low enantioselectivities in the DPM rearrangement in solution [37]; and the ionic auxiliary strategy, which generates impressive enantioselectivity in the solid-state, fails to induce any stereoselectivity in DPM rearrangements in solution. Considering these observations, it remains a challenge to develop a method to accomplish stereoselective DPM rearrangements of dibenzobarrelene derivatives in homogenous solutions. Therefore, we intended to study whether supramolecular interactions of chiral additives with achiral dibenzobarrelenes may be used to influence the photoreactivity of the latter in solution. For that purpose the dibenzobarrelene chromophore was functionalized with ureido or thioureido substituents, since these functionalities are strong hydrogen bonding donors, which may associate with (chiral) anions [38,39]. Moreover, the versatile use of urea and thiourea derivatives in organocatalysis has been demonstrated in several examples [40-44]. Herein, we report the synthesis of ureido- and thioureido-substituted dibenzobarrelene derivatives 1e–i, along with first studies of their photochemical properties in the absence and in the presence of anions.

Results

The bisureido- and bithioureido-substituted dibenzobarrelene derivatives 1e–i were synthesized by the reaction of the known bis(diaminomethyl)-substituted derivative of dibenzobarrelene 1d [45] with a slight excess of the corresponding isocyanate or isothiocyanate (Scheme 3). The resulting products precipitated
from the reaction mixture and were isolated in good yields (72–86%) by direct filtration, except for the thioureido-substituted derivative 1i, which was crystallized from ethyl acetate to give crystals containing one molecule of ethyl acetate as indicated by $^1$H NMR spectroscopy and elemental analysis. All products were fully characterized by $^1$H and $^{13}$C NMR spectroscopy, mass spectrometry, and elemental analysis. The solubility of the dibenzobarrelene derivatives 1c–g is very low in most organic solvents (e.g., <5 mg/l in acetonitrile at 20 °C). In contrast, the 3,5-bis(trifluoromethyl)phenyl-substituted derivatives 1h and 1i have significantly improved solubility in organic solvents; i.e., compound 1h has good solubility in acetone, acetonitrile and alcohols, while thiourea 1i dissolves in most polar organic solvents.

Because of their favorable solubility in organic solvents, the dibenzobarrelene derivatives 1h and 1i were used for the systematic photochemical studies. In both acetone and acetonitrile, irradiation of the bisureido-substituted derivative 1h gave the dibenzosemibullvalene 2h as the major photoproduct (Scheme 4). After irradiation of dibenzobarrelene 1h in acetonitrile solution, product 2h was isolated in 60% yield by crystallization directly from the reaction mixture. The structural assignment of 2h was based on the characteristic $^1$H NMR shifts of the two singlets for the protons at C$^{8b}$ (3.22 ppm) and C$^{4b}$ (4.63 ppm). Irradiation of compound 1h through a quartz filter ($\lambda > 254$ nm) resulted in rapid conversion of 1h. The photolysate contained ca. 60% of 2h, as determined by $^1$H NMR spectroscopic analysis. The byproducts could not be identified. In contrast, no byproducts were formed when the irradiation was carried out through Duran glass ($\lambda > 310$ nm); however, in this case a longer irradiation time was required. For example, after irradiation of a solution of 1h in acetonitrile ($10^{-3}$ M) through Duran glass for 8 h, TLC analysis still indicated the presence of the starting material, whereas in acetonitrile solution full conversion was observed after 3 h irradiation under otherwise identical conditions. The reaction was significantly faster in the presence of anions: The irradiation of a solution of 1h and two molar equiv of tetrabutylammonium chloride (TBAC) in acetonitrile for 3 h (10$^{-3}$ M, $\lambda > 310$ nm) led to complete conversion, and the semibullvalene 2h was obtained in 84% yield after column chromatography. Similar results were obtained in the presence of carboxylate or sulfonate salts.

The irradiation of the bisthioureido-substituted dibenzobarrelene derivative 1i in various organic solvents did not induce the DPM rearrangement, even in acetonitrile, as indicated by TLC and $^1$H NMR spectroscopic analysis of the reaction mixture. Instead, $^1$H NMR spectroscopic analysis revealed slow decomposition of the dibenzobarrelene derivative 1i upon irradiation with no formation of distinct photoproducts. In contrast, the irradiation of compound 1i in the presence of 2 molar equiv of either tetrabutylammonium chloride (TBAC) or tetrabutylammonium (S)-camphor-10-sulfonate (SCS) in acetonitrile for 4–6 h converted the dibenzobarrelene 1i into the dibenzosemibullvalene 2i (Scheme 4), as indicated by the characteristic singlets of the dibenzosemibullvalene structure in the $^1$H NMR spectrum ($8b$-H: 3.43 ppm; $4b$-H: 4.76 ppm, in acetone). The dibenzosemibullvalenes 2h and 2i were identified and fully characterized by $^1$H NMR and $^{13}$C NMR spectroscopy, elemental analysis and/or mass spectrometry.

To assess whether the influence of the anions on the photo-reactivity of the dibenzobarellenes is caused by complex formation, the propensity of the urea and thiourea functionalities to associate with anions was investigated by spectrophotometric titrations of selected tetrabutylammonium salts with derivatives 1h and 1i (Figure 1). Upon the addition of TBAC, a slight change of the absorption bands of the urea derivative 1h was observed with the exception of the absorption maxima at

![Scheme 4: Di-π-methane rearrangements of ureido- and thioureido-substituted dibenzobarrelene derivatives 1h and 1i.](image-url)
280 nm which remained essentially unaffected during the titration. The latter absorption band was assigned to the dibenzobarrelene unit, by comparison with the absorption of the resembling dibenzobarrelene derivative 1d [45]. This observation indicates that the complexation of the chloride anion has no significant influence on the dibenzobarrelene chromophore, but rather on the trifluoromethyl-substituted phenyl substituents. The absorption of the thioureido-substituted derivative 1i changed significantly upon the addition of the sulfonate salt SCS. Specifically, the absorption maximum at 272 nm was red shifted by ca. 15 nm, along with an overall increase of the absorption. In addition, an isosbestic point at 248 nm was observed during the titration process, which indicates an equilibrium between two different absorbing species, i.e., the free and complexed ligand. Because of the predominant absorption of the arylthiourea unit, it was not possible to assess the influence of complexation on the dibenzobarrelene chromophore. The binding isotherms from the spectrophotometric titration were fitted to a 1:1 stoichiometry and the resulting binding constants of the complexes were determined to be $K_0 = 1.1 \times 10^4 \text{ M}^{-1}$ for 1h-TBAC and $K_0 = 1.8 \times 10^4 \text{ M}^{-1}$ for 1i-SCS (Figure 1). In addition, it was observed that the $^1$H NMR spectroscopic signals of the NH protons of 1h (from 6.63 and 9.34 to 7.66 and 10.20) as well as the one of the methine proton (from 4.54 to 4.35) and of the OH proton (from 5.22 to 5.14) of the mandelate were significantly shifted upon the addition of (S)-mandelate (SMD) [in (CD$_3$)$_2$SO)]. The corresponding Job plot confirms the 1:1 complex between 1h and SMD (Supporting Information File 1). Moreover, complex formation was confirmed by a weak NOE effect, as determined by ROESY NMR experiments, between the protons in the ortho position of the phenyl group of the mandelate and the bis(trifluorophenyl) groups of 1h. Since it was demonstrated that the ureido- and thioureido-substituted dibenzobarrelene derivatives 1h and 1i associate with anions, experiments were carried out to assess whether a stereoselective DPM rearrangement of 1h may be induced by a bound chiral anion. The initial experiments were performed with (S)-mandelate (SMD). Thus, a complex of the dibenzobarrelene 1h with SMD was irradiated in acetone solution at different concentrations and with varied host–guest ratios (Table 1, entries 1–5). The enantiomeric ratio (er) of the dibenzoisumbellvalene product was determined by $^1$H NMR spectroscopy with SMD as chiral shift reagent, as it turned out that this additive induces a significant separation of the protons of the enantiomers of 2h (Supporting Information File 1). The absolute configuration of the products was not determined. The photoreaction proceeded rapidly with full conversion in 4–6 hours with moderate stereoselectivity (68:32 er) in the presence of 1.1 molar equiv of the chiral mandelate. Variations of the host–guest ratio ($c_{1h}:c_{anion} = 1:0.5, 1:2.1, 1:5$) led to a decrease of the stereoselectivity. In addition, changes in the concentration of the dibenzobarrelene 1h did not have a significant influence on the stereoselectivity of the reaction. Based on these results, the following experiments were carried out with a concentration of 0.25 mM for the dibenzobarrelene derivative 1h and 1.1 molar equiv of the chiral additive (Table 1, entries 6–10). Notably, the (R)-enantiomer of mandelate induced the same extent of stereoselectivity with the reverse ratio of products. For comparison, the photoreaction of dibenzobarrelene 1h was performed in the presence of other chiral anions, namely (R)-thiazolidine-4-carboxylate (RTZ), (S)-camphor-10-sulfonate (SCS), (R)-carnitine (RCN), and (2S,1R)-[benzylxoy]carbonyl]-2-pyrrolidinocarboxylate (SCP) (Figure 2). In each case, the induced stereoselectivity was significantly lower than that induced by (S)-mandelate.
Table 1: DPM rearrangements of dibenzobarrelene 1h in the presence of chiral anions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent a</th>
<th>Anion b</th>
<th>0.25 / mM</th>
<th>1.0:5:1anion</th>
<th>er c</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Acetone</td>
<td>SMD</td>
<td>0.25</td>
<td>1:0.5</td>
<td>45:55</td>
</tr>
<tr>
<td>2</td>
<td>Acetone</td>
<td>SMD</td>
<td>0.25</td>
<td>1:1.1</td>
<td>32:68</td>
</tr>
<tr>
<td>3</td>
<td>Acetone</td>
<td>SMD</td>
<td>0.50</td>
<td>1:1.1</td>
<td>33:67</td>
</tr>
<tr>
<td>4</td>
<td>Acetone</td>
<td>SMD</td>
<td>0.50</td>
<td>1:2.1</td>
<td>41:59</td>
</tr>
<tr>
<td>5</td>
<td>Acetone</td>
<td>SMD</td>
<td>0.50</td>
<td>1:5.0</td>
<td>47:53</td>
</tr>
<tr>
<td>6</td>
<td>Acetone</td>
<td>RMD</td>
<td>0.25</td>
<td>1:1.1</td>
<td>67:33</td>
</tr>
<tr>
<td>7</td>
<td>Acetone</td>
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<td>1:1.1</td>
<td>59:41</td>
</tr>
<tr>
<td>8</td>
<td>Acetone</td>
<td>SCS</td>
<td>0.25</td>
<td>1:1.1</td>
<td>44:56</td>
</tr>
<tr>
<td>9</td>
<td>Acetone</td>
<td>SCP</td>
<td>0.25</td>
<td>1:1.1</td>
<td>53:47</td>
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<td>10</td>
<td>MeCN-MeOH 1:1</td>
<td>RCN</td>
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<td>1:1.1</td>
<td>47:53</td>
</tr>
<tr>
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<td>1:1.1</td>
<td>40:60</td>
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<tr>
<td>12</td>
<td>Methanol</td>
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<td>1:1.1</td>
<td>48:52</td>
</tr>
<tr>
<td>13</td>
<td>Ethanol</td>
<td>SMD</td>
<td>0.25</td>
<td>1:1.1</td>
<td>49:51</td>
</tr>
<tr>
<td>14</td>
<td>2-Propanol</td>
<td>SMD</td>
<td>0.25</td>
<td>1:1.1</td>
<td>50:50</td>
</tr>
<tr>
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<td>Acetone-THF 1:9</td>
<td>SMD</td>
<td>0.25</td>
<td>1:1.1</td>
<td>45:55</td>
</tr>
<tr>
<td>16</td>
<td>Acetone-EtOH 1:9</td>
<td>SMD</td>
<td>0.25</td>
<td>1:1.1</td>
<td>35:65</td>
</tr>
<tr>
<td>17</td>
<td>Acetone-Benzene 1:9</td>
<td>SMD</td>
<td>0.25</td>
<td>1:1.1</td>
<td>44:56</td>
</tr>
</tbody>
</table>

aConditions described in the Experimental Section; amount of 2h in reaction mixture: >90% in all cases. aExcept for SCN used as tetrabutylammonium salts. c er = enantiomeric ratio, determined by 1H NMR spectroscopic analysis with 5 molar equiv of SMD as the shift reagent; estimated error: ±3% of the given data. Each measurement was carried out twice to ensure the reproducibility.

The influence of the solvent on the DPM rearrangement of compound 1h was also investigated in the presence of (S)-mandelate (Table 1, entries 11–17). The low solubility of 1h in non-polar solvents required the addition of 10% acetone as co-solvent to give a homogeneous solution. Notably, a small but significant stereoselectivity of the DPM rearrangement of 1h was only observed in acetone or ethyl acetate/acetonitrile (32:68 and 35:65 er), whereas in acetonitrile (40:60 er), THF (45:55 er) or MeOH, EtOH or 2-ProOH (50:50 er) the DPM rearrangement of compound 1h proceeds with very low or no selectivity.

In additional experiments, the photoreactions of the thioureido-substituted dibenzobarrelene derivative 1i were studied with chiral mandelate, camphorsulfonate and binaphthyl phosphonate in a variety of solvents including acetone, acetonitrile, ethyl acetate, dichloromethane, and benzene. Although the DPM rearrangement of the dibenzobarrelene 1i took place readily upon irradiation and the semibullvalene photoproducts were isolated by column chromatography in very good yields, none of these products proved to be enantiomerically enriched, as determined by 1H NMR experiments with SMD as the chiral shift reagent.

Discussion

It is well established that the regio- and stereoselectivity of a photoreaction may be induced by the selective preorganization of the substrates by hydrogen bonding between neutral organic functionalities with an appropriate substitution pattern or by complexation of crown-ether units to cationic guest molecules [1-3]. In contrast, the selective anion recognition has not been employed systematically to influence the photochemical properties of a substrate, although such supramolecular recep-
tor–anion interactions have been used in the organocatalysis of ground-state reactions [40–44]. It should be noted that the supramolecular interactions between anions and ureido- or thioureido-substituted fluorophores have been used elegantly for the fluorometric detection of the anion [46], and the photophysical background has been evaluated in detail [47], but the influence of the binding event on the photochemical properties has not been assessed. In this regard, the studies of the photoreactivity of the dibenzobarrelene derivatives 1h and 1i provide useful initial information about the potential of anion-controlled photoreactions.

The fact that the DPM rearrangement of ureido-substituted dibenzobarrelene derivative 1h takes place even without external sensitizers suggests that an efficient intersystem crossing (ISC) process exists for the excited chromophore 1h that directs the photoreaction predominately to the triplet pathway. The 3,5-bis(trifluoromethyl)phenyl substituent may be responsible for the ISC, because m-bis(trifluoromethyl)benzene has an ISC quantum yield of $\Phi_{\text{ISC}} = 0.12$ ($\lambda_{\text{ex}} = 254$ nm) in the gas phase, and the latter compound is able to sensitize a triplet-state E/Z-isomerization of alkenes [48]. On the other hand, the thioureido-substituted dibenzobarrelene derivative 1i does not undergo a DPM rearrangement upon direct irradiation, despite the potentially sensitizing 3,5-bis(trifluoromethyl)phenyl substituents. Notably, not even the commonly employed sensitizer acetone is capable of inducing the DPM rearrangement of 1i. Considering the different photophysical and photochemical properties of the carbonyl and thiocarbonyl chromophores [49], it may be that a similar difference exists between urea and thiourea functionalities. Thiocarbonyl groups usually have high ISC rates, but they are also prone to self-quenching [49] and act as efficient quenchers for triplet reactions [50]. Thus, in analogy to the properties of the thiocarbonyl chromophore, it is proposed that the thioureido functionality in 1i quenches the triplet excited-state, most likely by the intramolecular self-quenching of the two proximate thiourea groups. Interestingly, upon association of the thiourea units with anions, the DPM reactivity of compound 1i is regained. This observation is consistent with the shorter reaction time of the DPM rearrangement of the ureido-substituted derivative 1h upon association with anions. Since the photometric titrations clearly indicate complex formation, it may be assumed that the decreased reaction times are due to restricted molecular flexibility of the ureido- and thioureido substituents within the complex. Specifically, the deactivation of the excited-state by conformational relaxation is suppressed upon complex formation leading to increased quantum yields of the photoreaction. Nevertheless, in the case of the thioureido-substituted derivative 1i additional effects need to be considered to explain the drastic change of the photochemical properties. Apparently, the quenching effect of the thioureido substituents on the triplet reaction is no longer effective after the association with anions. Presumably, the complexed anions affect the properties of the C=S bond in 1i, leading to changes in excited-state reactivity, as has been shown for hydrogen bonded thiocarbonyl compounds in a theoretical study [51]. For comparison, it should be noted that the ISC rate constant of the thioureido-substituted anthracene 4 (Figure 3), $k_{\text{ISC}} = 1.1 \times 10^{9}$ s$^{-1}$ (CH$_3$CN), even decreases by one order of magnitude upon association with acetate [27]. In that case, however, the absorption of the anthracene and the (trifluoromethyl)phenylthiourea part are well separated and the anthracene is excited selectively at lower energy. Moreover, as there is only one thioureido substituent attached to the anthracene in 4, self-quenching can only take place in a bimolecular process, which is negligible at the low concentration employed in these experiments.

It was demonstrated that the complexation of chiral carboxylates by the ureido substituents of the dibenzobarrelene derivative 1h may be employed, in principle, to induce a stereoselective DPM rearrangement. The lack of stereoselectivity in competitive proic solvents, namely alcohols, indicates the relevance of the hydrogen bonding between the anion and the urea group for chiral induction. As the best selectivities were observed in the presence of 1 molar equiv of the mandelate ion, it may be deduced that the stereoselectivity of the reaction mainly originates from a 1:1 complex between 1h and the mandelate SMD (1h-SMD) (Figure 4), thus resembling known complexes, in which a bisurea receptor uses all four NH hydrogen for chelating hydrogen bonding to carboxylate in a 1:1 complex [52–54]. The fact that mandelate induces a significantly higher selectivity than the other employed anions may be explained by additional interactions of the hydroxy or phenyl substituent of the mandelate with the bis(trifluoromethyl)phenyl substituent or with the ureido substituent. Presumably, in complex 1h-SMD one initial vinyl–benzo bridging (pathway a or b) is preferred due to steric or conformational restraints; however, this effect is only small, but significant, as indicated by the moderate stereoselectivity (68:32 er).
At present, the reason for the lack of stereoselectivity of the DPM rearrangement of the thioureo-substituted dibenzobarrelene \( \text{Ii} \) upon complexation of chiral anions is not clear. Nevertheless, it has been shown that neighboring aryl substituents decrease the anion-binding ability of thiourea derivatives because of the steric repulsion between the ortho-substituents and the sulfur atom [55]. This effect may also suppress the formation of a stable 1:1 complex between the chelating thiourea functionalities in \( \text{Ii} \) and anions, such that an inducing effect of the anion on the photoreaction of the dibenzobarrelene is not operative.

