Photochemical Transformations of Proteinogenic and Non-Proteinogenic Amino Acids

Axel G. Griesbeck*

Abstract. The photochemistry of N-activated enantiomerically pure \( \alpha \)-amino acids is described with emphasis on chemo-, regio-, stereo-, and spin selectivity. An especially valuable chromophore is the phthalimido group. The first excited singlet states are short-lived and deactivated (chemically) via homolytic CH cleavage or (physically) via electron-transfer steps. The first excited triplet states are chemically deactivated via electron-transfer reactions and subsequent deprotonation/coupling steps. A wide variety of product types were synthesized, and potential target molecules were available by tuning the reaction conditions. Also remote groups can be activated by means of electron-transfer steps, which represents an attractive new synthetic protocol for macrocyclization.

1. Introduction

Amino acids can be photochemically activated by means of chromophoric groups at the nitrogen and the carbon terminus, respectively. Whereas for C-activation only little is known, N-activation via acylation is a straightforward and well-studied method, especially in functional group protection chemistry. An especially promising chromophore is the phthalimido group, the photophysics of which has been intensively studied in the last two decades. The major advantages are: long-wavelength-shifted absorption (300–320 nm), low reduction potential (\(-1.4 \text{ V vs. SCE in acetonitrile}\)), and clear single/triplet differentiation (short-lived \( ^1\pi\pi^* \), long-lived \( ^3\pi\pi^* \)) which is a prerequisite for spin-selective transformations. Phthalimide groups can be easily introduced using a variety of chemical methods without loss of enantiomeric purity of the chiral starting materials.

2. Results and Discussion

2.1. Unprotected N-Phthaloyl-Amino Acids

2.1.1. Photodecarboxylation: Gly, Ala, Abu, Val, Leu, Ile, Phe, Asp, Glu

Photodecarboxylation is the dominant pathway for C-protected N-phthaloyl-\( \alpha \)-amino acids 1 (Scheme 1). This reaction had already been described by Kanaoka and coworkers [1]. We could confirm this observation for H-atom as well as D-atom transfer [2]. The irradiation could be performed by triplet sensitization (acetone or benzophenone) or by direct excitation in solution (e.g., in acetonitrile) or in the solid state. Secondary photoreactions were not observed in the alanine, the phenylalanine, and the phenylglycine case, whereas amino-acid derivatives with longer linear or branched alkyl chains did show additional reactivity. Essential for this efficient reaction seems to be a H-bond in the ground state of the substrate. The most favorable geometry for a strong H-bonding interaction is the seven-membered ring formed intramolecularly in N-acylamino acids. Larger ring systems are less favorable, and consequently, \( \beta \)-alanine or higher derivatives of \( \alpha \)-amino acids were completely photostable under the reaction conditions. In the cases of the glutamic-acid and the aspartic-acid derivatives (R = \((\text{CH}_2)_n\text{COOH}\) with \(n = 1, 2\) ) selective decarboxylation of the \( \alpha \)-carboxy group was achieved without further decarboxylation of the \( \beta \)- or \( \gamma \)-carboxy group.

Racemic products 2 were formed from chiral (enantiomerically pure) deuterated substrates as was proven at the stage of the free \( \alpha \)-[\( ^2\text{H} \)]-amines. Thus, \( \pm \)-\( \alpha \)-[\( ^2\text{H} \)]-benzylationine is available from phenylglycine in 60% yield. From quenching and sensitization experiments was concluded that...
this reaction is initiated by a triplet-sensitized excited state proton-transfer (ESPT)/electron-transfer sequence followed by extrusion of CO₂ and H-(back) migration. Since remote carboxyl groups do not form the H-bond mentioned above, this initial proton-transfer step is less probable.

2.1.2. Electron-Transfer Chemistry

Interfering: Met and Cys, Ser and Thr, Tyr and DOPA

During our investigation on the photodecarboxylation of C-unprotected α-amino acids, methionine became a substrate of central importance. This amino acid is an useful precursor to vinylglycine in an elegant thermal reaction and we tried to develop a similar efficient photochemical route. There existed already a literature report about the quantitative photodecarboxylation of phthaloylmethionine (PHT = Met 3) [1]. When repeating this experiment, however, we found an unusual behavior: 3 is stable when irradiated in acetonitrile and cyclized to the tetracyclic product 4 when irradiated in acetone or acetonitrile in the presence of benzophenone [3] (Scheme 2).

Under less polar conditions (e.g., in benzene), decarboxylation was observed in low yields. Obviously, in this case the first reaction event must be an electron transfer from the S-atom to the phthalimido acceptor group. Subsequently, the phthalimide radical anion forms the lactone ring via nucleophilic attack at the carboxy group. Analogous reactions with intermediate radical cations are well-documented in the literature. Loss of a distal α-proton converts the S-radical cation into a C-radical which combines with the imide-localized C-radical to give 4. Beside the remarkable structure of compound 4 and the efficiency of its formation, a surprising aspect of the methionine photochemistry is its spin selectivity: the singlet state of 3 is deactivated >95% to the ground state whereas the corresponding triplet state cyclizes with a quantum yield of ca. 0.25. The ‘normal’ behavior of phthalimide singlets, however, is rapid intersystem crossing to the triplet manifold. This photophysical process is largely suppressed for the donor-acceptor substrate 3. A possible explanation is, that the singlets are deactivated by an electron-transfer/back electron-transfer process. If so, other substrates with similar geometry should also be prone to spin-selective reactions. Consequently, we investigated the cysteine skeleton in some detail [4]. The starting materials were easily available from cysteine and penicillamine, respectively.

The results with these starting materials A (5) (Schemes 3 and 4, Table 1) were more complex than with the methionine substrate 3. This is due to the fact that the thioalkyl group is now in the right position for inducing β-elimination. This elimination preferentially occurs in the singlet photochemistry leading to the enamide B (6). Product D (7a) derives from a two-photon decarboxylation/electron-transfer cyclization process and is characteristic for the triplet photochemistry. In competition to these two pathways which originate from the same primary process, always products were identified with an intact carboxy group. In the penicillamine example this was the tricyclic compound 7b.

The formation of these products is initiated by primary electron transfer from the thioalkyl group to the excited phthalimide electron acceptor. This PET (photoinduced electron transfer) is much more efficient from the triplet than from the singlet state. It can be concluded from the results obtained with cysteine and penicillamine, that back electron transfer dominates the photochemistry of the singlets (Scheme 4).

In the S-methylated substrate 8 (Scheme 5, Table 2) the γ-Hs (γ with respect to the imide-carbonyl groups) are activated solely
in acetonitrile (singlet path which has also been proven by quenching experiments) with formation of the benzazepinecarboxylic 11. This compound is not formed via primary electron transfer from the S-atom because radical ion-pair formation always gives rise to deprotonation from the terminal methyl group and thus leads to the formation of thiazinoindoles 10a and 10b, respectively. The precursor to 11 is the corresponding $\alpha$-methylthio-substituted compound which undergoes Norrish II cleavage ca. 100 times more efficient than the primary $\gamma$-H abstraction.

The C-unprotected amino-acid derivatives of threonine and serine have two possible sites of electron-donor functionalities: the carboxy and the hydroxy group (Scheme 6, Table 3). The products 13-17 (17 is a photoaddition product of MeOH to the radical cation of 13) which were formed from the threonine derivative 12 originate from all possible combinations: 13 is formed by decarboxylation and $\beta$-elimination of the hydroxide, 14 is the product of ET (electron transfer) from the hydroxy group, 15 the secondary decarboxylation product, and 16 the product of primary decarboxylation.

The diastereoisomeric $N$-propenyl compounds $BE$ and $13Z$ were the dominating products deriving from the triplet pathway (solvent-sensitized as for Entry 1 or benzophenone-sensitized as for Entry 3). The $13E/13Z$ ratio in the benzophenone case clearly differs from the acetone photolysis, indicating the possibility of secondary photochemical isomerization. An additional amount of 27% of 14 and the corresponding decarboxylation product 15 resulted in acetonitrile as products of singlet 12. Low-conversion photolysis clearly showed that 15 is a secondary product from 14. The carbinol 17 is on one hand the minor product of photodecarboxylation and, on the other hand, the photoaddition product of $H_2O$ to the radical cation of 13.

A third group of PET-active donor-acceptor couples were the aromatic amino

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**Scheme 5**

![Scheme 5](image)

**Scheme 6**

![Scheme 6](image)

**Scheme 7**

![Scheme 7](image)