### Conclusion

In summary, it was demonstrated that the photochemical properties of the bisureido- and bistiureido-substituted dibenzobarrelene derivatives \( \text{Ih} \) and \( \text{Ii} \) may be influenced by complex formation with appropriate anions. In general, the photo-reactivity of the substrates is significantly increased upon association with anions. Specifically, the DPM rearrangement of the thioureo derivative \( \text{Ii} \) to give the dibenzo-semibullvalene \( \text{2i} \) can only be performed successfully when the self-quenching of the triplet state is suppressed by complex formation. At the same time it was shown in preliminary experiments that the association of chiral carboxylates with \( \text{Ih} \) induces a stereoselective DPM rearrangement. So far, the selectivities are very low; however, these observations demonstrate that anion-controlled stereoselective DPM rearrangements may be accomplished in principle. Therefore, it is proposed that this methodology may be optimized in future studies, thus providing a complementary tool to perform stereoselective photoreactions based on supramolecular interactions.

### Experimental

**General remarks:** The NMR spectra were recorded on a Bruker Avance 400 (\(^1\text{H NMR: 400 MHz; }^{13}\text{C NMR: 100 MHz}\)) and a Varian NMR system 600 (\(^1\text{H NMR: 600 MHz; }^{13}\text{C NMR: 150 MHz}\)). \(^1\text{H NMR chemical shifts are relative to tetramethylsilane (} \delta_{\text{TMS}} = 0.00 \text{ ppm} \), and \(^{13}\text{C NMR chemical shifts refer to either the signal of tetramethylsilane (} \delta_{\text{TMS}} = 0.00 \text{ ppm} \) or the solvent signals [(\(\text{CD}_3\))\textsubscript{2}CO: 29.8 ppm, (\(\text{CD}_3\))\textsubscript{2}SO: 39.5 ppm]. Absorption spectra were recorded on a Varian 100 Bio spectrometer at 25 °C. Melting points were determined on a Büchi 510K and are uncorrected. Mass spectra were recorded on a Hewlett-Packard HP 5968 (EI) and a Finnigan LCQ Deca instrument (ESI). Elemental analyses were performed on a KEKA-tech EuroEA combustion analyzer by Mr. H. Bodenstedt, Organic Chemistry I, University of Siegen. TLC analyses were performed on silica-gel sheets (Macherey-Nagel Polygram Sil G/UV\(254\)). Unless otherwise mentioned, commercially available chemicals were reagent grade and were used without further purification. Tetrabutylammonium hydroxide in MeOH (1.0 M) and (S)-camphor-10-sulfonic acid were obtained from Aldrich. (\(R\))-Mandelic acid and (S)-mandelic acid were obtained from Fluka. (\(R\))-Thiazolidine-4-carboxylic acid and (2S)-1-[(benzyloxy)carbonyl]-2-pyrrolidinecarboxylic acid were obtained from Acros. (\(R\))-Carnitine was obtained from Alfa-Aesar. Preparative column chromatography was performed on MN Silica Gel 60 M (particle size 0.04–0.063 mm, 230–440 mesh).

Irradiations were performed with a TQ150 middle-pressure mercury lamp (Heraeus, UV-Consulting Peschi), which was placed inside a quartz cooling tube. The reaction mixture was placed ca. 10–15 cm in front of the lamp.

**General procedure for the preparation of bisurea- and bistiurea derivatives of dibenzobarrelene (GP1):** The isocyanate or isothiocyanate derivative (1.1 molar equiv) was added to a stirred solution of 11,12-bis(aminomethyl)-9,10-dihydro-9,10-ethenoanthracene (\(\text{1d}\), 0.45–10.0 mmol) [45] in CH\(_2\)Cl\(_2\) (3 mL/mmol) at 0 °C. A white or pale yellow solid precipitated shortly after the addition of isothiocyanate. The mixture was stirred for 2 h at room temperature, and the solid collected by filtration or recrystallization directly from the reaction mixture depending on the solubility of the product.

11,12-Bis(\(N\,\text{-n-butylureidomethyl}\))-9,10-dihydro-9,10-ethenoanthracene (\(\text{1e}\)): Prepared from dibenzobarrelene \(\text{1d}\) (554 mg, 2.00 mmol) according to GP1, collected by filtration and dried in vacuo. Yield 732 mg (1.77 mmol, 79%), white powder, mp > 320 °C (dec.). \(^1\text{H NMR (400 MHz, (CD}_3\))\textsubscript{2}SO\): \(\delta\) 0.88 (t, \(J = 7\) Hz, 6H, CH\(_3\)), 1.23–1.34 (m, 8H, CH\(_2\)), 2.95–2.99 (m, 4H, CH\(_2\)NH), 3.83 (d, \(J = 7\) Hz, 4H, CH\(_2\)C=C), 5.08 (s, 2H, CH), 5.83–5.85 (m, 4H, NH), 6.91, 7.22 (AA′BB′- system, 8H, CH\(_3\)). \(^{13}\text{C NMR (100 MHz, (CD}_3\))\textsubscript{2}SO\): \(\delta\) 14.1...
11,12-Bis(N'-phenylureidomethyl)-9,10-dihydro-9,10-ethanoanthracene (1f): Prepared from dibenzobarrelene 1d (131 mg, 0.50 mmol) according to GP1 and collected by filtration and obtained as a white powder (179 mg, 0.36 mmol, 72%), mp 309–312 °C (dec.). 1H NMR [400 MHz, (CD3)2SO]: δ = 4.07 (d, J = 5 Hz, 4H, CH2), 5.15 (s, 2H, CH), 6.37 (t, J = 5 Hz, 2H, NH), 6.90–6.93 (m, 6H, CHar), 7.20–7.41 (m, 12H, CHar), 8.29 (2H, NH). 13C NMR [100 MHz, (CD3)2SO]: δ 37.9 (CH2), 53.3 (CH), 118.3 (CHar), 121.5 (CHar), 123.0 (CHar), 124.6 (CHar), 129.0 (CHar), 140.8 (Cq), 143.5 (Cq), 146.5 (Cq), 158.5 (Cq=O). MS (EI): m/z (%) = 500 [M]+. Anal. Caled for C34H28N4O2 (500.6): C, 76.78; H, 5.64; N, 11.19. Found: C, 76.68; H, 5.67; N, 11.12.

11,12-Bis[N'-[4-n-butylphenyl]ureidomethyl]-9,10-dihydro-9,10-ethanoanthracene (1g): Prepared from dibenzobarrelene 1d (0.12 g, 0.45 mmol) according to GP1, collected by filtration and dried in vacuo. White amorphous solid, yield 0.21 g (34 mmol, 76%), mp > 320 °C. 1H NMR [400 MHz, (CD3)2SO]: δ = 0.89 (t, J = 7 Hz, 6H, CH3), 1.26–1.55 (m, 8H, CH2(CH2)CH3), 2.47–2.50 (m, 4H, PhCH2CH2, partly overlapped with the solvent signal), 3.97 (d, J = 6 Hz, 4H, C=CHCH2), 5.14 (s, 2H, CH), 6.06 (t, J = 6 Hz, 2H, NH), 6.90–6.92 (m, 4H, CHar), 7.03–7.05 (m, 4H, CHar), 7.25–7.29 (m, 8H, CHar), 8.42 (2H, NH). 13C NMR [100 MHz, (CD3)2SO]: δ 14.2 (CH2), 22.1 (CH2), 33.7 (CH2), 34.5 (CH2), 37.9 (CH2), 53.3 (CH), 118.4 (CHar), 123.0 (CHar), 124.6 (CHar), 128.8 (CHar), 135.3 (CHar), 138.4 (Cq), 143.5 (Cq), 146.5 (Cq), 155.9 (Cq=O). MS (EI): m/z (%) = 613 [M]+. Anal. Caled for C40H32N4O2 (612.8): C, 78.40; H, 7.24; N, 9.14. Found: C, 78.12; H, 7.25; N, 9.09.

11,12-Bis[N'-[3,5-bis(trifluoromethyl)phenyl]ureidomethyl]-9,10-dihydro-9,10-ethanoanthracene (1h): Prepared from dibenzobarrelene 1d (0.13 g, 0.50 mmol) according to GP1. After filtration of the precipitate, the product was purified by recrystallization from CH2Cl2/hexane and obtained as a white solid (0.33 g, 0.41 mmol, 82%), mp > 300 °C. 1H NMR [600 MHz, (CD3)2CO]: δ = 4.66 (d, J = 4 Hz, 4H, CH2), 5.36 (s, 2H, CH), 6.92 (m, 4H, CHar), 7.30–7.32 (m, 4H, CHar), 7.73 (3H, mp, 4H, CHar overlapping with NH), 8.25–8.26 (m, 4H, CHar), 9.57 (br s, 2H, NH). 13C NMR [150 MHz, (CD3)2CO]: δ = 43.4 (CH2), 54.2 (CH2), 117.9 (CHar), 121.5 (CHar), 123.6 (CHar), 125.3 (CHar), 127.0 (CHar), 132.0 (CHar), 142.4 (Cq), 144.1 (Cq), 146.8 (Cq), 182.4 (Cq=O). UV (MeCN): λmax (log ε) = 230 (4.49), 246 (4.49), 272 (4.48), 280 (4.47). MS (ESI): m/z (%) = 803 (100) [M+H]+. Anal. Caled for C56H22F12N2O2 (804.7): C, 53.73; H, 3.01; N, 6.96; S, 7.97. Found: C, 53.58; H, 2.79; N, 6.84; S, 7.97.

General procedure for the synthetic photolysis in solution (GP2): Solutions of the substrate (10−3–10−2 mol/l) were placed in a Duran flask (acetonitrile) or quartz test tube (other solvents), and argon gas was bubbled carefully through the solution for at least 20 min. The solution was irradiated for 4–15 h with stirring until the starting material was fully converted as determined by TLC or 1H NMR spectroscopic analysis. After evaporation of the solvent in vacuo, the photolysate was analyzed by 1H NMR spectroscopy. In preparative experiments, the photoproduc was isolated by recrystallization or column chromatography.

4b.8b-Dihydro-8c,8e-bis[N'-[3,5-bis(trifluoromethyl)phenyl]ureidomethyl]dibenzo[a,j]cyclopropa[d]pentacene (2h): Prepared by irradiation of 1b (48.0 mg, 0.06 mmol) in acetone solution according to GP2 and obtained as white crystals (29.0 mg, 0.04 mmol, 60%), mp 246–247 °C. 1H NMR [600 MHz, (CD3)2CO]: δ = 3.22 (s, 1H, CH), 3.78 (dd, J = 15, 6 Hz, 1H, CH2), 3.82 (dd, J = 15, 6 Hz, 1H, CH2), 3.94 (dd, J = 15, 6 Hz, 1H, CH2), 4.44 (dd, J = 15, 6 Hz, 1H, CH2), 4.63 (s, 1H, CH), 6.42 (t, J = 5 Hz, 1H, NH), 6.53 (t, J = 5 Hz, 1H, NH), 6.99–7.05 (m, 4H, CHar), 7.21–7.25 (m, 3H, CHar), 7.36–7.38 (m, 1H, CHar), 7.49 (s, 2H, CHar), 8.09 (s, 2H, CHar), 8.13 (s, 2H, CHar), 8.75 (s, 1H, NH), 8.81 (s, 1H, NH). 13C NMR [150 MHz, (CD3)2CO]: δ = 41.3 (CH2), 41.4 (CH2), 46.7 (CH2), 53.3 (Cq), 58.8 (Cq), 67.4 (CH), 115.6 (CHar), 115.6 (CHar), 115.7 (CHar), 119.3 (Cq), 119.3 (CHar), 123.4 (CHar), 123.4 (CHar), 124.5 (Cq), 126.5 (Cq), 126.6 (CHar), 128.1 (CHar), 128.2 (CHar), 128.3 (CHar), 130.7 (Cq), 131.1 (CHar), 140.1 (Cq), 142.7 (Cq), 143.4 (Cq), 146.4 (Cq), 155.4 (Cq=O). UV (MeCN): λmax (log ε) = 229 (4.49), 246 (4.86), 272 (4.01), 280 (4.13). MS (ESI): m/z (%) = 771 (100) [M–H]+. Anal. Caled for C38H12F12N2O2 (772.6): C, 55.97; H, 3.13; N, 7.25. Found: C, 55.58; H, 2.85; N, 7.04.
for the experiment. Used as 0.1 M stock solution in the respective solvent required was prepared according to the literature procedure [57], and the tetrabutylammonium salt of (S)-camphor-10-sulfonate SCS used as 0.1 M stock solutions in acetone.

nium hydroxide (1.0 M in MeOH) [56]. The resulting salts were tion of the corresponding chiral acids with tetrabutylammo-

SMD

RTZ

SCP

acids: fitted in the aromatic region. MS (ESI): m/z (%): 771 (100) [M − H]. An analytical sample was obtained by recrystallization from ethyl acetate/hexane and contained one equiv of ethyl acetate as the lattice solvent. Anal. Caled for C98H92F12N2O2·EtOAc (860.7): C, 55.82; H, 3.75; N, 6.51. Found: C, 55.93; H, 3.51; N, 6.45.

4b,8b-Dihydro-8c,8e-bis[N^−]-[3,5-bis(trifluoromethyl)phenyl]thiourea]dibenzo[a]cyclopropa[c,d]pentalene (2i): Prepared by photoinduction of 1i (0.20 g, 0.25 mmol) in acetonitrile solution in the presence of 2 molar equiv of ammonium chloride according to GP2. After the irradiation the inorganic components were removed by column filtration (SiO2; EtOAc/hexane 1/2, v/v), and the residue was recrystallized from ethyl acetate/hexane to give light yellow crystals (104 mg, 0.13 mmol, 52%), mp 181–182 °C. 1H NMR [600 MHz, (CD3)2CO]: δ 1.20 (t, J = 7 Hz, 3H, CH3), 3.43 (s, 1H, CH), 4.05 (q, J = 7 Hz, 2H, CH2), 4.22 (d, J = 13 Hz, 1H, NHCH), 4.29 (d, J = 13 Hz, 1H, NHCH/H/C), 4.48 (d, J = 13 Hz, 1H, NHCH/H/C), 4.74 (d, J = 13 Hz, 1H, NHCH/H/C), 4.76 (s, 1H, CH), 7.00–7.09 (m, 5H, CHar), 7.24–7.28 (m, 3H, CHar), 7.36–7.38 (m, 1H, CHar), 7.67 (s, 2H, CHar), 7.81 (s, 1H, NH), 7.89 (s, 1H, NH), 8.23 (s, 2H, CHar), 8.32 (s, 2H, CHar), 9.45 (s, 1H, NH), 9.53 (s, 1H, NH). 13C NMR [150 MHz, (CD3)2CO]: δ 14.5 (CH3), 20.8 (CH2), 44.2 (CH2), 45.2 (CH2), 50.3 (Cq), 57.2 (CH), 59.7 (CH), 65.1 (Cq), 116.5 (CHar), 116.7 (c), 121.5 (CHar), 121.6 (CHar), 122.1 (CHar), 122.5 (CHar), 123.8 (CHar), 124.3 (CHar), 124.3 (CHq), 124.9 (CHar), 126.4 (CHar), 126.4 (CHar), 126.6 (CHar), 126.9 (CHq), 130.6 (CHar), 130.6 (CHar), 130.8 (CHar), 130.9 (CHar), 131.1 (Cq), 131.1 (Cq), 133.7 (Cq), 137.7 (Cq), 141.8 (Cq), 142.0 (Cq), 149.9 (Cq), 150.8 (Cq), 181.4 (C=O), 181.8 (C=S), two Cq signals are overlapped in the aromatic region. MS (ESI): m/z (%): 803 (100) [M − H]. Anal. Caled for C98H92F12N2O2·EtOAc (892.8): C, 53.81; H, 3.61; N, 6.28; S, 7.18. Found: C, 54.03; H, 3.28; N, 6.32; S, 7.09.

Preparation of the tetrabutylammonium salts of chiral acids: The tetrabutylammonium salts of the chiral carboxylates SMD, RMD, RTZ, and SCP were prepared by the neutralization of the corresponding chiral acids with tetrabutylammonium hydroxide (1.0 M in MeOH) [56]. The resulting salts were used as 0.1 M stock solutions in acetone.

The tetrabutylammonium salt of (S)-camphor-10-sulfonate SCS was prepared according to the literature procedure [57], and used as 0.1 M stock solution in the respective solvent required for the experiment.

Photoreaction of dibenzobarrelene derivatives 1h and 1i in the presence of chiral anions: The dibenzobarrelene derivatives 1h or 1i (50 μmol) were dissolved in a stock solution (0.55 mL of 0.1 M stock solution, 55 μmol, 1.1 equiv) of the chiral tetrabutylammonium salt, and the solvent was removed in vacuo. The resulting residue was re-dissolved in the solvent of choice (200 mL). Argon gas was bubbled through the solution for 20 min to remove residual oxygen from the solvent. The reaction container (DURAN, λ > 310 nm) was placed ca. 15 cm in front of the light source, and the solution was irradiated for 3–4 h (TLC control). The solvent was removed in vacuo and the major photoproduction purified by column chromatography (SiO2; hexane:acetone:ethyl acetate = 4:1:1, v/v/v). The photoproduction was analyzed by 1H NMR spectroscopy in the presence of 5 equiv of tetrabutylammonium SMD as chiral shift reagent.

The enantiomeric ratio of the semibullvalene mixture was determined by the integration of the aromatic proton signals from each isomer (δ in the range of 8.4–8.7 ppm), and by the integration of the NH and cyclopropane CH signals. Each spectroscopic measurement was repeated twice to ensure the reproducibility.

Supporting Information

1H NMR and 13C NMR spectra of compounds 1e–i and 2h–i; 1H NMR spectra of 2h with (S)-mandelate (SMD) at different molar ratios and corresponding Job plot; 1H NMR spectra of 2h with (S)-mandelate (SMD) as chiral shift reagent.

Supporting Information File 1
Supporting Information for: Effects of anion complexation on the photoactivity of bisureido- and bisthioureido-substituted dibenzobarrelene derivatives. [http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-37-S1.pdf]

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References


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Supramolecular FRET photocyclodimerization of anthracenecarboxylate with naphthalene-capped \( \gamma \)-cyclodextrin

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Abstract

\( \gamma \)-Cyclodextrin (CD) derivatives with a naphthalene moiety anchored to one or two of the glucose units of the CD were synthesized in order to investigate the effects of flexible and rigid capping upon complexation, as well as Förster resonance energy transfer (FRET) and photochirogenic behavior of anthracenecarboxylate (AC) moieties. UV−vis, circular dichroism and fluorescence spectral studies revealed that two AC molecules are simultaneously included in the modified \( \gamma \)-CD cavity to form a right-handed screw and also that the naphthalene cap efficiently transfers the singlet energy to AC included in the CD cavity via the FRET mechanism. Compared to native \( \gamma \)-CD, the modified \( \gamma \)-CDs showed much higher first association constants \((K_1)\) but relatively lower second association constants \((K_2)\) for AC, leading to two-fold larger overall affinities \((K_1K_2)\). Photocyclodimerization of AC with these modified \( \gamma \)-CDs produced more head-to-head (HH) dimers in much better enantiomeric excesses (ee) for \textit{anti}-HH dimer compared to native \( \gamma \)-CD. Interestingly, FRET excitation further enhanced the chemical and optical yields of \textit{anti}-HH dimer up to 36% and 35% ee, for which the highly efficient FRET sensitization within the CD cavity, minimizing the “contamination” from the achiral “outside” photoreaction, is responsible. FRET sensitization also enabled us to achieve the catalytic photocyclodimerization of AC with a sub-equivalent amount of chiral supramolecular host.