**Table 3. Irradiation of 12**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent*</th>
<th>Conditions</th>
<th>Conversion [%]</th>
<th>13 [%]</th>
<th>14 [%]</th>
<th>15 [%]</th>
<th>16 [%]</th>
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<tr>
<td>1</td>
<td>acetone</td>
<td>pyrex</td>
<td>82</td>
<td>88 (0.69)</td>
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<td>acetone</td>
<td>pyrex</td>
<td>100</td>
<td>68 (0.94)</td>
<td>15</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>acetone</td>
<td>pyrex/BP*</td>
<td>100</td>
<td>92 (0.80)</td>
<td>8</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>benzene</td>
<td>pyrex</td>
<td>60</td>
<td>61 (0.91)</td>
<td>13</td>
<td>19</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>benzene</td>
<td>pyrex/10% H_2O</td>
<td>100</td>
<td>51 (0.82)</td>
<td>6</td>
<td>25</td>
<td>15</td>
</tr>
<tr>
<td>6</td>
<td>methanol</td>
<td>pyrex</td>
<td>100</td>
<td>100</td>
<td>35</td>
<td>40*</td>
<td></td>
</tr>
<tr>
<td>7</td>
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<td>pyrex</td>
<td>100</td>
<td>100</td>
<td>55</td>
<td>45</td>
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* 0.01M soln. of 12, 300 nm, 13°, 24 h, N_2, RPR-208 Rayonet reactor.

# 1H-NMR (200 MHz) normalized to 100%.

* Values in parentheses refer to the $13E/13Z$-ratio.

* 0.004M soln. of benzophenone (BP).

* Additionally 25% of 17 formed.
acids tyrosine and dihydroxyphenylalanine (protected as the methyl ester 19 and the acetal 20) (Scheme 7, Table 4). The phenylalanine substrate 18 has already been reported to undergo exclusively decarboxylation when irradiated in acetone. When, however, acetonitrile was used as solvent, as side reaction a Norrish II cleavage to give phthalimide and the diastereoismeric cinnamic acids (path B) was observed (Entry 2). This result already indicated the possibility of PET steps leading to a pair of aryI radical cation and phthalimide radical anion. From intermolecular PET reactions of phthalimides with electron-rich arenes, it is known that aryI radical cations serve as efficient source of benzyl radicals. It is remarkable that the C-protected DOPA derivative 20 did not even give traces of decarboxylation and solely the ring-enlargement product 21 with excellent diastereoselectivity (Scheme 8).

The mechanism of the formation of this interesting (and completely photostable) compound is indicated in Scheme 8: After triplet sensitization and electron transfer, a triplet radical ion pair is formed which deprotonates to give the triplet 1,4-biradical 3BR. This biradical cannot undergo 2,3-bond cleavage due to the additional spin barrier. Thus, ISC and subsequent C–C bond formation are favored for the DOPA case. In summary, the combination of electron-donating groups (SR, OR, aryI) with the carboxylic-acid functionality leads in some cases to highly complex PET photochemistry which can, however, be selectively tuned by solvent effects and the oxidation potentials of the donor functional groups.

### 3. C-Protected N-Phthaloyl-Amino Acids

#### 3.1. Homolytic CH Activation: Abu, Val, Leu, Ile, Tle

The preferred position for homolytic CH cleavage by an electronically excited carbonyl compound is the γ-CH bond. In 22, only δ-CH’s were available, and when irradiated in benzene (or alternatively, in somewhat lower yields, also in acetonitrile) the benzopyridolizidine 23 was formed in excellent yields and with high diastereoselectivity (Scheme 9). In the presence of a suitable triplet sensitizer, no reaction was observed [6].

This spin selectivity was also observed for the substrates 24a–d, indicating that only the singlet excited states are capable of homolytic γ-CH and δ-CH activation.

The N-phenylaloyl methyl ester of 2-aminobutyric acid (24a), valine (24b), isoleucine (24c), and norvaline (24d) gave the corresponding photoisomerization products 25 which could be deprotected to give the free β,γ-unsaturated amino acids. For 24a and 24b, we showed explicitly that no epimerization occurred at the stereogenic center even after prolonged irradiation [7] (Scheme 10). This synthetic approach to the important class of β,γ-unsaturated amino acids worked with high yields for γ-branched substrates, whereas the 2-aminobutyric acid derivative 24a gave only 20% (isolated yield) of a 1:1 diastereoisomeric mixture.

### Table 4. Irradiation of 18, 19, and 20

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Solvent</th>
<th>Time</th>
<th>Conversion (%)</th>
<th>A [%]</th>
<th>B [%]</th>
<th>C [%]</th>
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<td>1</td>
<td>18</td>
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<td>1d</td>
<td>100</td>
<td>100</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>18</td>
<td>acetone</td>
<td>1d</td>
<td>100</td>
<td>80</td>
<td>20</td>
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<td>19</td>
<td>acetone</td>
<td>1d</td>
<td>80</td>
<td>–</td>
<td>65</td>
<td>35</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>acetone</td>
<td>0.5d</td>
<td>80</td>
<td>–</td>
<td>–</td>
<td>100 (89:11)</td>
</tr>
</tbody>
</table>

*) 0.05M solns. of 18–20, 300 nm, 20°, N₂, RPR-208 Rayonet reactor.

b) 1H-NMR (250 MHz) normalized to 100%.

c) Ca. 1:1 trans/cis-mixture of αβ-unsaturated acids.

d) Values in parentheses refer to the trans/cis-ratio.
The tricyclic ‘double Yang product’ showed one set of resonance lines in $^1$H- and $^{13}$C-NMR, indicating that only one out of eight possible diastereoisomers was formed. The X-ray structure analysis of 29 showed that the cyclobutane ring is trans-fused with respect to the ester group. Thus, the isopropyl group in the corresponding precursor molecule 28 also must be located trans.

Molecular mechanics (MM2) and semi-empirical (PM3) calculations indicated that the most important factor for the reactivity of N-alkyl-phthalimide singlets is the angle $\angle (C-H-O=C)$. The one-photon transformation reported for the isoleucine case was not observed for 26a, i.e., deuterium was incorporated at the $\alpha$-position of product $27D$ when the reaction was performed in deuterated MeOH [8]. Thus, a sequence of a primary (singlet) Yang cyclization and a secondary (triplet) Norrish II cleavage leads to the formation of the benzazepine-carboxylates 27. We were not able to detect (by NMR or GC) the intermediary isopropyl-substituted intermediate 28 (Scheme 12). Thus, the secondary Norrish reaction must be much more efficient, at least by a factor of 50. This assumption is reasonable, because quantum yields for Norrish II cleavage reactions ($\Phi_r$) with triplet acetophenone derivatives are in the order of 0.7–1.0 [9], whereas for the corresponding reactions with singlet phthalimides $\Phi_s$ are in the order of 0.02–0.05 [4].

A remarkable effect was observed with the N-phthaloylleucine tert-butyl ester 26b: beside 50% of the regular Yang cyclization/Norrish II cleavage product $27H$, another 50% of a cyclobutanol 29 was observed (Scheme 13). The tricyclic ‘double Yang product’ showed one set of resonance lines in $^1$H- and $^{13}$C-NMR, indicating that only one out of eight possible diastereoisomers was formed. The X-ray structure analysis of 29 showed that the cyclobutane ring is trans-fused with respect to the ester group. Thus, the isopropyl group in the corresponding precursor molecule 28 also must be located trans.

Molecular mechanics (MM2) and semi-empirical (PM3) calculations indicated that the most important factor for the reactivity of $N$-alkyl-phthalimide singlets is the angle $\Delta (C-H-O=C)$ which is $100\pm5^\circ$ for reactive substrates and $82\pm5^\circ$ for unreactive substrates (basis of calculation: twelve substrates). The dihedral angle $\omega (C_p-C=C-O-H)$ can approach optimal values of $0^\circ$ to maximum $35^\circ$ for all substrates. This correlation is the basis of the competition between (slow, but thermodynamically favorable) $\beta$- vs. (rapid) $\gamma$- or $\delta$-CH abstraction in the photochemistry of $N$-phthaloyl-$\alpha$-amino acids.

Another important feature of this spin selectivity is the stereoselectivity of the second H-migration step in the formation of the isomerization products 25: beside 25d, all products were formed diastereometrically (and consequently enantiomerically) pure, i.e., the stereogenic $\alpha$-hydroxymide center is formed highly stereoselective. We suppose that the second H-migration (which involves always the $\alpha$-H) is rapid and rotation about the $C_{\alpha}-N$-bond cannot compete at the singlet 1,4-biradical stage. Thus, the second H-transfer always involves the same diastereotopic face of both the imide-carbonyl groups.

3.2. Application: Syntheses of Isodehydrovaline and Vinylglycine

Acivicin (30a) has been characterized as an antimicrobial, antimetabolitic and effective antitumor agent. The retrosynthesis of this compound and of the corresponding $\beta$-alkylated derivatives leads to $\beta$-unsaturated amino acids as 1,3-dipolarophiles. For the synthesis of 30a, we...
needed vinylglycine 31a which was at this time not available by a photochemical route (Scheme 14).

Isothiourea (31b) was available by the photosomeration process in good yields and high diastereoselectivity. Thus, we have focused on the preparation of branched derivatives of 30 and investigated 1,3-dipolar cycloaddition reactions of chloro- and bromonitro oxide with isothiourea substrates [10]. Optimal results were obtained with the reoxidized substrate 32 which added to the nitrile oxides in situ prepared from the oximes 33 with good diastereoselectivity (83:17). The adducts 34a,b were deprotected to give the desired 30b (Scheme 15).