Introduction

Chiral photochemistry, often characterized by low optical yields, remains a great challenge for chemists [1-3]. This situation reflects primarily the difficulty in efficiently transferring the stereochemical information of the chiral source to the substrate in the electronically excited state. Thus, a supramolecular approach in chiral photochemistry could be a promising strategy.
for critically controlling the stereochemical outcome via intimate, long-lasting contacts with the photosubstrate through non-covalent interactions in the ground state [4-11]. The geometrical and functional complementarity and the subsequent induced fit between chiral host and guest substrate should play a crucial role in determining the stereochemical fate of chiral photoreaction, and therefore the design of chiral host is considered to be one of the most important aspects for manipulating stereoselectivity in supramolecular photochirogenesis.

We have recently focused our attention on enantiodifferentiation in the photocyclodimerization of anthracene-carboxylate (AC) as a representative bimolecular photochirogenic system for the elucidation of the factors and mechanism that control supramolecular photochirogenesis [12-22]. Photocyclodimerization of AC leads to the formation of four stereoisomeric cyclodimers 1–4, of which syn-head-to-tail (HT) 2 and anti-head-to-head (HH) 3 are chiral (Scheme 1). This chiral photoreaction turned out to be an ideal benchmark system for...

**Scheme 1:** Biphenyl-capped (5), naphthalene-capped (6), and naphthalene-appended γ-cyclodextrin (7).
exploring and comparing the performance of various chiral hosts, such as cyclodextrins (CDs), proteins and chiral hydrogen-bonding templates. γ-CD can significantly accelerate the photocyclodimerization of AC by forming a 1:2 host–guest complex with AC in aqueous solutions [12]. Altering the chiral environment of γ-CD by rim modification is a convenient, yet effective, tool for manipulating the stereoselectivity of AC photocyclodimerization. In our previous studies, we have shown that a capping modification of γ-CD causes a dramatic switching of stereoselectivity in AC photodimerization [12,22]. Thus, by using native γ-CD the chiral cyclodimer 2 is obtained in 41% enantiomeric excess (ee), whereas biphenyl-capped γ-CD 5 yields antipodal 2 in −57% ee (Scheme 1) [22]: Where the positive/negative sign of ee indicates a higher yield of first/second eluted enantiomer detected on the chiral HPLC analysis. These observations prompted us to design and synthesize a more rigidly capped 6A,6C-(2,6-naphthalenedicarboxyl)-γ-CD 6. This modification further enabled us to trigger the photocyclodimerization via Förster resonance energy transfer (FRET) sensitization.

Results and Discussion

Naphthalene-capped γ-CD 6 was synthesized by the reaction of 6A,6C-ditosyl-γ-CD [23] with disodium 2,6-naphthalenedicarboxylate in DMSO. An attempt to synthesize the regioisomeric 6A,6D-ditosyl-2,6-naphthalenedicarboxylate with disodium 2,6-naphthalenedicarboxylate was unsuccessful, presumably due to the longer distance between the A and D glucose units to be bridged by the 2,6-naphthalenedicarboxylate unit. For the purposes of comparison, naphthalene-appended γ-CD 7 was synthesized by reacting γ-CD with 2,6-naphthalenedicarboxylic acid. Modified γ-CD 7 was found to be sparingly soluble in water, probably due to the intermolecular aggregation of 7 by successive penetration of the naphthalene moiety into the cavity of another CD. The solubility of 7 was significantly enhanced by adding sodium carbonate. In contrast, capped γ-CD 6 showed a much higher solubility in water, as the naphthalene cap can hardly interact with another CD.

The complexation behavior of AC with modified γ-CDs 6 and 7 was investigated by UV–vis, circular dichroism and fluorescence spectral studies. As shown in Figure 1, the addition of 7 to an aqueous solution of AC (0.2 mM) caused an evident bathochromic shift of the 1La band of AC, which is probably due to the stacking complexation of two AC molecules in a single γ-CD cavity.

Modified γ-CDs 6 and 7 showed moderate circular dichroism signals in the naphthalene-absorbing region. As shown in Figure 2, naphthalene-appended γ-CD 7 at 0.2 mM concentration gave a bisignate circular dichroism signal even in the absence of AC. As the intensity (Δε) decreased at lower concentrations, this bisignate signal is thought to be a real exciton coulplet arising from the self-aggregation of 7, where the included naphthalene chromophores are arranged in a right-handed screw [24]. As can be seen from Figure 3, naphthalene-capped γ-CD 6 gave only weak induced circular dichroism signals at the 1La and 1Bb bands of the naphthalene chromophore, the intensity of which was not concentration-dependent.

The addition of AC (0–0.26 mM) to the above solutions of 7 or 6 (0.2 mM) produced a strong positive exciton coulplet at the 1Bb transition of AC (Figure 2 and Figure 3) which overwhelmed the inherent signals. The positive coulplet observed indicates the right-handed helical conformation of the two AC molecules in the γ-CD cavity [24].
Fluorescence spectral behavior was examined at a lower host concentration in order to observe the fluorescence from both the 1:1 and 1:2 complexes with AC. Upon the addition of AC (0–0.05 mM) to a solution of 7 (0.02 mM), the naphthalene fluorescence at 373 nm was gradually reduced in intensity with an accompanying increase of AC fluorescence at 426 nm. The reduction of fluorescence intensity amounted to 27% at an AC concentration of 0.0375 mM, even although the absorbance of 0.0375 mM AC is only 11% of 0.02 mM naphthalene at the excitation wavelength (296 nm) and the internal filter effect of AC at 350–400 nm is negligible (absorbance <0.1). Considering the nice spectral overlap of the naphthalene fluorescence with the AC absorption (Figure 4), we conclude that Förster resonance energy transfer (FRET) is operating from naphthalene-appended 7 to AC residing in the cavity. Further addition of AC up to 0.05 mM caused a global decrease of the fluorescence of both 7 and AC, which can be rationalized by the increased formation of a 1:2 complex at the higher AC concentration, leading to efficient FRET and photocyclodimerization in the cavity.

Nonlinear least-squares fits of the UV–vis spectral titration data to the stepwise 1:2 complexation model gave binding constants for each step: \( K_1 = 1050 \text{ M}^{-1} \) and \( K_2 = 18600 \text{ M}^{-1} \) for 6 and \( K_1 = 620 \text{ M}^{-1} \) and \( K_2 = 22300 \text{ M}^{-1} \) for 7 at 25 °C. When compared to the corresponding values reported for native \( \gamma \)-CD (\( K_1 = 182 \text{ M}^{-1} \) and \( K_2 = 56700 \text{ M}^{-1} \)) [12], the first binding constant was enhanced by a factor of 3.5–5.8 by introducing the naphthalene moiety, whilst the second binding constant was reduced by a factor of 2.5–3.0, thus making the overall binding constant \( K_1K_2 \) approximately twice as high. It is known that the small \( K_1 \) for native \( \gamma \)-CD is due to the oversized cavity which cannot provide tight contacts for a single AC molecule. Only when a second AC is introduced into the same cavity, are close contacts possible for two AC molecules with \( \gamma \)-CD walls thus leading to a much larger \( K_2 \). We attribute the enhanced \( K_1 \) values for 6 and 7 to the increased hydrophobicity of the naphthalene-modified \( \gamma \)-CD cavity. On the contrary, the naphthalene moieties reduce the \( K_2 \) values, probably due to steric hindrance and the restricted conformation and orientation available for ACs in the cavity. The higher overall affinities \( (K_1K_2) \) for 6 and 7 than for native \( \gamma \)-CD indicate the positive effect of aromatic modification on AC complexation.

An aqueous buffer solution (pH 9) of AC (0.4 mM) and modified \( \gamma \)-CD (2 mM) was photoirradiated at 360 nm with a Xenon lamp fitted with a band-pass filter. The product distribution and the ee of chiral photodimers, both determined by chiral HPLC, are shown in Table 1. As a general tendency, the HH dimers were preferred by introducing the aromatic substituents. Thus, the HH/HT ratio was dramatically enhanced from 0.12 for native \( \gamma \)-CD to 0.4–1.0 for biphenyl- or naphthalene-modified \( \gamma \)-CDs 5–7. In particular, the use of the capped \( \gamma \)-CD 6 led to the preferential formation of chiral 3 in 34% yield at 0 °C. The increased hydrophobicity around the primary rim of these modified \( \gamma \)-CDs favors inclusion of the non-polar aromatic part of AC near the primary portal and the polar carboxylate part near the secondary portal to give the HH-oriented precursor complex. In contrast, the HT-oriented precursor complex, in which one of AC’s carboxylate is positioned at the primary rim, should be less stable due to increased hydrophobicity, leading to the switching of product population to HH dimers.

Closer examination of the product distributions revealed the contrasting behavior of the anti/syn ratio in HT versus HH...
dimers. As can be seen from the \textit{anti}/\textit{syn} ratios for the HT and HH dimers shown in Table 1, the modifications of γ-CD only slightly alter the 1/2 ratio from 0.9 for native γ-CD to 1.1–1.4 for 5–7. In sharp contrast, the 3/4 ratio was more susceptible to rim modification, in particular rigid capping was enhanced from 1.2 for native γ-CD to 1.5 for biphenyl-capped 5 and even to 2.3–3.3 for naphthalene-capped 7, but was practically unaffected at 1.0–1.2 for naphthalene-appended 7. These results are quite reasonable, as the electrostatic repulsion of the carboxylate anions of two ACs in the CD cavity should be stronger in an HH-oriented complex than in an HT-oriented one due to the shorter inter-anion distance in the former. In summary, naphthalene-capping greatly enhances the formation of HH, in particular \textit{anti}-HH, dimers as a combined effect of increased hydrophobicity and electrostatic repulsion.

The hydrophobic modifications at the primary rim reduced the ee of chiral HT dimer 2, suggesting that the achiral substituent introduced altered the chiral environment of γ-CD cavity. In this context, it is interesting to note that naphthalene-capped 6 and naphthalene-appended 7 give 2 in 29% and 37% ee, respectively, which are only slightly smaller than that obtained with native γ-CD (41% ee), whereas biphenyl-capped 5 gave antipodal 2 in ~58% ee under comparable conditions (Table 1). Molecular model examinations indicated that the biphenyl group, attached to the A and D glucose units of γ-CD 5, covers half of the primary rim. In the HT-oriented precursor complex of AC with 5, one of the carboxyloxy groups is inevitably exposed to the bulk water through the narrowed primary rim, leading to a highly restricted conformation, which significantly differs from the original one achieved in the native γ-CD cavity. In contrast, the naphthalene moiety is anchored to only one glucose unit in 7 or to the A and C glucose units in 6, leaving a larger opening for the carboxyloxy tail of the AC and more freedom for the HT-oriented AC pair in the cavity, a situation similar to native γ-CD. Based on these considerations, we may conclude that the steric restriction caused by the capping group, rather than its rigidity, is the real cause of the chirality switching observed for 5.

Interestingly, the use of naphthalene-capped 6 greatly improved the chemical and optical yields of 3, while native γ-CD, biphenyl-capped 5, and naphthalene-appended 7 afforded almost racemic or antipodal 3 in much smaller chemical and optical yields. The HH-oriented AC pair in a complex precursor to 3 is likely to conceal the hydrophobic anthracene moiety inside the cavity with the carboxyloxy groups being exposed to the bulk water near the secondary rim of γ-CD. The enhanced chemical and optical yields observed for 3 should reflect the totally altered chiral environment, which favors the formation of one of the diastereomeric HH-oriented precursor complexes in the modified CD cavity of 6. By lowering the temperature to 0 °C, the system was optimized to give \textit{anti}-HH 3 in 34% yield with an ee of 30%, which is much higher than the corresponding values obtained with native or any other capped γ-CDs so far examined in aqueous solutions [20,22].

### Table 1: Photocyclodimerization of 2-anthracenecarboxylate (AC) in the presence of native and modified γ-cyclodextrins (CDs).

<table>
<thead>
<tr>
<th>Host</th>
<th>λ/nm</th>
<th>CD/AC</th>
<th>T/°C</th>
<th>Relative yield/%d</th>
<th>\textit{HH}/HT</th>
<th>\textit{anti}/\textit{syn}</th>
<th>ee/%e,f</th>
</tr>
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<tr>
<td>γ-CD9</td>
<td>365</td>
<td>5</td>
<td>0</td>
<td>43</td>
<td>0.12</td>
<td>0.9</td>
<td>1.2</td>
</tr>
<tr>
<td>5*</td>
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<td>5</td>
<td>35</td>
<td>40</td>
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<td>6</td>
<td>360</td>
<td>5</td>
<td>20</td>
<td>38</td>
<td>0.51</td>
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<tr>
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<td>360</td>
<td>5</td>
<td>10</td>
<td>34</td>
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<tr>
<td>300</td>
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<td>27</td>
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<tr>
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<td>32</td>
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<td>1.2</td>
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<td>23</td>
</tr>
<tr>
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Notes:
- a: Irradiated in pH 9 aqueous buffer at 0–35 °C with a Xenon lamp fitted with a band-pass filter; [AC] = 0.4 mM (fixed); [CD] = 0.12 or 2 mM.
- b: Irradiation wavelength.
- c: Host-guest ratio.
- d: Relative yield and ee determined by chiral HPLC on a tandem column of Intersil ODS-2 (GL Science) and Chiralcel OJ-R (Daicel); error in ee: ±0.7%.
- e: Positive/negative ee sign corresponds to the excess of the first/second-eluted enantiomer, respectively. Ref [12].
- f: Ref [20].

Irrespective of the irradiation conditions (Table 1), the \textit{anti}-\textit{syn} ratio for the HT and HH dimers is nearly 1:2, with a slight drop in the ratio for the HH dimer, as expected from the natural γ-CD cavity. The largest change in the \textit{anti}/\textit{syn} ratio is observed with γ-CD 7, which contains a naphthalene group at the primary rim. This group is thought to have a significant effect on the \textit{anti}/\textit{syn} ratio, as the \textit{anti}-\textit{syn} ratio changes from 1.2 for native γ-CD to 1.3 for the modified γ-CD, indicating a slight enhancement of the \textit{anti}-\textit{syn} ratio. The \textit{anti}/\textit{syn} ratio for the HH dimer is also affected by the capping group, with a slight drop in the ratio from 1.2 for native γ-CD to 1.0 for the modified γ-CD, indicating a slight enhancement of the \textit{anti}-\textit{syn} ratio.
We further examined indirect FRET excitation (intramolecular photosensitization) of AC included in host 6. Mechanistically, FRET excitation of AC is highly advantageous from the photochirogenic point of view, since the static energy transfer to an AC molecule accommodated in the CD cavity is much faster and more efficient than the dynamic energy transfer to an AC in bulk solution (even if it exists), thus minimizing the unfavorable achiral “outside” photoreaction. Irradiation of an aqueous solution containing 0.4 mM AC and 2 mM 6 was performed at 300 nm, where 98.5% of the incident light was absorbed by the naphthalene moiety of 6 and therefore it is possible to examine the effects of FRET excitation on the distribution and ee of cyclodimers. As can be seen from Table 1, FRET excitation at 300 nm gave 3 in 36% yield and 35% ee, both of which are appreciably higher than the corresponding values obtained upon direct AC excitation at 360 nm. The enhanced stereoselectivity is attributed to the smaller contribution of the photoreaction outside the CD cavity, where the HT dimers are favored and chiral 2 and 3 produced should be racemic. To the best of our knowledge, this is the first example of FRET sensitization applied to photochirogenesis.

In supramolecular photochirogenesis, an excess amount of the chiral host is often the prerequisite for minimizing contamination from undesirable racemic photoreactions occurring outside chiral host. In the present system, it is likely that only AC that is included in the CD cavity can be FRET-sensitized by naphthalene, since the FRET efficiency is inversely proportional to the sixth power of donor–acceptor distance. We expected therefore that the AC photocyclodimerization could be catalyzed even with a sub-equivalent amount of the chiral FRET host. Indeed, the FRET-sensitized photocyclodimerization of AC with 0.3 equiv of 6 gave dimer 3 in 32% yield and 30% ee, which are only slightly decreased from the original 36% yield and 35% ee obtained with 5 equiv of 6 (Table 1). In contrast, the chemical yield of 3 was reduced from 34% to 22% and the ee from 30% to 18% upon direct AC excitation at 360 nm.

Conclusion
In the present work, naphthalene-appended and -capped γ-CDs were synthesized to investigate the effects of naphthalene capping and of FRET excitation on the complexation and supramolecular photochirogenic behavior of AC. Compared to native γ-CD, the naphthalene-modified γ-CDs showed 3.5–5.8 fold larger first binding constants and 2.5–3.0 fold smaller second binding constants, which resulted in roughly two-fold larger overall affinities, due to increased cavity hydrophobicity. Fluorescence spectral examination revealed that the FRET from the excited naphthalene on CD rim to AC included in the CD cavity is operative upon excitation of the naphthalene chromophore at 296 nm. Circular dichroism spectral studies revealed that the two AC molecules are arranged in a right-handed screw sense in the CD cavity. Direct excitation at 360 nm of AC accommodated in the cavity of modified γ-CD afforded HH cyclodimers (despite electrostatic repulsion between the HH-oriented carboxylate anions of the AC) in combined yields of up to 51%, which is much higher than that (11%) obtained with native γ-CD. In particular, both the chemical and optical yields of HH dimer 3 were significantly enhanced from 6% to 34% and from 17% ee to 30% ee by introducing a naphthalene-cap to γ-CD. More interestingly, FRET sensitization by exciting the naphthalene-cap of 6 at 300 nm afforded HH dimer 3 in a further enhanced yield of 36% with an ee of 35%. In the FRET sensitization, the high stereoselectivity was maintained even when the host/guest ratio was reduced to 0.3, thus achieving catalytic supramolecular photochirogenesis.

Experimental
General. FAB mass spectra were measured on a JEOL JMS-DX303 mass spectrometer. NMR spectra were recorded on a Bruker DRX-600 or a JEOL JNM-EX 400 spectrometer. UV–vis, fluorescence, and circular dichroism spectra were recorded in a UNISOKU USP-203CD cryostat with a JASCO V-560 spectrophotometer, JASCO FP-6500 luminescence spectrometer, and JASCO J-810 spectropolarimeter, respectively. Photoirradiation was performed in a UNISOKU USP-203 cryostat with an appropriate interference filter for 300 nm or 360 nm. Irradiated samples were subjected to chiral HPLC analysis on a tandem column of Intersil ODS-2 (GL Science) and Chiralcel OJ-R (Daicel) with a 36:64 mixture of acetonitrile and water as eluent [12].

Syntheses of modified γ-CDs 6 and 7. For 6: 6A,6C-ditosyl-γ-CD (321 mg, 0.2 mmol) and disodium 2,6-naphthalenedicarboxylate (52 mg, 0.2 mmol) were dissolved in 10 mL DMSO, and the mixture heated at 90 °C for 3 d. After cooling, the solution was concentrated to 0.5 mL under vacuum, trifluoroacetic acid added and the solution added dropwise to 30 mL acetonitrile to give a precipitate. The precipitate was collected by filtration and purified by reverse-phase chromatography to give pure 6 (15.3 mg, 5.2% yield). 1H NMR (400 MHz, D2O): δ 8.14 (1H, s), 8.02 (1H, s), 7.78 (1H, d, J = 8.4 Hz), 7.69 (1H, d, J = 8.5 Hz), 7.62 (2H, d, J = 8.6 Hz), 4.97 (7H, m), 4.88 (2H, m), 4.79 (2H, m), 4.39 (2H, m), 4.31 (1H, m), 4.18 (1H, m), 3.99–3.64 (13H, m), 3.63–3.31 (19H, m), 3.13 (4H, m), 2.56 (1H, d, J = 11.1 Hz), 2.39 (1H, d, J = 11.1 Hz), 2.27 (1H, d, J = 11.2 Hz), 2.21 (1H, m), 1.60 (1H, br). 13C NMR (150 MHz, D2O): δ 167.85, 166.52, 133.85, 133.41, 132.71, 132.25, 131.98, 129.86, 129.50, 128.72, 125.94, 125.38, 102.36, 102.01, 101.84, 101.75, 101.67, 101.53, 81.21, 80.70, 80.07, 79.74, 74.86, 73.57, 73.26, 72.99, 72.81, 72.69, 72.61, 72.49, 72.31, 72.06, 71.94, 71.83, 71.68, 71.53, 71.22, 70.55, 68.13, 66.09, 60.23, 60.04, 59.91, 59.83.
58.52. HR–FAB-MS: Calc. for [6+Na]⁺, C₆₀H₈₆NaO₄₂
1499.43, found: 1499.43.

For 7: 2,6-naphthalenedicarboxylic acid (216 mg, 1 mmol) and γ-CD (1296 mg, 1 mmol) were dissolved in 10 mL DMF, to which DCC (310 mg, 1.5 mmol) and HOBT (54 mg, 0.4 mmol) were added and the solution stirred at room temperature for 2 d. The reaction mixture was poured into 150 mL dry acetone to give a white precipitate. The precipitate was collected by filtration, dissolved in 10% aqueous methanol and then subjected to reverse–phase HPLC separation to give 7 (194 mg, 13% yield).

1H NMR (600 MHz, 4:1 DMSO-d₆–D₂O): δ 8.58 (1H, d, J = 12.4 Hz), 8.54 (1H, s), 8.13 (1H, dd, J = 8.5, 2.6 Hz), 8.10 (1H, d, J = 8.5 Hz), 7.99 (1H, d, J = 8.8 Hz), 7.96 (1H, d, J = 8.6 Hz), 4.93 (1H, d, J = 3.3 Hz), 4.89 (1H, d, J = 3.3 Hz), 4.83 (6H, m), 4.64 (1H, m), 4.36 (1H, m), 3.66–3.52 (24H, m), 3.52–3.39 (14H, m), 3.38–3.26 (18H, m). 13C NMR (150 MHz, 4:1 DMSO-d₆–D₂O): δ 167.71, 166.09, 149.51, 137.12, 134.64, 130.64, 130.49, 129.11, 126.42, 126.01, 124.42, 108.82, 104.01, 101.81, 82.30, 81.25, 81.17, 81.12, 81.04, 80.73, 73.30, 73.07, 72.97, 72.70, 72.47, 72.39, 69.46, 64.89, 60.22, 60.08, 59.89.

HR–FAB-MS: Calc. for [7+Na]⁺, C₆₀H₈₆NaO₄₂ 1517.44, found: 1517.45.

Supporting Information

Supporting Information File 1
NMR and HR–MS data of compounds 6 and 7. [http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-38-S1.pdf]

Acknowledgements

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Photoinduced electron-transfer chemistry of the bielectrophoric \(N\)-phthaloyl derivatives of the amino acids tyrosine, histidine and tryptophan

Axel G. Griesbeck\(^*\), Jörg Neudörfl and Alan de Kiff

Abstract

The photochemistry of phthalimide derivatives of the electron-rich amino acids tyrosine, histidine and tryptophan \(8–10\) was studied with respect to photoinduced electron-transfer (PET) induced decarboxylation and Norrish II bond cleavage. Whereas exclusive photodecarboxylation of the tyrosine substrate \(8\) was observed, the histidine compound \(9\) resulted in a mixture of histamine and preferential Norrish cleavage. The tryptophan derivative \(10\) is photochemically inert and shows preferential decarboxylation only when induced by intermolecular PET.

Introduction

Phthalimides are versatile electron acceptors in photoinduced electron-transfer (PET) reactions. \(N\)-Alkylated phthalimides typically absorb in the 295 nm region with extinction coefficients around \(10^3\). The quantum yields for intersystem crossing \(\Phi_{\text{ISC}}\) significantly change with the substitution on the imide nitrogen, e.g., \(\Phi_{\text{ISC}} = 0.5\) for \(N\)-isobutylphthalimide and \(\Phi_{\text{ISC}} < 0.01\) for \(N\)-arylphthalimides \([1]\). If necessary, the population of the triplet state is also possible by sensitization, e.g., with triplet sensitizers such as acetone or benzophenone. With a triplet energy \(E_T\) of 293–300 kJ mol\(^{-1}\) and a ground-state reduction potential \(E^0\) of \(-1.85\) V vs Fe/Fe\(^+\), electronically excited phthalimides are potent electron acceptors \([2]\). The rich photochemistry of this chromophore has recently been reviewed \([3,4]\). Intramolecular hydrogen abstraction is an archetype process for electronically excited carbonyl groups (Norrish type II reaction). The 1,4-biradicals formed by \(\gamma\)-CH transfer can undergo several subsequent reactions, among which are secondary H transfer, cyclization, or fragmentation. The excited imido...
group is at the same time an efficient electron acceptor and can be reduced by numerous donor groups.

As a model compound for neutral aliphatic amino acids, the photophysical and photochemical properties of \(N\)-phthaloylvaline methyl ester (1) have been studied by nanosecond laser flash photolysis (\(\lambda_{\text{exc}} = 248 \text{ or } 308 \text{ nm}\)) [5]. The quantum yield of fluorescence is low (\(\Phi_F = 10^{-2}\)), whereas that of phosphorescence at −196 °C is large (0.5). The triplet properties of 1 at room temperature and in ethanol at low temperatures are known: Triplet acetone, acetophenone and xanthone in acetonitrile are quenched by 1 via energy transfer; the rate constant is almost diffusion-controlled and somewhat smaller for benzophenone. The sole product from the photolysis of 1 is the double hydrogen transfer product 2. On the other hand, phthaloyl derivatives of C-protected \(\alpha\)-amino acids (e.g., derivatives of Gly, Ala, Val, Ile, Phe) undergo efficient photodecarboxylation to yield the corresponding amines, \(\beta\)-amino acids are converted to benzazepines, and \(\gamma\)-amino acids to benzopyrrolizidines (Scheme 1). For example, the glutamic acid derivative 3 resulted in the formation of a diastereomeric mixture of benzopyrrolizidinones 4 [6]. For a specific system, \(N\)-phthaloyl methionine (5), we have detected bielectrophoric behavior in that the electron transfer from the thioether group competes efficiently with decarboxylation when the reaction is triplet-sensitized [7]. Photodecarboxylation is followed by PET cyclization to give 6, whereas the lactone 7 originates from PET-induced sulfur oxidation and radical ion trapping without subsequent decarboxylation. Similar effects were observed for the cysteine and \(S\)-methyl cysteine derivatives [8].

Other proteinogenic amino acids that, in principle, should also be able to show bielectrophoric behavior with aromatic side chains similar to phenylalanine are tyrosine, histidine and tryptophan. The photochemistry of the phthalimide derivatives of these three amino acids are described in this publication.

**Results**

**Synthesis of phthalimide substrates**

The C-protected \(N\)-phthaloyl amino acids 8–10 were available from tyrosine, histidine, and tryptophan (Figure 1). The phthalimide derivatives were prepared either by thermal reaction of phthalic anhydride with the corresponding amino acids or by the Nefkens procedure [9]. The latter procedure yields enantiomerically pure products (by optical rotation), whereas the thermal method leads to partial epimerization.

![Figure 1: Phthalimides from tyrosine 8, histidine 9 and tryptophan 10.](image1.png)

**Scheme 1:** Three phthalimide/amine acid model reactions: Norrish II process of 1, PET decarboxylation of 3, PET competition of 5.
Scheme 2: PET decarboxylation/photocleavage of 8 and 9.

Photochemistry of the tyrosine and histidine derivatives 8 and 9

The colorless phthalimides from tyrosine and histidine 8 and 9, respectively, were photochemically active and gave decarboxylation and cleavage products. In contrast to photolysis in pure acetone [10], irradiation of the tyrosine substrate 8 in basic water/acetone resulted solely in the decarboxylation product 11. Under identical conditions, the histidine derivative 9 resulted in a 1:4 mixture of phthaloyl histamine 12 and phthalimide (13) (Scheme 2). In both cases, the photolyses were clean processes and the products were isolated in high yields after complete conversion. The tyramine derivative 11 was isolated by crystallization in near quantitative yield.

Photochemistry of the tryptophan derivative 10

In contrast to all other – colorless – phthalimides of the proteinogenic amino acid series, the tryptophan derivative 10 is bright yellow. This compound, which we crystallized and whose solid-state structure was determined by X-ray diffraction analysis (Figure 2) [11], has also been described in literature as a yellow compound [12,13]. The color is not the consequence of any impurity and did not vanish after several recrystallizations and, more importantly, was also observed for the methyl ester and the decarboxylation product, the N-phthaloyl tryptamine (14). Compound 10 represents a donor–ethylene bridge–acceptor situation and intramolecular electron transition (ET) is feasible. The UV spectra of the three substrates 8–10 (Figure 3) showed in fact two major absorption peaks for 8 and 10 at 280 and 300 nm, whereas the histidine derivative 9 only exhibits the typical phthalimide absorption at $\lambda_{\text{max}} = 282$ nm. The red-shifted absorption of 10 has a tailing that explains the color of this compound and derivatives as CT state absorption
and is additionally red-shifted by 10 nm on changing the solvent from ether to acetonitrile or methanol, respectively. It is remarkable that under solid-state conditions the molecular conformation of 10 in the crystal lattice is synclinal with respect to the indole and the phthalimide groups as well as for the indole and the carboxy groups, indicating a ground-state electronic interaction between the donor indole and the acceptor phthalimide (Figure 2). Such interactions also in solution phase would facilitate decay processes from the excited singlet or triplet state. This concept has also been described by Gawronski et al. from exciton CD Cotton effects that have been measured for a series of bichromophoric systems based on phthalimide–linker–donor triads [12]. Concerning the photochemistry of 10, a remarkable difference to all other phthalimide derivatives occurred: Neither direct excitation nor triplet (acetone, benzophenone) sensitized conditions led to substrate conversion even after prolonged irradiation. Only the use of the PET catalyst 2,4,6-triphenylpyrylium tetrafluoroborate enabled quantitative conversion to give a 4:1 mixture of the decarboxylation product, N-phthaloyl typtamine (14) and the cleavage product 13 (Scheme 3).

Additionally, the fluorescence spectra (Figure 4) indicated a charge-transfer excited-state formation from the tyrosine and tryptophan derivatives, 8 and 10, respectively, by showing dual emission at 310 and 370 nm.

Discussion
Two reaction modes were observed with the phthalimides 8–10: (a) Norrish type II cleavage of the central N–C bond to give the N-unsubstituted phthalimide 13, and (b) photochemical decarboxylation. Analysis of the energetics of the PET between the phthalimide acceptor (see Introduction) and the arene donor side chains of the corresponding amino acid leads to the conclusion that PET is exergonic with $\Delta G = -0.1$ to $-0.3$ V for all cases: The redox potentials of the three amino acids tryptophan, histidine and tyrosine are reported to be 1.02 V [14], 1.17 V [15] and 0.93 V [16].

Due to this narrow redox potential window, similar electron-transfer properties can be expected. Among the amino acids investigated herein, tryptophan is described in biological electron-transfer processes as the most active hole transport molecule [17]. Thus, it can be concluded that the excited charge-transfer state from 10, as can be interpreted from its fluorescence spectrum, is rapidly deactivated radiatively as well as non-radiatively by back electron transfer (BET). In contrast to 10, electron transfer from the electronically excited tyrosine compound 8 is followed by oxidation of the carboxyl anion and subsequent decarboxylation to give N-phthaloyl tyramine (11). If BET from the radical cation state of 10 can be retarded (i.e., produced by an intermolecular PET), the corresponding decarboxylation proceeds to give N-phthaloyl tryptamine (14) (Scheme 3). The histidine derivative 9 is expected to undergo PET with oxidation of the aryl group with the lowest efficiency and thus a Norrish II process ($\gamma$-hydrogen transfer with subsequent central bond cleavage) prevails here (Scheme 4). This process, which was also detected as the minor pathway for the histidine case can, of course, also be described as an electron-transfer induced process followed by $\alpha$-deprotonation.

Conclusion
The photochemistry of three bielectrophoric phthaloyl derivatives of tyrosine (8), histidine (9) and tryptophan (10) follows two distinct pathways, fragmentation and decarboxylation. Both routes can be described as initiated by electron transfer. Intramolecular transfer in the tyrosine substrate 8 leads to efficient decarboxylation whereas for the tryptophan substrate 10 this process can only be initiated by intermolecular electron transfer suggesting efficient back electron transfer in the photoexcited substrate.
Experimental

Synthesis of N-phthaloyl tyrosine (8) [18]. A well ground mixture of 2.00 g (13 mmol) of L-tyrosine and 2.45 g (13 mmol) of phthalic anhydride were added to a 10 mL flask with a magnetic stirring bar. The flask was heated in an oil bath, stirred at 150–160 °C for 20 min and then the mixture was allowed to cool to room temperature. Recrystallization of the crude solid material from ethanol gave 3.67 g of N-phthaloyl tyrosine (8) (88%) as colorless needles; mp 161–163 °C (lit. 162–164 °C); [α]D20 −183.8 (c 1.0, EtOH) (lit. −182.4); 1H NMR (300 MHz, DMSO-d6): δ (ppm) = 3.22 (dd, 2H, J1 = 13.6 Hz, J2 = 11.8 Hz), 5.01 (dd, 1H, J1 = 11.9 Hz, J2 = 5.0 Hz), 6.53 (d, 1H, J = 8.5 Hz), 6.91 (d, J = 8.5 Hz), 7.84 (s, 4H), 9.14 (s, COOH).

13C NMR (75 MHz, DMSO-d6): δ (ppm) = 33.1 (t, 1C), 53.2 (s, 1C), 115.1 (d, 2C), 123.4 (d, 2C), 127.2 (s, 1C), 129.7 (d, 2C), 130.8 (s, 2C), 134.9 (d, 2C), 155.8 (s, 1C), 167.1 (s, 2C), 170.2 (s, 1C).

Synthesis of N-phthaloyl histidine (9) [19]. L-histidine 3.0 g (14 mmol) and 1.52 g (14 mmol) of Na2CO3 were dissolved in 100 mL water and 3.14 g (14 mmol) of N-carbethoxy phthalimide was added to the solution. The mixture was allowed to stir at room temperature for 2 h. After acidification with 2 M HCl, the solvent was removed under reduced pressure. The colorless residue was heated under reflux in 10 mL MeOH for 20 min. After cooling, the residue was removed by filtration and washed with 100 mL MeOH to give 3.40 g of N-phthaloyl histidine (9) (83%) as a colorless solid; mp >260 °C; 1H NMR (300 MHz, DMSO-d6): δ (ppm) = 3.37 (d, 2H, J = 6.6 Hz, H 7), 4.91 (dd, 1H, J1 = 9.5 Hz, J2 = 6.5 Hz), 6.81 (s, 1H), 7.73 (s, 1H), 7.84 (s, 4H). 13C NMR (75 MHz, DMSO-d6): δ (ppm) = 33.1 (t, 1C), 53.2 (s, 1C), 115.1 (d, 2C), 123.4 (d, 2C), 127.2 (s, 1C), 129.7 (d, 2C), 130.8 (s, 2C), 134.9 (d, 2C), 155.8 (s, 1C), 167.1 (s, 2C), 170.2 (s, 1C).

Synthesis of N-phthaloyl tryptophan (10) [18]. A mixture of 2 g (9.8 mmol) of L-tryptophan and 1.04 g (9.8 mmol) of Na2CO3 was dissolved in 100 mL of water. To this solution, 2.15 g (9.8 mmol) of N-carbethoxy phthalimide were added. The mixture was stirred at room temperature for 1 h. After filtration the solution was acidified with 2 M HCl and the precipitate collected. Recrystallization from aqueous acetone gave 3.12 g of N-phthaloyl tryptophan (10) (95%) as yellow needles; mp 170 °C; [α]D20 −247.5 (c 1.0, EtOH) (lit: −249.6); 1H NMR (300 MHz, DMSO-d6): δ (ppm) = 3.55–3.62 (m, 2H), 5.13 (dd, 1H, J1 = 10 Hz, J2 = 6.7 Hz), 6.89 (s, 1H, J = 7.3 Hz), 7.00 (t, 1H, J = 8 Hz), 7.49 (d, 1H, J = 8.1 Hz), 7.26 (d, 1H, J = 8.2 Hz), 7.80 (s, 4H), 10.74 (s, COOH). 13C NMR (75 MHz, DMSO-d6): δ (ppm) = 24.1 (t, 1C), 52.7 (d, 1C), 109.8 (s, 1C), 111.5 (d, 1C), 117.9 (d, 1C), 113.5 (d, 1C), 121.0 (d, 1C), 123.4 (d, 2C), 126.9 (s, 1C), 130.9 (s, 2C), 134.9 (d, 2C), 136.1 (s, 1C), 167.2 (s, 2C), 170.4 (s, 1C).

Photolysis of N-phthaloyl tyrosine (8). A water-cooled solution (c = 2.1 × 10−3 mol/l) of 8 and 0.5 equiv K2CO3 in 100 mL of an acetone/water mixture (1:1) was irradiated at 300 nm.
The authors thank the Deutsche Forschungsgemeinschaft (DFG) for project funding.

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11. The crystallographic data for the tryptophan derivative 10 has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-784387.
The arene–alkene photocycloaddition

Ursula Streit and Christian G. Bochet*

Abstract

In the presence of an alkene, three different modes of photocycloaddition with benzene derivatives can occur; the [2 + 2] or ortho, the [3 + 2] or meta, and the [4 + 2] or para photocycloaddition. This short review aims to demonstrate the synthetic power of these photocycloadditions.

Introduction

Photocycloadditions occur in a variety of modes [1]. The best known representatives are undoubtedly the [2 + 2] photocycloaddition, forming either cyclobutanes or four-membered heterocycles (as in the Paternò–Büchi reaction), whilst excited-state [4 + 4] cycloadditions can also occur to afford cyclooctadiene compounds. On the other hand, the well-known thermal [4 + 2] cycloaddition (Diels–Alder reaction) is only very rarely observed photochemically (vide infra). Photocycloadditions are not limited to simple alkenes, and even the thermally very stable benzene core has been shown to become quite reactive upon excitation with photons. It can be converted into benza- lene [2,3] and fulvene when excited to its first excited-state, or to Dewar benzene [4,5] via excitation to its second excited-state (Scheme 1) [6].
alkenes with arenes. The last part includes a related class of cycloadditions with arenes, where the aromaticity on the final compounds is restored. In this review, we will call this class “non-classical” photocycloadditions.

**Review**

**Classical photocycloaddition of alkenes to arenes**

While the meta photocycloaddition of benzene is very well documented in the literature and has been used many times in organic synthesis, the ortho and particularly the para photocycloadditions have not received as much attention since both types occur rarely and are usually low yield reactions. However, also in these two cases, the complexity of the products is considerably increased with respect to that of the reactants, as a new ring and up to four new stereocenters are formed.