The synthesis and use of vinylglycine was another challenge. Vinylglycine (31a, X = Y = H), a natural amino acid, acts as an inhibitor of pyridoxal-dependent aspartate aminotransferases and is also considered as an important intermediate in several biogenetic pathways. A number of thermal processes leading to vinylglycine have been developed using other amino acids such as homoserine, glutamic acid, and methionine or carbohydrates as starting materials. The most successful synthetic approach up to now is the thermolysis of N,C-protected methionine sulfoxide, developed and optimized by Rapoport and coworkers [11]. Simple photoisomerization of the methyl2-phthalimido-butyrate 24a gave only low yields. In this case, radical combination is faster than the second H-migration step. Assuming, that an increase in migratory ability or in leaving group ability of the second fragment X should favor the formation of a C=C-bond, we investigated several possible substrates with X = OH, OR, SR, S(O)R, Br, and Cl [12]. The most efficient approach to vinylglycine uses the N-phthaloyl derivative of methionine sulfoxide (35) (Scheme 16).

Other useful substrates in this context were the δ-chloro- and δ-bromo-substituted amino acids 37 and 38 (from homoserine lactone). Even the simple methionine ester 36, available in two steps from methionine, gave C,N-protected vinylglycine 39 upon irradiation in HCl-saturated MeOH (in contrast to the photochemistry in acetonitrile – vide infra). The overall yields for the photoeliminations are between 75–85% and thus can compete with the most efficient thermal processes. A further advantage of this reaction is its applicability in peptide transformations, i.e., N-terminal Met-substituted peptides could be selectively transformed into N-terminal vinylglycine-substituted peptides.

Summarizing the reactivity of simple alkyl-substituted phthalimides, three types of products can be obtained: photoisomerization into 32, and 1,3-dipolar cycloaddition reactions into 33, 34a,b, 35, 36, and 37, 38.

**Scheme 15**

- (i) PCC, Alox, CH2Cl2 (98%)
- (ii) NH2NH2xH2O, then HCl
- PCC = pyridinium chlorochromate
- Alox = aluminum oxide
- DME = 1,2-dimethoxyethane

**Scheme 16**

- (i) PhH2O, microwave
- (ii) H2O2, acetone
- (iii) MeOH, HCl (g)
- (iv) MeI
- (v) NaHCO3, H2O
- (vi) for X = Cl: HCl, MeOH, reflux
- (vii) for X = Br: (1) HBr, H2OAc,
  (2) (MeO)2CMes2, MeOH, AcCl
- (viii) CH3CN

ization (A), ring-enlargement (B), and cyclization (C) products. In most cases, these products were formed with high diastereoselectivity, in all cases enantiomerically pure.

3.3 Electron-Transfer Chemistry: Met and Cys, Ser and Thr, Tyr and DOPA
As already described, methionine behaved rather unusual when irradiated as its N-phthaloyl derivative in acetone (formation of the tetracyclic lactone 4). In contrast, the methyl ester 36 behaved decent: only an 1:1 mixture of the diastereoisomeric tricyclic lactames 40 was formed as result of triplet sensitization [3] (Scheme 17). We could not detect any product from the excited singlet state. A slight change in reaction conditions, however, opened a photochemical channel also for the singlet state (HCl/Methanol — vide supra).

Thus, homolysis of the γ-CH bond which is the dominant process for singlet excited phthalimides is avoided in electron-donor-substituted substrates. This effect can be circumvented by reducing the bond energy of the γ-CH bond via heteroatom incorporation. The C-protected cysteine derivatives 41 are attractive substrates for this purpose. Two product families were formed under the reaction conditions: the benzazepine-1,5-diones A derive from a two-photon sequence, i.e., ring enlargement and subsequent Norrish II cleavage of the α-thioalkylated intermediate. The isoidolothiazines B derive from a one-photon process, i.e., photoinduced electron transfer, generating the S radical cation, subsequent deprotonation of the terminal thioalkyl group, and C=C bond formation [13] (Scheme 18, Table 5).

Furthermore, as shown by the experiments with the S-methyl-cysteine 41a and the penicillamine derivatives 44, the products are formed with high spin selectivity. In the presence of an excess of triplet quencher, solely product 42 was formed from 41a. Consequently, the γ-blocked substrate 44 remained unchanged under these conditions (Scheme 19).