The first “classical” \([2\pi + 2\pi]\) photocycloaddition of benzene was described by Angus and Bryce-Smith in 1959 [7]. However, Ayer, Bradford and Büchi had obtained similar ortho products some four years earlier and recorded their findings in a patent [8]. The meta photocycloaddition was discovered in 1966 independently and almost simultaneously by Wilzbach and Kaplan [9] at Argonne, and by Bryce-Smith, Gilbert and Orger [10] at Reading. The para mode was the last to be discovered fifteen years later, again by Wilzbach and Kaplan [11]. Subsequently, considerable effort has been invested in an attempt to understand and further develop benzene photocycloadditions. This has resulted in some very spectacular results, among which is the application of the meta photocycloaddition in the total synthesis of natural products, particularly by Wender [12]. The field has been reviewed on several occasions mainly by Cornelisse [13], Mattay [14,15], Wender [16], Hoffmann [17] and de Keukeleire [18] with a focus on the meta mode.

**Excited-states involved**

Photocycloadditions of arenes with alkenes are usually trigged by the photoexcitation of the arene moiety. If the first excited singlet state of benzene is involved \(S_1\), excited at 254 nm in an electric dipole forbidden transition, \(\epsilon = 20.4\), only the meta mode is allowed to occur in a concerted fashion according to molecular orbital symmetry rules [19,20].

Concerted ortho and para photocycloadditions of olefins are forbidden to occur from the first excited-state, but they are formally allowed from the second excited-state of benzene \(S_1\). The fact that ortho and para cycloadducts are nevertheless observed to be formed can be explained if charge transfer processes are invoked, if reaction occurs in a non-concerted fashion (where the Woodward–Hoffmann rules do not apply), or from the second singlet excited-state. However, more recent computational work using a VB description of the structures has shown that such cycloadditions can take place from the \(S_1\) excited-state without barrier through a conical intersection, which is common to all three cycloadducts [21], at least for the benzene/ethylene system.

Quenching and sensitizing experiments were carried out to elucidate the spin state of the excited species involved. Mattay has shown that the quantum yield of the photocycloaddition of...
1,3-dioxoles with benzene is halved for all three occurring modes (ortho, meta and para) if the reaction is carried out under an atmosphere of xenon rather than argon [22]. Xenon accelerates the singlet–triplet intersystem crossing by the heavy-atom effect, and thus decreases the singlet excited-state lifetime of the arene. Mattay considered this as direct proof that the addition of benzene to 1,3-dioxoles takes place primarily via the singlet excited-state of benzene. Ferree et al. had earlier provided evidence that the meta photocycloaddition occurs from the singlet excited-state; they observed that 6-phenyl-2-hexene undergoes cis–trans isomerization upon sensitizing with acetone and benzophenone, whereas the photocycloaddition to the meta product could only be triggered via direct irradiation [23].

Mode selectivity

Photocycloadditions are usually atom-economical, meaning that all atoms of the starting material end up in the final compound. Furthermore, photocycloadditions of alkenes with arenes are “step-economical”, as the complexity can be increased considerably in a single step. With these unprecedented possibilities to efficiently create diverse molecules with high complexity, synthetic applications should abound. One should, however, keep in mind, as Wender wrote some years ago, that: “Any reaction with the potential to produce a highly complex product also has the potential to provide a highly complex product mixture, if its selectivity is not controlled” [12]. Control of mode-, regio- and stereoselectivity is absolutely crucial if one aims at obtaining defined photocycloadducts in relevant yields.

The mode selectivity is predicted by the electronic properties of the two reaction partners involved. The (simplified) Weller equation determines whether or not electron transfer will occur from an excited-state (Equation 1) [24,25]. For the reaction of an excited aromatic moiety with an alkene, this means that if the change in free energy, determined by the Weller equation, is negative.

\[
\Delta G_{ET}^{\text{rad}} = \frac{E_{\text{red}}^\text{excit} - E_{\text{red}}^\text{excit}}{2} + \Delta E_{\text{coul}}
\]  

with \(\Delta G_{ET}^{\text{rad}}\) = free enthalpy of the radical ion pair formation, \(\Delta E_{\text{coul}}\) = coulomb interaction energy of the radical ions and \(E_{\text{red}}^\text{excit} = \frac{1}{2}\) half wave potential of donor and acceptor.

If electron transfer pathways dominate, substitution reactions are found to prevail. However, if the electron transfer is endergonic, ortho photocycloaddition can be observed. Mattay also observed that when \(\Delta G_{ET}^{\text{rad}}\) rises above 1.5 eV, meta photocycloadditions prevail (Scheme 3) [24].

However, these limits are not very sharp and a lack of mode selectivity may be observed in borderline regions (Scheme 4) [26]. These findings are consistent with the proposal that ortho photocycloadditions are the major reaction pathway when a certain degree of charge transfer is involved.
Meta photocycloadditions

Mechanism

The meta photocycloaddition reaction was extensively reviewed in 1993 by Cornelisse [13], who gave also a summary of mechanistic suggestions and debates up to that date. The now commonly accepted mechanism of this reaction involves the excitation of the benzene moiety to its first excited-state (1B2u) and subsequent formation of an exciplex with the alkene moiety (Scheme 5).

The occurrence of such exciplexes has been detected by emission spectroscopy [22,27]. The two new sigma C–C bonds are formed concertedly from the exciplex. The reaction is thought to proceed through a slightly polarized intermediate, which explains the observed regioselectivity when the arene is disymmetrically substituted. While the bridging carbon atom is slightly positively charged, the termini of the allylic moiety carry a partial negative charge. It was shown that the formation of the sigma bonds is the rate determining step, as isotope effects were only observed when the addition occurred directly at the deuterium-substituted site [28]. On the other hand, it was also proposed that a biradical intermediate is involved in this photocycloaddition mechanism. Nevertheless, all attempts to trap a biradical or a zwitierionic intermediate have so far been unsuccessful. A very clever plan to test whether a biradical intermediate is indeed involved was carried out by Reedich and Sheridan [29]: By incorporating a diazo group into the last formed bond of the cyclopropyl ring in the meta photocycloadduct [30], they would be able to see whether the biradical formed by the extrusion of nitrogen gave the same products as the meta photocycloaddition (Scheme 6).

This was indeed the case, as very similar ratios of the two distinct stereoisomers C and D were found to be formed from the diazo compounds A and B as well as from the photocycloaddition of o-xylene to cyclopentadiene. This finding seems to indicate that a biradical structure is indeed involved in the meta photocycloaddition pathway; however, whether this biradical is an intermediate with a well-defined half-life or whether it is only just a transitory species remains so far unclear [31].

Regioselectivity

The meta photocycloaddition reaction creates a compound containing up to six new stereocenters in a single step from planar achiral starting materials. If substituents are added to the arene and the complexity of the olefin is increased, a great
diversity of products can be created. However, not all of these products are accessible via such a photocycloaddition, as many possibilities can be ruled out due to the intrinsic selectivity of the reaction.

There are two distinct regioselectivities involved in the meta photocycloaddition. The first is with regard to the substitution pattern on the aromatic ring. The influence of electron donating and electron withdrawing substituents on the reactivity is mainly on the polarized intermediate shown in Scheme 5. While electron donating substituents are usually known to direct the addition towards the 2,6-mode, they therefore end up on the positively polarized one-carbon bridge, whilst electron withdrawing substituents trigger a 2,4-addition and end up at one of the negatively polarized carbon atoms on the three-membered bridge (Scheme 7) [13,18].

A second possibility to obtain different regioisomers occurs in the last step of the reaction. The recombination of the biradical may afford regioisomers when unsymmetrical olefins or additional substituents on the aromatic moiety are involved (Scheme 8).

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If the olefin contains substituents, an issue of stereoselectivity is added to the regioselectivity. The addition can either occur from the exo or endo exciplex to the aromatic moiety (Scheme 9).

The observed preference for endo photocycloaddition [34-36] has been rationalized by secondary orbital overlap, which supports attack on the olefin from the endo position [37].

An excellent example for such intermolecular selectivity was published a few years ago by Piet et al. (Scheme 10) [38].

They observed a very selective endo 1,3-photocycloaddition across the substituent on the aromatic moiety in the reaction of cyclopentene with a protected isoidoline. This reaction has been reported to produce very high yields; however, the lack of regioselectivity in the biradical cyclopropane formation gives the two regioisomers in a ratio of 8:5.

Intramolecular reactions

The first intramolecular meta photocycloaddition was reported in 1969 by Morrison and Ferree [39]. The intramolecular reaction was shown to be very efficient when three atoms tethers were employed, but the quantum yield drops considerably when four atoms tethers are involved [40], apart from some exceptional cases when the freedom of the tether is restricted and a suitable conformation can be found [41]. The influence of the incorporation of oxygen in the tether has been reviewed by de Keukeleire [42].

The selectivities mentioned above may change in intramolecular reactions. In this mode, the endo approach of the alkene cannot be achieved without introducing significant strain, which usually outweighs secondary orbital interactions, and thus exo rather than endo adducts are obtained [40].

In the intramolecular mode, either 2,6- or 1,3-addition to the tether can be observed (Scheme 11) [43].

1,3-Addition is usually observed selectively when electron donating groups are attached to the aromatic moiety ortho to the
tether or if the olefin contains additional cis substituents; this is due to repulsion of the substituents on the olefin with the hydrogen atoms of the tether in the \textit{exo}-addition which prevents the 2,6-addition mode. Intramolecular \textit{meta} photocycloadDITIONS that occur at positions 1,3 relative to the tether may give either a linear or an angular isomer (Scheme 12) [44].

Calculations of the relative stabilities are a useful tool to predict the selectivity. If no additional substituents are present, the linear compounds are slightly more stable [40]. However, some examples show that this selectivity can be changed [45]. The linear and angular isomer names are derived from the opening of the cyclopropane ring to afford linearly and angularly fused triquinanes.

Asymmetric \textit{meta} photocycloadditions

The \textit{meta} photocycloaddition has the potential to convert planar (thus achiral) molecules into three-dimensional chiral molecules. It is therefore not surprising that many attempts have been made to render this process enantioselective. The main strategy in this perspective is the introduction of a chiral center directly on the tether in an intramolecular photocycloaddition, and to carry out the reaction in a diastereoselective way. The best known example of this approach was implemented in the total synthesis of (±)-α-cedrene published by Wender et al. in 1981 (Scheme 13) [46].

Following this very elegant and highly efficient synthesis, the \textit{meta} photocycloaddition attracted much interest in the field of total synthesis of natural products. In addition, studies aimed at understanding and predicting the diastereoselectivity of this photocycloaddition were undertaken. For example, the group of Sugimura has shown that chiral 2,4-pentanediol tethers are very efficient for face recognition (Scheme 14) [47,48].

The chirality at the position 2 of the tether completely directs the diastereoselectivity. Compounds having a 2\textit{R} configuration react uniquely at the \textit{si} face of the vinyl group, leading to the \textit{R} configuration at the newly formed stereocenter. However, the reaction lacks regioselectivity in the formation of the cyclopropane ring, and both regioisomers are obtained. A similar ap-
A completely different approach to an asymmetric meta photocycloaddition was made by Van der Eycken. He showed that meta photocycloaddition carried out in a chiral cavity (β-cyclodextrin) affords the photocycloaddition product in 17% ee (Scheme 15) [52].

Further diversification

Meta photocycloaddition can be considered as very regio- and stereoselective if the appropriate substituents are chosen. The only reaction step notoriously lacking regioselectivity is the closing of the cyclopropane ring. Therefore, in many examples, the isolation of the two regioisomers of the meta photocycloaddition is described. However, a possibility to interconvert one compound into the other by thermal [53] as well as photochemical [47,54] means was found (Scheme 16).

Acidolysis of meta photocycloaddition compounds has been studied by Gilbert [55]. He observed that the cyclopropane ring opens upon protonation of the double bond. If the meta photocycloaddition product contains a substituent at position 1, ring opening affords bicyclo[3.2.1]octane derivatives, whilst if no substituent is present at position 1, a hexahydronaphtalene is the preferred product of ring opening. Other electrophiles also have the tendency to add to the double bond. Wender has shown in his total synthesis of (+)-α-cedrene, that bromine readily adds and triggers the opening of the cyclopropane ring [46]. Rearrangement of the resulting allylic bromide to the more stable regioisomer at this stage occurs readily and debromination can be achieved on treatment with tributyltin hydride. Penkett has shown that 3-chloroperbenzoic acid (m-CPBA) can take the role of an electrophile in the epoxidation of the double bond [56] and also demonstrated that the meta photocycloaddition products containing a methoxy group at position 1 can be converted in a Heck-type reaction [57,58]. The intermediate palladium σ-complex, formed by insertion, opens the cyclopropane ring and arylated bicyclo[3.2.1]octane derivatives are directly obtained are usually not useful as such, and cleavage of the cyclopropyl ring must be carried out to access naturally occurring polycyclic systems. Many investigations have already been achieved by different research groups to diversify the molecules accessible by this synthetic route: The cyclopropyl ring of the meta product is opened to give either bicyclo[3.3.0]octane or bicyclo[3.2.1]octane derivatives (Scheme 17).
obtained. Thermolysis of the meta photocycloaddition product results in [1,5]-sigmatropic shifts. The shift can either be a shift of a hydrogen [54] or a carbon [59] atom to afford tetrahydropentalenes.

There are also radical approaches to the opening of the cyclopropyl ring. Under Birch reaction conditions, the cyclopropane ring can be reduced to the hexahydropentalene [45,60,61]. Radicals can also add to the double bond and induce the opening of the cyclopropane ring; for example, thiophenoxy radicals have been found to be very efficient for such reactions [44,62,63]. Another possibility to react radicals with meta photocycloadducts was demonstrated by Wender et al., who showed that acetonitrile radicals can be added to the olefin and open the cyclopropane ring to yield a hexahydropentalene [64].

**Application in total synthesis**

There are several reviews that describe a large number of applications of the meta photocycloaddition to the total synthesis of complex polycyclic molecules. A recent publication by Chappell and Russell discusses comprehensively and in detail many examples from α-cedrene and the following 25 years [40]. We will therefore focus on the most recent examples of total synthesis applications.

Several times, Fenestranes have been the targets of total synthesis by meta photocycloaddition reactions [65]. Penkett, described very recently an access to fenestranes in a single step (not counting the one-step preparation of the substrate) [66].

The reaction could also be carried out in a two step sequence. He observed that the starting material undergoes a selective 1,3-addition to one of the tethers. The subsequent cyclopropane ring closure gives mainly the linear fused meta product in 23% yield. The meta compounds and two rearranged ortho products were isolated from the reaction mixture in a combined yield of 60%. The major meta product can be converted into the fenestran by further irradiation (Scheme 18). This second [3 + 2] addition reaction can be accelerated by the addition of sensitizers and could be quenched with piperylene. The proposed mechanism involves a homolytic cleavage of the cyclopropane ring to afford the linear triquinane biradical, which undergoes addition to the double bond. Wender achieved the total synthesis of fenestranes from meta photocycloaddition products some years earlier by cyclization using radicals in acetonitrile under reflux [67].

Another very recent application of the meta photocycloaddition has been published by Gaich and Mulzer [68]. They achieved the total synthesis of Penifulvin B and C in five steps after meta photocycloaddition (Scheme 19).

This first enantioselective total synthesis of the naturally occurring [5.5.5.6]fenestranes is highly efficient. The photocycloaddition occurs by an intramolecular 1,3-exo attack of the olefin to the aromatic moiety. The cyclopropane ring closure is, in this case, not regioselective at all, and leads to a 1:1 mixture of products. However, the undesired photocycloadduct can be converted to the desired compound via a thermal vinylcyclopropane–cyclopentene rearrangement. All obtained photocycloaddition compounds can be converted into the target by this means. The cyclopropane ring was opened by a Birch-type reduction. Oxidation of the primary alcohol and ozonolysis of the double bond afforded the hemiacetal after spontaneous cyclization. Subsequent oxidation and deprotection afforded the desired compound. In the same paper, the total synthesis of the naturally occurring epimer of Penifulvin B (Penifulvin C) was described, which was achieved by replacing the trans-olefin by the cis-olefin and following the same sequence of steps. One year earlier the same group accomplished the total synthesis of Penifulvin A via a meta photocycloaddition [69].

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**Scheme 18: Double [3 + 2] photocycloaddition reaction affording fenestran.**
Not only fenestrans are accessible from the meta photocycloaddition products. Wang and Chen have recently published an approach towards the core of Lancifodiactone F [70]. This triterpenoid contains three fused and one spiro cycle and is a very challenging target. Initial attempts to construct the fused seven-, six- and five-membered core were unsuccessful. Introduction of a trimethylsiloxy group on the tether and an oxygen substituent on the aromatic ring were crucial for the photocycloaddition to proceed in good yield (Scheme 20).

The additional tetrahydrofuran cycle helps to constrain the four unit tether. Only with these additional features does the cycloaddition step occur with a remarkable yield of 89%. The photocycloaddition occurs selectively 1,3-exo to the tether. The stereochemistry on the trimethylsiloxy substituent was shown to have no influence on the photochemistry, but it helped to direct the olefin group towards the arene moiety. The linear and angular fused compounds were elaborated to give a common intermediate containing the fused five-, six- and seven-membered ring pattern without further purification.

**Ortho photocycloaddition**

There is little data on the selectivity of the ortho photocycloaddition in the literature. However, Mattay discovered that the regioselectivity of the ortho photocycloaddition is dependent on the electronic properties of the two reaction partners [14]. He reported that 1,2-addition usually prevails when a high degree of charge transfer is involved in the exciplex ($\Delta G_{ET}$ below 0.5 eV). A substituent at position 1 stabilizes the charge which develops on the aromatic ring, and therefore favors the 1,2-ring closure of the intermediate (Scheme 21).

This selectivity is not very high and as the degree of charge transfer decreases, the selectivity decreases. The role of CT is
also supported by the fact that regioselectivity is usually higher in polar solvents where charge separation is favored [71,72]. Substituted olefins may add in an \textit{exo} or \textit{endo} fashion. While electron-deficient alkenes give mixtures of both possible products, electron-rich compounds show stereoselectivity towards the \textit{exo} products (Scheme 22) [73].

Ortho photocycloaddition can, however, also take place from the triplet excited-state by sensitization. The triplet excited-state is believed to have a higher biradical and less zwitterionic character [73]. \textit{Ortho} photocycloaddition of triplet excited benzenes have been extensively studied by Wagner and his group. They investigated [2 + 2] photocycloadditions of alkanophenones, which occur from the triplet excited-state and via 1,4-biradicals [74-77]. The occurrence of such radicals has been proven by the insertion of a cyclopropyl radical trap in the olefin. Upon irradiation of this modified starting material, the \textit{ortho} cycloadduct could no longer be isolated (Scheme 23) [78].

Naphthalenes are known to undergo preferably \textit{ortho} photocycloadditions (Scheme 24), whilst higher arenes usually react with olefins in an [2 + 2], [4 + 2] or [4 + 4] cycloaddition mode.

The \textit{ortho} photocycloaddition gives access to bicyclo[4.2.0]octanes which usually undergo thermal electrocyclic ring opening to yield eight-membered ring systems (Scheme 25) [73,80].

Another possibility to further transform the intermediates are Diels–Alder cycloadditions of the dienes formed by the \textit{ortho} photocycloaddition [81]. Furthermore, Scharf demonstrated that he could trigger a photochemical rearrangement to produce a \textit{para} photocycloaddition product upon sensitization [82]. However, there also exists some examples where the [2 + 2] cycloadduct is stable enough to be isolated as such, and in good yield (Scheme 26) [83,84].

Ortho photocycloaddition is almost exclusively observed with alkenes. The photocycloaddition products usually undergo ring opening to cyclooctatetraenes [85] or to other rearrangement products [86] (Scheme 27).
Ortho photocycloadducts are known to be very unstable as such. However, if they have the possibility to stabilize by rearrangement, products can be isolated often in high yield. A very good example of this was published by Kalena et al. some years ago [87] who observed that 2-alkenyl-7-hydroxy-4-chromanone could undergo ortho photocycloaddition to afford the tetracyclic compounds shown in Scheme 28.

The initial enol tautomerizes to the α,β-unsaturated ketone, which can be isolated in moderate yield. Anisole photocycloaddition precursors did not afford similar tetracyclic compounds under the same irradiation conditions. However, under slightly acidic conditions (chlorinated solvents or additional p-toluene-sulfonic acid) the photocycloaddition to the same compound could be restored.

Some years later, the same group reported that irradiation of the same starting material in methanol instead of benzene afforded the compound apparently formed by meta photocycloaddition [88]. However this meta photocycloaddition product has some issues. Addition occurs 2,6 across an electron-withdrawing substituent; this is unfavorable in a direct [1,3]-addition (due to the polarization in the polarized intermediate; see the chapter on "Meta photocycloadditions"). Furthermore, Kalena et al. could show that the compound is also formed upon irradiation of the ortho photocycloaddition product under slightly different irradiation conditions.
A very unconventional [2 + 2] photocycloaddition to afford caged polycyclic structures has been recently described (Scheme 29) [89,90].

If the irradiation is carried out in the presence of conjugated dienes or a second arene (usually higher aromatics), this photocycloaddition can also be carried out in a [4 + 4] mode to afford bicyclo[4.2.2]decatrienes and more complex homocycles [91,94,95].

In the non-sensitized irradiation of dianthryls, the [4 + 4] photocycloaddition [91] pathway is usually observed; upon sensitizing in the triplet excited-state, the [4 + 2] mode prevails (Scheme 31). Such [4 + 4] photocycloadditions have also been observed intermolecularly with very high yields [96].

There are few examples leading to para products in high yield. However, one example is the intramolecular photocycloaddition of a cinnamoylamide and a benzamide moiety (Scheme 32) [97]. This reaction is very efficient and leads to high yields of the bicyclo[2.2.2]octadiene derivative.

In this example, the cinnamoylamide is sensitized by benzil to its triplet excited-state. The proposed mechanism involves the reaction of the olefin with the ipso position of the aromatic ring affording a spiro biradical intermediate. Recombination of these radicals proceeds further until formation of the final compound. Some years later, Kohmoto showed that similar enamides linked to a naphthyl moiety underwent preferably ortho photocycloaddition if the naphthyl moiety is sensitized [98].

By attaching the double bond very close to the aromatic moiety, the photocycloaddition leads to the desired cage compound in high yield. Surprisingly, the compound is fairly stable and can be recrystallized from hexane.

**Para photocycloaddition**

Para photocycloaddition giving access to bicyclo[2.2.2]octadiene systems by a formal Diels–Alder type reaction is very rare, and little is known about this mode. It is known that higher aromatics are more likely to undergo para cycloadditions [91], and that it is the main mode when allenes are involved [92]. A high yielding example of a para photocycloaddition with an allene has been published by Haddaway et al. (Scheme 30) [93].
Intramolecular photocycloaddition affording multicyclic compounds via [4 + 2].

Scheme 33: Intramolecular photocycloaddition affording multicyclic compounds via [4 + 2].

Irradiation of a naphthyl precursor containing only a two atom tether to the olefin afforded the para photocycloadduct (Scheme 33) [99].

However, Kalena et al. noted that the para product might also be derived from the ortho product upon further irradiation: The para product undergoes a sequence of ring opening/Michael addition of the solvent to give the final compound. However, neither the direct ortho nor the para product have been observed. The main changes from the previous papers of Kalena et al. were the replacement of the phenyl by a naphthyl group, and a two atom tether of the olefin. These two modifications are able to trigger different mode selectivity. As previously mentioned, the reaction with alkanophenones proceeds through a 1,4-biradical intermediate. The same reaction applied to this naphthyl derivative would lead initially to the formation of the four-membered ring. The five-membered ring will be preferred but the radical formed cannot recombine and fragments back to the starting material. Once the four-membered ring containing a primary exocyclic radical is formed, recombination either directly α to the carbonyl (construction of two fused cyclobutane ring systems) or delocalization of the radical to the para position can take place and the para product is formed.

Non-classical photocycloadditions of alkenes with arenes

Not only can the benzene moiety of arenes undergo cycloadditions upon exposure to light but, depending on the substitution pattern, other reactive sites may be involved. Carbonyl groups are also known to undergo different types of photochemistry. Thus, benzophenones, acetophenones and benzaldehydes are not only used as sensitizers but can, under specific circumstances, also be directly involved in photochemical reactions to form new structures.

Formation of benzoepines

Sakamoto et al. reported that irradiation of ortho acylphenyl methacrylates can lead to photocycloaddition to afford benzoxepine structures in very high yield (Scheme 34) [100].

![Scheme 34: Photocycloaddition described by Sakamoto et al.](image)

This very unusual reaction involves the formation of a new aryl C–C bond and the loss of the aryl C–O bond, and is therefore clearly a rearrangement product. Furthermore, Sakamoto showed that this reaction was not limited to benzophenones, but also occurred with acetophenones, albeit in slightly lower yields. For this completely new reaction Sakamoto has proposed a mechanism involving a ζ-hydrogen abstraction to form a biradical intermediate (Scheme 35, E).

The resulting biradical cyclizes to form the spiro compound F upon recombination of the biradical. Re-aromatization affords the carboxylate G, which further attacks the carbonyl group. The alcohol intermediate H may cyclize by addition to the double bond to afford the final benzoxepine compound.

In the same year, a slightly different reaction was reported by Jones et al. [101] who triggered the formation of unusual photocycloaddition products by irradiation of ortho allyloxy-substituted anthraquinones (Scheme 36).

During their study on the photo-release of bioactive aldehydes, Jones et al. discovered that, under anaerobic conditions, the
dihydroquinone intermediate loses water to form the zwitter-ionic structure (Scheme 37).

From this intermediate, cyclization can take place to form a spiro compound; further re-aromatization to form the enol, lactolization and cyclization explains the formation of the benzoxepine structure [101].

Griesbeck et al. reported the formation of benzoxepines from the benzophenone analogue upon irradiation at slightly lower
wavelengths [102]. The formation of the compound was observed in 50% yield, along with a diastereoisomeric mixture of dihydrobenzofurans in 40% yield (Scheme 38). Analogues of the dihydrobenzofuran formed upon irradiation of ortho-alkyl-oxyphenyl ketones have already been described in the literature and the reactions are known to take place via a δ-hydrogen abstraction by the ketone triplet, followed by cyclization of the 1,5-biradical intermediate [103].

Griesbeck et al. investigated the mechanism for this photocycloaddition, as he suggested that the mechanism proposed by Jones is unlikely, because the regiochemistry of proton catalyzed addition of alcohols to enols or enol ethers has the opposite regiochemistry to that observed in the product [102]. Furthermore, an electron transfer intermediate was ruled out, as the reaction is not thermodynamically feasible according to the Weller equation. Therefore, he proposed that the benzoxepine structure is achieved via a pseudo-Paterno–Büchi pathway (Scheme 39), while the dihydrobenzofurans arise from a Norrish-type II reaction and cyclization.

Griesbeck supports his proposed mechanism by flash laser photolysis, where a long lived (some seconds) intermediate with an UV absorption band at 380 nm was observed. This absorption band fits well with TD-DFT calculations. He proposes that re-aromatization of this intermediate takes place via a zwitterionic species or through a proton catalyzed pathway.

We recently found in our laboratories that the intramolecular photocyclodaddition of allenylated salicylaldehydes affords a benzoxepine derivative and an apparent para photocycloadduct (Scheme 40) [104]. The product distribution is dependent on the substitution pattern of the aromatic core.

Introduction of bulky tert-butyl substituents at positions 3 and 5 on the aromatic ring yields up to 94% of the para photocycload-
dition product, while other substituents gave yields of up to 44% of the benzoxepine compound. Pericyclic reaction mechanisms for these two photocycloadditions have been proposed, but no hard evidence has so far been obtained. The mechanism of this unprecedented reaction is currently under investigation in our laboratory.

Conclusion
In summary, we have described in this overview the applicability of the intriguing photocycloaddition of olefins with arenes. These reactions have been shown to afford compounds with a high increase in complexity in only one reaction step. We have discussed the diverse selectivities of the reaction, mechanisms as well as further modifications, and some of the most recent applications in total synthesis. Thus, while meta photocycloadditions are uncommon and, in particular, ortho photocycloadditions are indeed giving potentially interesting benzoxepines, benzophenones or benzaldehydes, we have consequently been less investigated. We have discussed these last two modes, which were exemplified by a few high yielding examples. Finally, we have reviewed the use and the reaction mechanism of the photocycloaddition of carbonyl substituted aromatics: Irradiation of ortho allyloxy, acrylic or allenylxy substituted antraquinones, benzophenones or benzaldehydes indeed give potentially interesting benzoxepines. There is little doubt that arenne photochemistry will continue to help the synthetic chemist to assemble complex and challenging targets in the coming years.

References
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Intraannular photoreactions in pseudo-geminally substituted [2.2]paracyclophanes

Henning Hopf1, Vitaly Raev1 and Peter G. Jones2

Abstract

The photoisomerization of the pseudo-geminal tetraene 11 furnishes the cyclooctadiene derivatives 13 and 15 with a completely new type of molecular bridge for a [2.2]paracyclophane which promise many interesting novel applications; the same is true for the photoisomerization of 22 to 23 and 24. The structures of these new hydrocarbons were established by X-ray crystallography and spectroscopic analysis; among the noteworthy structural features of 13 and 15 are unusually long carbon–carbon single bonds (>1.64 Å).

Introduction

Photodimerizations of crystalline aromatic or olefinic compounds are among the oldest known organic photoreactions. In this type of reaction the crystal lattice locks the relative orientation of the substrate molecules or their photoreactive groups. If the orientation is favorable for reaction, reactivity increases. Unlike photochemistry in homogeneous solution, this often leads to highly selective formation of the photoproducts. Schmidt coined the term “topochemical principle” or “topochemistry” for (non)reactivity determined by a limiting distance between the reactive groups [2-4]. Although the model found widespread acceptance, many exceptions to the concept were known from the very beginning [5]. Later, AFM techniques enabled experimental elucidation of solid-state photochemistry. This showed that the supramolecular arrangement of molecules in the crystal plays a more important role for reaction control than the simple alignment of double bonds. Long-range molecular movements within crystals upon photochemical reaction and even topotactic single-crystal to single-crystal reactions were found, although the latter are rare. The subject has been comprehensively covered by recent reviews [6-8].
Reactions of inclusion complexes are a variation of the solid-state photochemistry topic [9]. Here, co-crystals of a host compound and the starting materials of a photochemical reaction are used and the supramolecular arrangement [10] may control the regio- and stereoselectivity of the photo-process. The enantioselective photochemical conversion of chiral crystals into optically active products has also been described [11]. Some approaches utilize zeolites as supramolecular hosts for photo-reactions [12-14]. Internal complexation, or intracrystalline adsorption, occurs by diffusion of the guest into the channels and cavities of the zeolite crystal and is size- and shape-selective. Complexation of organic compounds may reversibly depend on temperature. The geometry of zeolite cavities restricts conformation and orientation of included guests and their reaction partners and leads to more selective reactions. In the absence of any low-energy electronic states of the zeolite, photoreaction occurs only with the included guest.

The common disadvantage of solid-state photoreactions is the difficulty in predicting and controlling reaction selectivity. It remains a challenge to find the suitable crystal, co-crystal, or inclusion complex for the desired regio- or stereoselective outcome of a given reaction. Therefore, an attractive strategy is to transfer the topochemical control from the solid state to a homogeneous solution using suitable templates. Such reactions are easier to analyze, design, and optimize.

Templated photochemistry in solution is possible if the photoreactive moieties can be brought into suitable positions for reaction. Such an arrangement may in principle be reached either by non-covalent bonding (e.g., hydrogen bonds) or by (cleavable) covalent bonds. The latter case can be realized if two (or more) reactive moieties are attached to a rigid scaffold, which is able to fix them in the correct position for reaction.

One such system is the generalized paracyclophane molecule 1 shown in Scheme 1. Here the distance between the benzene “decks” carrying the functional groups F₁ and F₂ can be adjusted both by the length of the two molecular bridges (variation of m and n), and by the relative orientation between these groups in terms of their relative positions in the aromatic subsystems. Although there will never be a continuum of intra-functional distances, numerous spatial arrangements of F₁ and F₂ are possible, keeping in mind that, for example, the molecular bridges of 1 – with the number of carbon atoms held constant – can be modified by introducing functionality into this part of the molecule, making the bridges more rigid, and/or by exchanging the benzene rings of 1 for other aromatic or heteroaromatic subsystems. The two bridges do not have to be of the same length nor the aromatic nuclei of the same type.

In our work we have so far concentrated our efforts on derivatives of [2.2]paracyclophane (1, m = n = 2) with the two functional groups usually in the so-called pseudo-geminal positions, that is, directly above each other as shown in 2. The intranuclear distance is approximately 3.1 Å in [2.2]paracyclophane and hence is less than the separation of the layers in graphite (3.4 Å) or between the base pairs of DNA (3.34 Å) [15]. In other words, the distance between the benzene rings of [2.2]paracyclophane and consequently of the two functional groups directly bonded to them is just slightly shorter than the length of a p-orbital, an ideal prerequisite for an intraannular reaction to take place should other factors, such as excessive strain, not prevent it. In principle, cyclophanes such as 1 are thus excellent model compounds for “molecular workbenches” [16-19] and we have already shown that certain pseudo-geminally substituted derivatives can be used as proxies for the crystal lattice in various solid-state reactions [20-22]. For example, on irradiation the unsaturated esters 3 photocyclize in excellent (up to quantitative) yield to the ladderane derivatives 4. In this case the cyclophane moiety is the “order-generating” part of the molecule and the originally flexible, unsaturated chain remain attached to each other by stable C-C-bonds; altogether the process amounts to a stiffening (rigidization) of the molecules 3. In the case of the bis amide 5 (Scheme 2), photodimerization to the corresponding cyclobutane derivative occurs readily, and the photoproduct can be saponified to the corresponding pseudo-geminal diamine and truxinic acid (6) in excellent yield, thus allowing its stereospecific synthesis. We believe that the use of the [2.2]paracyclophane scaffold as a removable spacer can be developed considerably further for the stereospecific synthesis of many other compounds.

Results and Discussion

However, the detailed stereochemical situation is in fact more complex, and the origin of the stereospecificity requires a more thorough analysis. For example, we have shown [22] by time-resolved photoelectron spectroscopy (TR-PES) that the pseudo-geminal divinyl derivative 7 can only react from its anti,anti-
conformation (anti referring to the orientation of the vinyl substituent to the neighboring ethano bridge) to yield the cyclobutane derivative 8. The syn,anti-conformation, which has been shown to be present as a conformer in the solid state by X-ray structural analysis does not photocyclize to 8. Moreover, syn,syn-7 is evidently too sterically hindered (by repulsion of the relevant hydrogen atoms as shown in Scheme 3) to be part of the conformational equilibrium.

Clearly, the situation is conformationally much more complex in cases such as the triene esters 3, where several conformations could be present in the ground state. To investigate this phenomenon we decided to simplify our substrates structurally and chemically by omitting any functional groups. In this contribution we report on the results obtained with two hydrocarbons 11 (Scheme 4) and 22 (Scheme 8).

Bis-ene-al 10 was obtained in excellent yield (97%) as a mixture of three isomers (Scheme 4) in a ratio of 70:15:1; the isomers were isolated by column chromatography and their
structures were established from their spectroscopic data, especially from their NMR spectra (see Experimental). Treatment of the cis,trans- and cis,cis-isomers of 10 with hydrochloric acid in aqueous THF converted them into the thermodynamically most favorable trans,trans-isomer.

Bis-diene 11, which was obtained in virtually quantitative yield from trans,trans-10 by a Wittig olefination, appears to be unstable in the solid state at room temperature, but in the refrigerator at −20 °C or in dilute (−0.1 M) solution in dichloromethane or chloroform it can be stored in the dark for at least 3 months without any detectable decomposition or polymerization.

Irradiation of 11 with a halogen lamp (1 kW, 10 cm distance, water cooling) for 16 h gave a mixture of products (Scheme 5), which contained two isomers of a cycloocta-1,5-diene derivative, 13 (as the main product) and 15 (syn- and anti-position, respectively, relatively to the bridge) together with the divinylcyclobutane derivative 14 in moderate yield (total yield 70%, ratio 13:14:15 = 43:5:8 by 1H NMR analysis). The expected ladderane 12 was not detected in the reaction mixture by NMR spectroscopy. Separation by column chromatography gave the pure divinylcyclobutane derivative 14, but the cyclooctadienes were not separated from each other. Fractional crystallization of the mixture of cyclooctadienes from CHCl₃/MeOH mixture gave an analytically pure sample of 13, which was characterized by single-crystal X-ray diffraction (Figure 1).

Further irradiation of compounds 13, 14 and 15 did not lead to any detectable photoproducts.

The success in preparing cyclobutane derivative 4 (n = 1) from the corresponding cinnamophane diester 3 (n = 1, quantitative yield) led us to attempt to prepare the corresponding cyclobutane dialdehyde derivative 16 (Scheme 6). Unfortunately, although this was the only product after 2 h of irradiation with a halogen 1 kW lamp, it appeared to be very unstable even below 0 °C, although it was stable enough for NMR identification. Wittig olefination of the irradiated mixture gave the divinylcyclobutane derivative 14 as the sole product and was isolable by column chromatography.

Interestingly, all three isomers of 10 (trans,trans-, cis,trans- and cis,cis-) under the above irradiation conditions furnish the same product: 16. It is hence likely that a rapid photoequilibration process precedes the ring closure to the final product.

Attempts to crystallize 14 from boiling ethanol led to a mixture of 14 and the cyclooctadiene derivative 15, which was separable by column chromatography. The divinylcyclobutane derivative 14 was completely converted into the cyclooctadiene derivative 15 within half an hour in boiling ethanol. The structure of 15 was confirmed by single-crystal X-ray analysis (Figure 2).

Molecules of 13 and 15 show common structural features. Despite the introduction of the new bridge C17–C24, the form of the original [2.2]paracyclophane is maintained to a considerable extent, with a flattened boat conformation of both six-membered rings (C4,5,7,8 and C12,13,15,16 remain essentially coplanar). However, the rings become significantly non-parallel (interplanar angles 14.4 and 13.4°, respectively). The new bridges C17–C24 are extremely long at 1.643(2) and 1.652(2) Å, respectively, even longer than the previously present bridges C1–C2 and C9–C10 at 1.57–1.60 Å. The steric crowding of 13 associated with the syn geometry is shown by,

Scheme 7: Cis–trans-isomerizations of the double bonds of the pseudo-geminal cyclophanes 11 and 19.

Figure 2: The molecule of compound 15 in the crystal. Ellipsoids correspond to 30% probability levels.

e.g., the short contact H18·H1A 1.91 Å; compound 15 has no intramolecular H···H < 2 Å.