Under triplet sensitization, the isoidolo-thiazines 43 and 45 were the only detectable (primary) products. For all substrates investigated in this series, both PET and γ-CH bond homolysis can be postulated as primary reaction events. The distance between the S-atom and the proximate carbonyl O-atom of the excited phthalimide group is between 2.2 Å (gauche-conformation) and 4.3 Å (anti-conformation, from AM1 calculations) in the ground-state conformers. Thus, electron transfer is not restricted by the donor-acceptor distance. Form an energetic point of view, both singlet and triplet excited states are capable of exergonic intramolecular electron transfer. Using the redox potentials for the model substrates dimethylsulfide (+1.21 V vs. SCE) and N-methylphthalimide (~1.37 V vs. SCE) and the singlet/triplet energies of N-methylphthalimide (3.8 eV and 3.1 eV), free energies were calculated for the electron transfer of ~1.2 eV (27.6 kcal/mol) from the first excited singlet state and of ~0.5 eV (11.9 kcal/mol) from the first excited triplet state, respectively. For compound 41, %ET of ~1.40 (peak potential) and E0.5 of ca. 1.60 V (irreversible) were determined. Using these values, ∆G0.5ET is ~0.8 eV for the singlet and ~0.2 eV for the triplet process.

Analogous PET reactions for γ-alkyl thiokeones have been studied in detail by Wagner and Lindstrom [14]. They used acetophenone substrates in order to completely circumvent the singlet channel. For substrates comparable to ours, a ratio of PET reaction to homolytic γ-CH activation of ca. three was reported. In case of the cysteine derivatives described here,
this ratio must be higher than twenty. Both the experiments with acetone and benzophenone ($E_T = 69 \text{ kcal/mol}$) as triplet sensitisers led to this conclusion. Less than 5\% benzazepine-1,5-dione 42 was found in the acetone-sensitized experiments. Due to the relatively low concentrations of benzophenone in the respective experiments, a small amount of singlet reactivity was always detected due to direct excitation of the phthalimide chromophore. The photoysis of 41b (with $R = \text{Ph}$) with 364 nm light (argon ion laser) indicated that in this special case also the $\gamma$-CH position is active in the triplet photochemistry. We assign this phenomenon to the pronounced steric shielding of the $\varepsilon$-CH position.

In the presence of piperylene ($E_T = 59.2 \text{ kcal/mol}$), the triplet states of 41 and 44 should be completely quenched. The experiments clearly showed that 42 is preferentially formed via the singlet channel and that the isoindoles are exclusively formed via the triplet channel.

Apparently, the triplet radical ions $3^1\text{RI}$ formed after intramolecular electron transfer from $3^1\text{A}^+$ are selectively deprotonated from the (kinetically more acidic) $\varepsilon$-CH position. The resulting 1,6-biradicals combine to the isoindoles 43 and 45 after spin inversion (Scheme 20).

From an energetic point of view (vide supra), electron transfer from the singlet excited state $1^1\text{A}^+$ should be even more efficient. There is, however, a pronounced decrease in conversion when the direct irradiations are compared with the triplet-sensitized reactions. Additionally, $\varepsilon$-CH activation was not observed for the singlet reactions. Thus, there must be a competing process much faster than the deprotonation reaction. We assume that this process is reverse electron transfer (RET) from the triplet radical ions $1^3\text{RI}$ which regenerates the ground states. Firstly, this process is highly exergonic, secondly, no spin barrier exists for this reaction. The formation of the precursor to 42 is therefore assumed to be due to a homolytic CH abstraction from the geometrical preferred $\gamma$-position and not to a PET process. In case of the triplet radical ion pairs, spin inversion must precede the RET process. Therefore, an efficient competition between this deactivation process and the heterolysis of the $\varepsilon$-CH bond exists.

The hydroxy-substituted amino acids serine and threonine were studied as the methyl esters 47a and 47b. Irradiation in acetone or acetonitrile led to cleavage of the central C–C bond with formation of N-phthaloylglycine 48 and the corresponding aldehydes [5] (Scheme 21). Use of the O-deuterated starting materials led to $\alpha$-deuterated 48 in racemic form. This cleavage is probably initiated by PET from the hydroxy group to the excited imide triplet followed by fast intramolecular proton transfer and cleavage of the C$_\gamma$–C$_\beta$ bond. Several catechol-protected derivatives of methyl ester 49 (R = Me, H) have been investigated in order to synthesize new structures for pharmaceuticals [15]. The photochemical ring-enlargement reactions proceeded with high efficiency and in high yields. It is remarkable to mention that no thermal processes are known which give benzazepinedione structures enantiomerically pure (Scheme 22).
3.4. Unreactive Substrates: Gly, Ala, and Phe

When irradiated for standard conversion times, the methyl esters of N-phthaloylglycine, alanine, and phenylalanine behaved photostable. This behavior was not surprising for glycine and alanine: in general, $\beta$-Hs are abstracted slowly, and this is also valid for $\gamma$-Hs, if a primary radical is produced and the geometry for H abstraction is unfavorable. For tert-leucine for example, the formation of a primary radical via $\delta$-H abstraction is effective due to the favorable geometry, i.e., the short C=O···H distance and the ca. 100° C=O···H angle. Thus, the reduced photochemical reactivity of the phenylalanine substrate is striking. Ground-state geometry is expected to be correct for abstraction of a benzylic H (like in the leucine case 26), and the radical produced thereafter is strongly stabilized. Long-term (2–3 d) irradiation of 51 in acetonitrile resulted in complete $\beta$-cleavage (Scheme 23). This might mean that radical combination is less favored due to fast methylcinnamate formation or due to the geometry of the intermediate 1,4-biradical with aryl-aryl interaction. Could there also be PET deactivation for 51? A hint came from the fluorescence decay data [5]. In nonpolar solvents (benzene, toluene) the singlet decay time was ca. 4 ns, in acetonitrile, this time increased by a factor of 3.6 (dual fluorescence with a 4- and a 22-ns contribution). A plausible explanation is delayed fluorescence via repopulation of the first excited singlet by back electron transfer from the radical ion pair. This process, similar as for other PET substrates, deactivates the singlets. Additionally, in this case the triplet of 51 is too low in energy to enable exergonic ET. Thus, due to different reasons, singlet and triplet states are less reactive than normal.

4. Remote Photodecarboxylation

4.1. The Glutamic-Acid Substrate Series

Apparently, there is a substantial difference between $\alpha$- and $\omega$-decarboxylation with respect to spin selectivity and the secondary processes. The $\alpha$-decarboxylation of N-phthaloylamino acids occurs efficiently under a variety of conditions (vide supra), whereas $\omega$-decarboxylation was never observed in the aspartic or glutamic cases. The 'remote' carboxylic group could be activated by transformation into the corresponding potassium salts [16][17]. Two illustrative examples for the effect of deprotonation were the N-phthaloyl derivatives of glutamic acid (52) and lysine (55) [18]. The first substrate, when irradiated under salt conditions (excess K$_2$CO$_3$ in an acetone/water mixture), was rapidly converted into the $\gamma$-aminobutyric-acid derivative 53. The subsequent cyclization step to give the benzopyrrolizidinone 54 was ca. 10 times slower. This ratio of $\gamma$-decarboxylation was also observed for the bis-phthaloyl-lysine derivative 55. In this case, only the 1,5-diaminopentane derivative 56 was formed indicating that the quantum yields for $\alpha$- vs. $\omega$-decarboxylation differ by at least a factor of 5 (assuming identical probability for excitation of each of the chromophoric groups). When the mixed protected lysine 57 was irradiated, clean formation of an 1:1 mixture of the two diastereoisomeric products 58 was observed (Scheme 24).

When trying to crystallize one of the stereoisomers, we received the dehydration product 59. We could show independently that this acid-catalyzed reaction proceeds with remarkable ease and efficiency with both stereoisomers. The low diastereoselectivity observed in the reaction of the lysine derivative 57 was also apparent in the photocyclization of the glutamic-acid derivative 60. In this case, an 1:1 mixture of cis- and trans-61 resulted after relatively short irradiation time. When directly using the potassium salt of 60, no trace of the simple decarboxylation prod-
uct was observed after quantitative conversion in a 1:1 acetone/water mixture. The two diastereoisomeric benzopyrrolizidinones were easily distinguishable by $^1$H-NMR: both $^2$HH couplings to H$_2$ were 8.5 Hz in the cis-isomer, whereas one $^2$HH coupling was no longer detectable in the trans-isomer. Treatment of this 1:1 product mixture with catalytic amounts of trifluoroacetic acid (TFA) led to near quantitative epimerization of trans-61 into the cis-diastereoisomer. By this method, we were able to isolate diastereomically pure cis-61 which was also identified by X-ray structure analysis (Scheme 25).