From the stereochemical viewpoint the above photocyclizations are quite complex. Not only can the pseudo-geminal substituents in principle adopt different conformations in the ground state, because of possible rotation around the various σ-bonds, but this situation becomes even more intricate when the substrates are photochemically excited. For example, on photoexcitation diradicals 17 (Scheme 7) should be the intermediates in conceivable cis–trans-isomerizations, e.g., 11→18, and these diradicals could undergo very different subsequent reactions (in which, of course, it could also be of importance whether these intermediates are singlets or triplets).

To test for the possible formation of radical intermediates in the above photocyclizations, we decided to prepare the biscyclopropane analog of 11, the bisvinylcyclopropane 19 (or one of its cis-isomers) and subject this presumably strained hydrocarbon to our photocyclization conditions. Of course, this system also has various options to react, among them the photoisomerization to a mono- or all-cis-diastereomer. If this process took place, it would involve the diradical 20, which could isomerize to 21 with release of strain. The process could also occur a second time to provide a pseudo-geminally substituted [2.2]paracyclophane, now carrying two cyclopentenyl substituents. Should these ring-enlarged paracyclophanes
Scheme 8: Preparation of the vinylcyclopropanes 22–24.

not be observed, this would not necessarily constitute a proof against diradical(oid) intermediates in these reactions. However, if derivatives such as 21 were among the photoproducts the involvement of radicals in the photoisomerizations would be indicated.

We therefore reacted the bis-aldehyde 9 with the ylide prepared from cyclopropylcarbinyl triphenylphosphonium bromide and obtained in quantitative yield a product mixture consisting of the three possible diastereomers E,E-, E,Z- and Z,Z-22 (Scheme 8), the latter being the main product as is often observed in classical Wittig reactions (product ratio 1:13:31; analysis by 1H NMR spectroscopy, see Experimental). The main product was separated by silica gel chromatography and its structure determined by X-ray crystallography (Figure 3).

The two independent molecules in the asymmetric unit are similar, with an r.m.s. deviation of 0.3 Å for all non-H atoms. As would be expected, the substituents are directed outwards from the ring systems. The non-bonded distances C17–C22 and C18–C23, across which bonds are to be formed are 3.34, 3.35 and 5.12, 4.93 Å; clearly the latter, in particular, can be reduced by suitable rotations.

Irradiation of Z,Z-22 with a 1 kW halogen lamp in a Pyrex flask over 12 h (Scheme 8) gave only two [2 + 2] cycloaddition products: The hydrocarbons 23 and 24 in 3:5-ratio with a total yield of 70%. The isomers were separated by column chromatography and their structures established by NMR spectroscopy and single-crystal X-ray analysis (Figure 4 and Figure 5); no other products could be detected.

As for molecules 13 and 15, but to a slightly lesser extent, the newly formed bridges C17–22 in 23 and 24 are significantly longer than a standard single bond at 1.612(2) and 1.614(2) Å, respectively. On the other side of the four-membered rings, the bond lengths C18–23 relax to 1.563(2) and 1.559(2) Å. The interplanar angles between the six-membered rings of the original [2.2]paracyclophane unit are 12.9 and 12.7°.

These results clearly show that the photocyclization occurs from the conformation in which the two pseudo-geminal substituents are rotated away from the nearest ethano bridge (anti,anti-conformation). The conformation with both of these groups syn-


-oriented towards this bridge, although in principle possible, is evidently not populated. Although in the crystalline state a syn,anti-conformation is preferred (Figure 3), no reaction takes place from this orientation on irradiation in solution. Since we have already demonstrated that a comparable situation prevails for the simplest compound studied in this series, hydrocarbon 7 (Scheme 3), we conclude that reaction from this anti,anti-conformation is the generally preferred reaction mode for derivatives of type 3 (Scheme 2). The production of 24, however, proves that the stereochemical information contained in the first double bond (E or Z) can be lost in the course of the photo-chemical reaction. Whereas this Z→E-isomerization process must involve a diradical intermediate of type 17, its lifetime is evidently too short to allow ring-expansion as depicted in Scheme 7. Whether this process might be induced thermally (vinylcyclopropane→cyclopentene rearrangement; [23]) is an open question.

Conclusion

Although the detailed mechanisms of the photoisomerization of the tetrane 11 to the cyclooctadiene-bridged cyclophanes 13 and 15 and the isomerization of 22 to 23 and 24 remain to be established, these processes allow the introduction of a completely new type of additional bridge into [2.2]paracyclophanes. For several of these new polycyclic molecules interesting preparative applications are conceivable, and we hope to report about them in the not too distant future.

Experimental

General: Melting points: Büchi 530 melting point apparatus, uncorrected. Thin layer chromatography (TLC): Macherey–Nagel Polygram SiG/UV254. Column chromatography: Merck Kieselgel 60 (70–230 mesh). IR: Perkin–Elmer Macherey–Nagel Polygram SilG/UV254. Column chromatography (50 mL of silica, CH₂Cl₂, filtered and concentrated were dried over anhydrous Na₂SO₄, then the combined organic phases were decanted. The aqueous layer was washed with sat. aq. Na₂SO₄ solution (25 mL) with a modified oxidation step (Swern oxidation rather than the Dess–Martin protocol); 4,15-bis[E-2-formylvinyl]-[2.2]paracyclophane (trans,trans-10) was prepared according to [20]; cyclopropylmethyltriphenylphosphonium bromide was purchased from ABCR; methyltriphenylphosphonium bromide was purchased from Acros. Reagents were used without further purification. Solvents used were of analytical grade; anhydrous THF was distilled from an LiAlH₄ dispersion with triphenylmethane as indicator.

4,15-Divinyl[2.2]paracyclophane (7): A freshly prepared solution of potassium tert-butoxide (4.26 g, 38.0 mmol) in anhydrous THF (50 mL) was added dropwise over 30 min to a cooled (ice/water bath), vigorously stirred dispersion of methyltriphenylphosphonium bromide (14.29 g, 40.0 mmol) in anhydrous THF (25 mL) under a N₂ atmosphere. The bath was re-cooled to 0 °C, after which a solution of 9 (2.64 g, 10.0 mmol) in anhydrous THF (30 mL) was added dropwise over 1 h. The mixture was left to stir in the melting ice/water bath overnight and sat. aq. Na₂SO₄ solution (25 mL) added with vigorous stirring. The mixture was stirred for 15 min and the organic layer decanted. The aqueous layer was washed with THF (3 × 20 mL, decanting), then the combined organic phases were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a solid residue (6.4 g). Column chromatography (50 mL of silica, CH₂Cl₂) gave 2.60 g (10 mmol, 100%) of pure hydrocarbon 7. ¹H NMR (200 MHz, CDCl₃) δ 6.81 (dd, 2H, J₁ = 10.9, J₂ = 17.4 Hz), 6.60–6.40 (m, 6H), 5.36 (dd, 2H, J₁ = 1.5, J₂ = 17.4 Hz), 5.08 (dd, 2H, J₁ = 1.5, J₂ = 10.9 Hz), 3.60–3.40 (m, 2H), 6.30–3.80 (m, 2H), 5.05–2.88 (m, 6H) ppm; ¹³C NMR (50.3 MHz, CDCl₃) δ 139.3, 138.0, 137.2, 135.5 (+), 134.6 (+), 132.4 (+), 129.8 (+), 114.6 (+), 35.0 (−), 32.5 (−) ppm; MS (EI, 70 eV) m/z (%): 261 (8), 260 (34), 131 (36), 130 (39), 129 (100), 128 (24), 115 (34).

4,15-bis(butadien-1-yl)[2.2]paracyclophane (11): A freshly prepared solution of potassium tert-butoxide (2.69 g, 24.0 mmol) in anhydrous THF (50 mL) was added dropwise over 30 min into the cooled (ice/water bath), vigorously stirred dispersion with triphenylmethane as indicator.
sion of methyltriphenylphosphonium bromide (8.57 g, 24.0 mmol) in 50 mL of anhydrous THF under a N₂ gas flow. The bath was removed and the mixture was stirred for 1 h at ambient temperature, then re-cooled to 0 °C, after which a solution of 10 (0.95 g, 3.0 mmol) in anhydrous THF (30 mL) was added dropwise over 1 h. The bath was removed and the mixture was stirred for an additional 2 h. The resulting mixture was poured into a vigorously stirred mixture of ice (200 g), water (100 mL) and conc. (37%)aq. HCl solution (100 mL), and the mixture stirred until the ice had completely melted. The precipitate was suction filtered on a glass frit, washed with dilute (1:3)aq. HCl (3 × 30 mL) and water (3 × 30 mL), and dissolved in CH₂Cl₂ (100 mL). The organic solution was dried over Na₂SO₄, filtered and concentrated under reduced pressure without warming to give a colorless solid residue (0.94 g, 3.0 mmol, 100%) of hydrocarbon 11, pure by NMR analysis. 1H NMR (200 MHz, CDCl₃) δ 6.60–6.24 (m, 2H), 5.28–4.89 (m, 4H), 3.57–3.28 (m, 2H), 3.11–2.74 (m, 6H) ppm; 13C NMR (50.3 MHz, CDCl₃) δ 138.7, 137.1 (+), 136.9, 136.7, 134.1 (+), 131.5, 131.1 (+), 129.7 (+), 129.2 (+), 116.1 (+), 34.4 (+), 32.0 (–) ppm.

Irradiation of 4,15-dibutadien-1-yl[2.2]paracyclophane – [2.2.2]tricyclophanes 13, 14 and 15. The solution of 11 (230.0 mg, 736 µmol) was irradiated by UV-lamp for 20 h. When the starting material was completely consumed (TLC monitoring), the reaction mixture was separated by column chromatography (silica, pentane) to give 14.3 mg of bis-vinyl derivative 14 and 145.8 mg of the mixture of cyclooctadienyl derivatives 13 and 15. Total yield 160.1 mg (70%).

Bis-vinyl derivative 14: 1H NMR (200 MHz, CDCl₃) δ 6.48 (dd, 2H, J₁ = 1.73, J₂ = 7.79 Hz), 6.35 (d, 2H, J = 1.73 Hz), 6.23 (d, 2H, J = 7.79 Hz), 6.33–6.15 (m, 2H), 5.21–5.05 (m, 4H), 4.28–4.17 (m, 2H), 3.70–3.33 (m, 2H), 3.07–2.69 (m, 6H) ppm; 13C NMR (50.3 MHz, CDCl₃) δ 140.1, 139.8, 139.5, 139.3 (+), 134.1 (+), 133.2 (+), 128.6 (+), 115.0 (–), 49.1 (+), 40.1 (+), 36.4 (–), 32.5 (–) ppm; MS (EI, 70 eV) m/z (%): 312 (8), 157 (31), 156 (41), 155 (100), 142 (12), 141 (56), 129 (16), 128 (21), 115 (16).

Anti-cyclooctadiene derivative 15: 1H NMR (600 MHz, CDCl₃) δ 6.45 (dd, 2H, J₁ = 1.84, J₂ = 7.80 Hz), 6.41 (d, 2H, J = 1.84 Hz), 6.31 (d, 2H, J = 7.80 Hz), 6.05–6.00 (m, 2H), 5.94–5.88 (m, 2H), 4.89–4.82 (m, 2H), 3.39–3.29 (m, 2H), 3.19–3.09 (m, 2H), 3.06–2.96 (m, 2H), 2.92–2.83 (m, 2H), 2.78–2.68 (m, 2H), 2.34–2.26 (m, 2H) ppm; 13C NMR (150.9 MHz, CDCl₃) δ 143.6, 140.2, 139.4, 136.6 (+), 132.9 (+), 131.4 (+), 130.7 (+), 128.8 (–), 48.5 (+), 36.3 (–), 33.3 (–), 27.2 (–) ppm; MS (EI, 70 eV) m/z (%): 312 (19), 157 (33), 156 (40), 155 (100), 142 (12), 141 (55), 129 (18), 128 (22), 115 (17). Syn-cyclooctadiene derivative 13: 1H NMR (200 MHz, CDCl₃) δ 6.40 (dd, 2H, J₁ = 1.68, J₂ = 7.92 Hz), 6.30 (d, 2H, J = 1.68 Hz), 6.19 (d, 2H, J = 7.92 Hz), 5.91–5.72 (m, 4H), 4.57–4.40 (m, 2H), 3.39–3.22 (m, 2H), 3.19–2.83 (m, 4H), 2.82–2.49 (m, 4H), 2.33–2.11 (m, 2H) ppm; 13C NMR (50.3 MHz, CDCl₃) δ 144.6, 139.7, 139.6, 139.4 (+), 134.4 (+), 130.8 (+), 130.4 (+), 129.5 (+), 54.2 (+), 36.4 (+), 33.6 (+), 27.7 (–) ppm; MS (EI, 70 eV) m/z (%): 312 (20), 157 (31), 156 (42), 155 (100), 142 (11), 141 (58), 129 (16), 128 (25), 115 (14).

4,15-Bis[(Z)-2-cyclopentylvinyl][2.2]paracyclophane (22): A freshly prepared solution of potassium tert-butoxide (898 mg, 8.0 mmol) in anhydrous THF (30 mL) was added dropwise over 30 min to a cooled (ice/water bath), vigorously stirred dispersion of cyclopropylmethyltriphenylphosphonium bromide (3178 mg, 8.0 mmol) in 30 mL of anhydrous THF under a N₂ gas flow. The bath was removed and the mixture stirred for 1 h at ambient temperature, then re-cooled to 0 °C, after which a solution of 9 (264 mg, 1.0 mmol) in anhydrous THF (30 mL) was added dropwise over 1 h. The bath was removed and the mixture stirred for an additional 2 h. The resulting mixture was poured into a vigorously stirred mixture of ice (100 g), water (50 mL) and conc. (37%)aq. HCl solution (50 mL) and the mixture stirred until the ice had completely melted. The precipitate was suction filtered on a glass frit, washed with dilute (1:3)aq. HCl (3 × 30 mL) and water (3 × 30 mL), and dissolved in CH₂Cl₂ (50 mL): The organic solution was dried over Na₂SO₄, filtered and concentrated under reduced pressure without warming to give a colorless solid residue (333 mg, 98%) of hydrocarbon 22, as a mixture of stereoisomers, pure by NMR. 1H NMR (200 MHz, CDCl₃) δ 6.53–6.26 (m, 8H), 5.35 (dd, 0.04H, J₁ = 8.6, J₂ = 15.5 Hz), 5.24 (dd, 0.30H, J₁ = 8.7, J₂ = 15.6 Hz), 4.77 (dd, 1.36H, J₁ = 10.3, J₂ = 11.3 Hz), 4.75 (dd, 0.30H, J₁ = 10.3, J₂ = 11.5 Hz), 3.59–3.32 (m, 2H, 3.07–2.69 (m, 6H), 1.59–1.33 (m, 2H), 0.88–0.17 (m, 8H) ppm; 13C NMR for main isomer (50.3 MHz, CDCl₃) δ 138.0, 137.4, 136.6, 135.0 (+), 133.6 (+), 132.9 (+), 130.9 (+), 126.5 (+), 34.4 (–), 32.7 (–), 10.4 (+), 6.8 (–), 6.5 (–) ppm; MS (EI, 70 eV) m/z (%): 340 (19), 171 (21), 170 (23), 169 (100), 155 (38), 142 (23), 141 (32), 129 (62), 128 (26), 115 (11).

Irradiation of 4,15-Bis[(Z)-2-cyclopentylvinyl][2.2]paracyclophane – [2.2.2]tricyclophanes 23 and 24: A solution of 22 (51.0 mg, 150 µmol) was irradiated by a halogen torch lamp from a distance of 15 cm for 12 h. When the starting material had been completely consumed (TLC monitoring), the reaction mixture was separated by column chromatography (silica gel, pentane) to give 13.4 mg of cis-[2.2.2]tricyclophane 23 and 22.3 mg of trans-[2.2.2]tricyclophane 24; total yield: 35.7 mg (70%).
Cis-[2.2.2]tricyclophane derivative (23): 1H NMR (200 MHz, CDCl\textsubscript{3}) δ 7.08 (d, 2H, J = 1.8 Hz), 6.46 (dd, 2H, J\textsubscript{1} = 1.8, J\textsubscript{2} = 7.8 Hz), 6.21 (d, 2H, J = 7.8 Hz), 4.53–4.41 (m, 2H), 3.21–2.89 (m, 6H), 2.69–2.29 (m, 2H), 1.66–1.48 (m, 2H), 0.79–0.64 (m, 2H), 0.59–0.46 (m, 2H), 0.24–0.09 (m, 4H) ppm; 13C NMR (50.3 MHz, CDCl\textsubscript{3}) δ 141.4, 140.5, 140.2, 136.4 (+), 133.6 (+), 127.9 (+), 48.4 (+), 46.8 (+), 36.5 (+), 33.3 (+), 9.8 (+), 7.8 (+), 4.7 (+) ppm; MS (EI, 70 eV) m/z (%): 340 (15), 171 (22), 170 (21), 169 (100), 155 (27), 142 (11), 141(19), 129 (44), 128 (20), 115 (11).

Trans-[2.2.2]tricyclophane derivative (24): 1H NMR (200 MHz, CDCl\textsubscript{3}) δ 6.44 (dd, 2H, J\textsubscript{1} = 1.7, J\textsubscript{2} = 7.8 Hz), 6.19 (d, 2H, J = 7.8 Hz), 6.15 (d, 2H, J = 1.7 Hz), 4.16–4.00 (m, 2H), 3.26–2.89 (m, 4H), 2.60–2.45 (m, 2H), 2.26–2.10 (m, 2H), 1.48–1.31 (m, 2H), 0.74–0.41 (m, 4H), 0.30–0.07 (m, 4H) ppm; 13C NMR (50.3 MHz, CDCl\textsubscript{3}) δ 141.4, 140.5, 140.2, 136.4 (+), 133.6 (+), 129.0 (+), 50.3 (+), 41.7 (+), 37.0 (+), 33.2 (+), 13.5 (+), 5.2 (+), 4.1 (+) ppm; MS (EI, 70 eV) m/z (%): 340 (15), 171 (21), 170 (21), 169 (100), 155 (27), 142 (11), 141(19), 129 (44), 128 (20), 115 (10).

X-ray structure determination
Numerical details are presented in Table 1. Data collection and reduction: Crystals were mounted in inert oil on glass fibres and transferred to the cold gas stream of the appropriate Oxford diffractometer. Measurements were performed with monochromatic Mo-K\textalpha\ radiation (\(\lambda = 0.71073 \AA\); 23) or mirror-focussed Cu-K\textalpha\ radiation (\(\lambda = 1.54184 \AA\); all others). Absorption corrections were performed for the Cu data sets only, on the basis of multiscan. Structure refinement: The structures were refined anisotropically against \(F^2\) (program SHEXL-97 [25]). Hydrogen atoms were included with a riding model. Exceptions and special features: For 23, hydrogen atoms of the three- and four-membered rings were refined freely but with C–H distance restraints. For (Z,Z)-22 and 23, which crystallize in non-

Table 1: Crystallographic data for compounds 13, 15, (Z,Z)-22, 23 and 24.

<table>
<thead>
<tr>
<th>Compound</th>
<th>13</th>
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<th>(Z,Z)-22</th>
<th>23</th>
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<td>C\textsubscript{24}H\textsubscript{24}</td>
<td>C\textsubscript{26}H\textsubscript{28}</td>
<td>C\textsubscript{26}H\textsubscript{28}</td>
<td>C\textsubscript{26}H\textsubscript{28}</td>
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<td>(M_r)</td>
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<td>312.43</td>
<td>340.48</td>
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<tr>
<td>Habit</td>
<td>colourless prism</td>
<td>colourless plate</td>
<td>colourless tablet</td>
<td>colourless tablet</td>
<td>colourless tablet</td>
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<tr>
<td>Cryst. size (mm)</td>
<td>0.2 × 0.1 × 0.08</td>
<td>0.08 × 0.06 × 0.015</td>
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centrosymmetric space groups, anomalous scattering was negligible and Friedel opposite reflections were therefore merged. For 24, the atoms C23–26 show a slight (9%) disorder. The disorder model was refined using a system of similarity restraints. Dimensions of the minor disorder component should be interpreted with great caution.

Crystallographic Data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications no. CCDC-797335 (13), -797336 (15), -797337 (Z), -797338 (23), -797339 (24). Copies of the data can be obtained free of charge from http://www.ccdc.cam.ac.uk/data_request/cif.

References


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Fine-tuning alkyne cycloadditions: Insights into photochemistry responsible for the double-strand DNA cleavage via structural perturbations in diaryl alkyne conjugates

Wang-Yong Yang, Samantha A. Marrone, Nalisha Minors, Diego A. R. Zorio and Igor V. Alabugin*

Abstract
Hybrid molecules combining photoactivated aryl acetylenes and a dicationic lysine moiety cause the most efficient double-strand (ds) DNA cleavage known to date for a small molecule. In order to test the connection between the alkylating ability and the DNA-damaging properties of these compounds, we investigated the photoreactivity of three isomeric aryl–tetrafluoropyridinyl (TFP) alkenes with amide substituents in different positions (%-, m-, and p-) toward a model π-system. Reactions with 1,4-cyclohexadiene (1,4-CHD) were used to probe the alkylating properties of the triplet excited states in these three isomers whilst Stern–Volmer quenching experiments were used to investigate the kinetics of photoinduced electron transfer (PET). The three analogous isomeric lysine conjugates cleaved DNA with different efficiencies (34, 15, and 0% of ds DNA cleavage for p-, m-, and o-substituted lysine conjugates, respectively) consistent with the alkylating ability of the respective acetamides. The significant protecting effect of the hydroxyl radical and singlet oxygen scavengers to DNA cleavage was shown only with m-lysine conjugate. All three isomeric lysine conjugates inhibited human melanoma cell growth under photoactivation: The p-conjugate had the lowest CC_{50} (50% cell cytotoxicity) value of 1.49 × 10^{-7} M.

Introduction
Triggering chemical processes with light offers numerous practical advantages. Not only does photochemistry open an additional dimension for the control of chemical reactivity by enabling many, otherwise impossible, synthetic transformations, but this mode of activation also provides useful spatial and temporal control of chemical processes that are required to
occur in the right place and at the right time. Such selectivity is particularly useful in biological applications such as cancer therapy where it accounts for the increasing importance of photodynamic therapy and related methods [1-11]. Previously, we expanded our studies of alkyne reactivity [12-23] to the design of photoactivated DNA cleavers, which combine a DNA-damaging part derived from diaryl alkynes and benzannelated enediynes with a cationic DNA-binding moiety.

The hybrid molecules that combined photoactivated alkynes with a dicaticionic moiety derived from lysine (C-lysine conjugates in Figure 1) displayed a combination of unique properties such as the ability to cause true double-strand (ds) DNA cleavage [24], amplification of ds cleavage dramatically at the lower pH of cancer cells [25], as well as the ability to recognize terminal phosphate monoester groups at the site of initial single-strand (ss) DNA damage and convert it into the more therapeutically important ds DNA damage [26].

We have shown that these compounds also could break intercellular DNA [27] and induce >90% cancer cell death at concentrations as low as 10 nM [25]. In spite of these remarkable properties, the mechanism of DNA cleavage by photoactivated alkynes and enediynes is still not fully understood.

Some light has been shed on the mechanism by the sequence selectivity of DNA cleavage in internally labeled DNA oligomers [28]. All enediyne-, alkyne-, and fulvene-based lysine conjugates displayed G-selective cleavage, especially at GG and GGG sites adjacent to the AT-tract, the preferred binding location for protonated amines. The G-selectivity is typical for oxidative DNA damage via PET for the most easily oxidized base, guanine. However, a noticeable amount of cleavage at a single G site in the AT-rich region is not consistent with purely oxidative DNA damage in the presence of spatially close GG and GGG sites, both of which are better sinks for the transient hole in the DNA. This observation suggests the presence of competitive DNA-cleavage mechanisms, such as guanine alkylation [29-35], which combine with the oxidative DNA damage to account for the efficient ds cleavage of plasmid DNA.

In the case of enediyne conjugate 2, the additional DNA-cleavage mechanism may be provided by either photo-Bergman cyclization [3,36-44] (akin to such well-known DNA cleavers as enediyne antibiotics) [45,46] or C1–C5 cyclization [47-52] (Figure 2). In the latter process, which transforms enediynes into indenes, four hydrogens are transferred from the environment (two as H-atoms and two as protons), and thus DNA can be damaged via H-atom abstraction in a particularly efficient manner.

Efficient DNA cleavage by the monoacetylene conjugate 1, which is capable of neither Bergman nor C1–C5 cyclization, suggests that other scenarios are possible and a more detailed understanding of alkyne photochemistry is vital for unraveling the mechanistic scenarios that account for DNA cleavage by these compounds (Figure 3) [25].

As illustrated in Figure 3, multiple reaction pathways are potentially unlocked by the photoactivation of alkyne conjugates. In the past, we observed dramatic differences in reactivity as a result of structural perturbations in the aryl moiety of diaryl alkynes. For example, introduction of strongly acceptor TFP substituents at the alkyne terminus changed the cyclization direction from the photo-Bergman closure to the C1–C5 cyclization due to the change in the nature of the key photo-physical step and the involvement of PET from 1,4-cyclohexadiene (1,4-CHD) to the enediyne excited singlet state. In contrast, substituents that accelerate the intersystem crossing (ISC) through a “phantom state” effect [53-55] direct reactivity along an alternative triplet cycloaddition pathway.

Our previous mechanistic studies suggested that neither singlet oxygen nor diffusing oxygen- and carbon-centered radical species play a significant role under the conditions where the most efficient ds cleavage by monoalkynes is observed (pH 6) [25]. From the narrowed list of mechanistic scenarios, base

Figure 1: Structure of C-lysine conjugates.
alkylation remains a likely origin of the photodamaging ability of such alkynes. Such reactivity is consistent with the above-mentioned ability of alkynes to act as electrophilic alkylating agents toward electron-rich π-systems observed in triplet photocycloaddition of TFP-substituted diaryl acetylenes [53].

The mechanism of triplet photocycloaddition involves a sequence of radical closures initiated by the formation of a triplet 1,4-diradical via the reaction of 1,4-CHD and the alkyne π,π*-triplet state. Although several plausible mechanistic pathways converge at the same homoquadricyclane product in Scheme 1, the maximum quantum yield of 0.50 along with the DFT activation barriers at the triplet hypersurface suggest that 5-exo-trig attack of electrophilic vinyl radical at the remaining 1,4-CHD double bond is the most likely subsequent step. Because this photocycloaddition occurs from the triplet state, the competition between triplet and singlet-state reactivity is likely to be important for the specifics of DNA photodamage. In particular, this competition would control the relative impor-

Figure 2: Alternative pathways of enediyne photoreactivity: photo-Bergman cyclization (left), C1–C5 cyclization (right), and triplet photocycloaddition (bottom). TFP = tetrafluoropyridinyl.
Scheme 1: Proposed mechanism of photocycloaddition of acetylene with 1,4-CHD.

Conjugates 1, 6, and 7 were prepared via coupling of the corresponding anilines 10a–c with Boc-protected lysine in the presence of POCI₃ in pyridine. The Boc groups were removed by treatment with gaseous HCl in MeOH.

Photochemical reactions of TFP-alkynes with 1,4-cyclohexadiene
Previously, Zeidan and Alabugin have shown that TFP-substituted aryl alkynes are powerful photochemical alkylating agents and attack a variety of π-systems (Scheme 3) [58].

We chose 1,4-CHD to probe alkyne photoreactivity because, similar to excited alkynes, 1,4-CHD displays multichannel reactivity and can act as a source of H-atoms, as a source of electrons in PET, or as a reactive π-system. Photocycloaddition of the three acetylene molecules with 1,4-CHD was investigated via irradiation in acetonitrile with a Luzchem LED photoreactor and UVB (310 nm) irradiation (Scheme 4). The m-substituted acetylene 4 provided the homoquadricyclane product 12 in 42% yield after 2 h of UV irradiation in the presence of 100 equiv of 1,4-CHD. Under the same conditions, the p-substituted acetylene 3 reacts with 1,4-CHD sluggishly and gave <5% of product after 8.5 h of UV irradiation according to the ¹H NMR spectrum of the reaction mixture. This observation suggests that the ISC to the triplet state with m-acetamidyl
Figure 4: \( p \), \( m \), and \( o \)-amidyl acetylenes and respective lysine conjugates.

Scheme 2: Synthesis of amido-substituted monoacetylenes and lysine conjugates. Reagents and conditions: a. \( \text{PdCl}_2(\text{PPh}_3)_2, \text{CuI} \), \( \text{HCCSiMe}_3/\text{Et}_3\text{N}, \text{rt} \); b. \( \text{CsF}, \text{pentfluoropyridine/DMF} \); c. \( \text{SnCl}_2, \text{EtOH}, \text{reflux} \); d. \( \text{(CH}_3\text{CO})_2\text{O}, \text{Et}_3\text{N/CH}_2\text{Cl}_2 \); e. \( \text{POCl}_3, \text{Boc-Lys(Boc)-OH/pyridine} \); f. \( \text{HCl(g)/MeOH} \).

Acetamides:

Ph-TFP

Acetylene 4 is more efficient than with \( p \)-acetamidyl acetylene 3, the lifetime of the triplet of 4 is longer than that of 3, or the triple state of 4 is more electrophilic than the triplet state of 3. However, when the reaction was repeated in neat 1,4-CHD, the corresponding homoquadricyclane product 11 was isolated in 95% yield after only 1 h of UV irradiation. This result indicates that the photoaddition reaction of 3 can occur efficiently under more favorable conditions when there is a higher probability of intercepting the reactive excited state via reaction with a \( \pi \)-system.

The photochemical reactivity for the \( o \)-substituted acetylene 5 was drastically changed (Scheme 5). In this case, photoexcitation leads to the formation of an oxygen–carbon bond between the amide group and the triple bond. The cyclized product, benzoxazepine 13, and the ketone product 14 were isolated. Whereas 13 was produced by a 7-endo cyclization (unprecedented in these systems), the ketone 14 can be formed either by direct hydration of the alkyne or by a known pathway that involves the corresponding six-membered product, a benzoxazine. The formation of benzoxazines has been previously reported by Roberts and coworkers, who suggested cyclization via triplet excitation following hydration [59-62]. The presence of vinyl peaks at 6.2 and 5.9 ppm in the reaction mixture and their quick disappearance upon the addition of a drop of water...
Scheme 3: Photochemical reactions of TFP-substituted aryl alkynes with selected π-systems. In short, the reaction proceeds through the photoinduced electron transfer from thiophene to the singlet excited state of the diaryl acetylene. The initially formed cyclobutene product undergoes further photorearrangement via a formal 1,3-shift.

Scheme 4: Photocycloaddition of amido acetylenes with 1,4-CHD.

suggest that benzoxazines are also the intermediate products in our case but are rapidly hydrolyzed during work-up and purification. Although one can suggest the intermediacy of the triplet diradical in the photocyclization of o-amido acetylene 6, this transformation does not require H-atom abstraction from an external H-atom source such as CHD and DNA, and thus the DNA-damaging ability of this chromophore is not expected to be significant.

Photophysics and kinetics of photoinduced electron transfer
The fluorescence quenching by triethylamine (Et$_3$N) was examined in order to gauge the relative efficiencies of these compounds as DNA photo-oxidizers (Figure 5).

In the quenching experiments, the meta-isomer 4 showed the largest Stern–Volmer constant ($K_{sv} = 45.51$) among the three
Scheme 5: Possible mechanism for photochemical hydration of diaryl acetylene moiety catalyzed by the ortho-amide substituent.

Figure 5: Stern–Volmer plots of three regioisomers, 3 (blue diamond), 4 (red square), and 5 (green triangle), in acetonitrile (10 μM). The solutions were excited at 310 nm.

Figure 6: Absorption spectra of three isomers, 3, 4, 5, and Ph-TFP in acetonitrile (10 μM).

The two- to three-fold increase in the rate of electron transfer from Et<sub>3</sub>N to the excited singlet state of the meta- and ortho-isomers in comparison to the para-isomer is consistent with the well-known photochemical ortho, meta effect of an acceptor substituent [56,57].

Although the fluorescence of all three isomers is quenched by the amine, the efficient quenching of singlet excitation in compound 4 can potentially lead to a stronger pH-dependency on the photochemistry of the respective lysine conjugate, which is controlled by the protonation-gated intramolecular electron transfer from the α-amino group [25]. Interestingly, the meta-isomer has a noticeably longer singlet lifetime than the other two isomers. A similar trend has been previously observed for the lifetimes of m-substituted enediynes [63].

The absorption spectra of all four acetylenes are shown in Figure 6. The core Ph-TFP-acetylene (Ph-TFP) chromophore without the amide group has no significant absorption at >320 nm.
The lowest absorptions of the para- and ortho-isomers 3, 5 are red-shifted ($\lambda_{\text{max}} \sim 330$ nm) as a consequence of increased conjugation in the ground state. In contrast, the absorption of the meta-isomer 4 is closer to that of Ph-TFP, with the lower energy absorption band appearing as a lower-intensity shoulder.

Efficiency of DNA photocleavage

The results of plasmid relaxation assay with three lysine conjugates are summarized in Figure 7.

Figure 7: Quantified DNA cleavage data for 1 (a), 6 (b) and 7 (c). Blue: Form I (supercoiled) DNA; red: Form II (relaxed) DNA; green: Form III (linear) DNA. Reported values represent the average of four experiments.

These experiments were carried out on 15 μM of lysine conjugate with 30 μM/base pair of pBR322 plasmid DNA at pH 6, 7 and 8. The DNA-cleaving ability of conjugates does not directly follow the order of the photocycloaddition of their acetamides. Although the m-substituted acetylene was more photoreactive toward 1,4-CHD, the corresponding conjugate 6 produced less DNA cleavage than conjugate 1. This suggests that either the difference in DNA binding overshadows the intrinsic differences in reactivity or the acetamide group is not a good surrogate for the lysine amides [64].

Nevertheless, both p- and m-lysine conjugates exhibit efficient ds DNA damage at pH 6 where the a-amino group of the lysine moiety is protonated and incapable of direct interference with the singlet photochemical process. On the other hand, compound 7, which is unlikely to be a strong alkylating agent in the excited state, was the least-efficient DNA cleaver and did not produce any ds breaks. Interestingly, all three C-lysine conjugates broke DNA more efficiently at lower pH.

Effects of radical scavengers on DNA cleavage

In order to get further insight into the mechanism of the DNA cleavage by the three conjugates, we used the plasmid relaxation assays for the cleavage with conjugates 1, 6, and 7 in the presence of hydroxyl radicals (glycerol, DMSO) and singlet oxygen (NaN$_3$) scavengers [65]. The results are summarized in Figure 8.

For compound 1 (Figure 8a), the hydroxyl radical scavengers have no effect at pH 6 while the singlet oxygen scavenger slightly decreases the amount of ds DNA cleavage. At pH 8, >10% of the protecting effect was observed for all of the scavengers. The protecting effect of the scavengers on the reactivity of conjugate 1 is insignificant considering the very large excess (>1000-fold) of the scavengers. Conjugate 1 still leaves no undamaged DNA and produces significant amounts of linear DNA at pH 6. This observation suggests that the main DNA damage mechanism by conjugate 1 is not sensitive to the presence of hydroxyl radical/singlet oxygen scavengers, which can only block the alternative minor mechanisms.

In contrast, the photocleavage by the meta-substituted conjugate 6 (Figure 8b) is inhibited by both types of scavengers among the three conjugates at pH 6. The hydroxyl radical scavengers, glycerol and DMSO, protected DNA from the cleavage by 33 and 26%, respectively, whereas NaN$_3$ showed ~43% protection. The large protecting effect of NaN$_3$, the singlet oxygen scavenger, is consistent with the efficient photoaddition reaction of its chromophore via triplet excitation. This suggests that m-conjugate is not tightly bound to DNA and the most damage is propagated via two different oxygen-centered species, likely to be generated via the triplet manifold. The hydroxyl radical scavengers protected DNA from ss DNA.
cleavage by compound 7, but the effect was small (Figure 8c). Only glycerol at pH 6 and glycerol and DMSO at pH 8 showed ~10% of protection. Little effect was observed for NaN₃, suggesting that the formation of singlet oxygen via triplet energy transfer is inefficient, possibly because of a short triplet lifetime and fast intramolecular photocyclization. The observed scavenger effects suggest different DNA damage mechanisms for the three lysine conjugates: Guanine oxidation and/or base alkylation for conjugate 1, guanine oxidation and generation of reactive oxygen species for conjugate 6, and guanine oxidation for conjugate 7.

Cell proliferation assay

The ability of compounds 1, 6, and 7 to inhibit cell proliferation in human melanoma cell lines was tested in the dark and under photoactivation (Figure 9).

According to the control experiments with all three conjugates in the dark, these compounds do not inhibit cell proliferation at concentrations of <1 μM. On the other hand, conjugate 1 displayed strong phototoxicity toward the human melanoma A375 cell line in the nanomolar range (CC₅₀ = 1.49 × 10⁻⁷ M) after 10 min of UV irradiation at 360 nm. Conjugates 6 and 7 also showed some phototoxicity. This result of cell proliferation inhibition by the conjugates is consistent with their respective DNA-cleaving abilities.

Conclusion

Three isomeric aryl-TFP alkynes with amide substituents in different positions (o-, m-, and p-) were synthesized, and the variations of their photochemical reactivity toward cyclohexadiene were investigated. Only p- and m-isomers were capable of alkylation 1,4-CHD. In contrast, the o-isomer only underwent an intramolecular reaction. The three analogous isomeric lysine conjugates cleaved DNA with different efficiencies: 15 μM of
the \( p \), \( m \), and \( o \)-conjugates 1, 6, and 7 produced 34, 15, and 0\% of ds DNA cleavage, respectively. The large DNA-protecting effect on reactivity of the \( meta \)-conjugate 6, imposed by hydroxyl radical/singlet oxygen scavengers, suggests triplet photoreactivity which leads to efficient sensitization of singlet oxygen. This observation is consistent with the efficient triplet reactivity of its chromophore. The inhibition of human melanoma cell growth by the three conjugates was also tested. The \( para \)-substituted conjugate 1 has the lowest CC\(_{50} \) value of \( 1.49 \times 10^{-7} \) M.

Supporting Information

Supporting information features details for experimental procedures, emission titration spectra, fluorescence decay traces, picture of plasmid relaxation assay, characterization data, and NMR spectra (\( ^{1}H \), \( ^{13}C \) NMR, HSQC, and HMBC).

Supporting Information File 1

Experimental details, characterization data, emission titration spectra, fluorescence decay traces, plasmid relaxation assays and NMR spectra (\( ^{1}H \), \( ^{13}C \) NMR, HSQC, and HMBC).

[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-93-S1.pdf]

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References


64. We have shown before that the α-amino group (which is missing in the acetamides) has an effect on the reactivity. See Ref. [25].

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