Epimerization at the stereogenic center of hydroxy lactames resulting in an 1:1 equilibrium has already been reported by us for the product of the N-phthaloylvaline-ester photoysis [7]. In the glutamic acid case reported herein, however, the epimerization equilibrium is >9:1 in favor of cis-61. Further treatment of cis-61 with TFA in an inert solvent led to the enamine 62, whereas in the presence of alcohols the cis-alkoxy lactames 63 were formed in high (>95:5) diastereoselectivity. These reactions proceed via intermediary acyliminium cations which are known to be reactive with a multitude of nucleophiles. Benzopyrrolizidines of this type have also been synthesized using the azomethine-ylide route developed for N-(trialkylsilylmethyl)imidazoles [19]. The low diastereoselectivity observed for the photocyclization of 60 is typical for an 1,5-triplet biradical reaction (in contrast to 1,4-triplet biradical reactions). The corresponding singlet reactions which also led to the benzopyrrolizidine skeleton, e.g., for the N-phthaloyl-t-tert-leucine substrate (22→23), proceeded highly diastereoselective.

4.2. Applications: Synthesis of Macrocyclic Products

The synthesis of macrocyclic ring systems via photoinduced electron-transfer cyclization is an attractive alternative to many ground-state reactions [20]. Dilution conditions could be avoided if there exist already strong donor-acceptor interactions in the ground state or the electron transfer occurs preferentially intramolecular (through-space- or through-bond-mediated). The reaction principle described in Chapter 4.1 was highly promising in this context. In order to elaborate scope and limitations of this decarboxylative cyclization reaction, we focused on the synthesis of medium- and large-ring compounds testing a variety of ring sizes (from 4 to 26), spacer groups (alkyl chains, ester, ether, amide, amine linker), and polyheterocyclic target arrangements [18].

Firstly, alkyl chains were used to separate the phthalamide and the carboxylate part. There was no trace of a cyclization product when N-phthalamide was irradiated under standard conditions, only N-methylphthalamide was formed. The homologous substrate, 3-phthalimidobutyric acid 64 (n = 2), did already give 10% of the benzazepine-1,5-dione X, a secondary product of the primarily formed cyclobutane 65 (n = 2) (Scheme 26).

Substrates with longer alkyl chains did result in the formation of the corresponding annulation products 65 in yields not lower than 61%. In all cases, also small amounts (ca. 5–10%) of the 'simple' decarboxylation products 66 were detected. Only the starting material with a trans-1,4-cyclohexane spacer (67) did show a slightly higher degree of decarboxylation leading to the monosubstituted cyclohexane 69. But also in this case, the cyclization product 68 was formed in good yield (Scheme 27). The latter example already indicated that a decrease in conformational flexibility of the connecting hydrocarbon chain is not crucial for the efficiency of the ring formation. Furthermore, the conversion of 67 into 68 showed that also o-branched carboxylic acids can be used as substrates in the title reaction. All medium- and large-ring hydroxy lactames could be easily crystallized from acetone, and the X-ray structures were determined for a series of macrocycles. No dimeric products could be detected through NMR or MS analysis, nor 'Kolbe dimers' neither cross-cyclization products.
In order to elaborate this photocyclization methodology further, we investigated other spacers connecting the electron-donating carboxylate and the electron-accepting phthalimide groups. The use of ether linkages was tested for substrate 70 and the crown-ether precursor 72. In both examples, the α-hydroxyacetic-acid moiety serves as the terminal building block.

Alternatively, the α-trimethylsilylmethoxy substituent has been developed by Yoon and Mariano as a versatile electron-donor group, which after oxidation via PET and desilylation is converted into an α-oxo-stabilized carbon radical [21]. Thus, the intermediate biradicals are identical in both approaches, however, the PET-decarboxylation route is not limited to substrates with terminal alkyl groups substituted by an electron donor at the α-position. The photocyclization products 71 and 73 were formed in high yields (73%, 65% after recrystallization) and essentially without by-products [18][22] (Scheme 28).

Medium- and large-ring lactones (macrolides) also constitute an interesting class of compounds which should be accessible by our method. The glutaric acid-derivative 74 could be successfully applied and the nine-membered azalactone 75 was formed in 67% yield and characterized by an X-ray structure analysis (Scheme 29).

Another highly important class of macrocyclic compounds are cyclic oligopeptides. In order to optimize the procedure for preparation of these targets, we investigated six substrates 76a–f with different spacer pattern [18][23]. The N-terminal spacer groups used in compounds 76a–c were glycine, β-alanine, and γ-aminobutyric acid. Similar as already described for the methylene-linked ester 72b, the glycine derivative 76a gave mainly reductive decarboxylation and only 26% of cyclization product 77a. A functional group which is linked in close proximity to the phthalimide chromophore seems to reduce the cyclization capacity of the (1,n)-biradical formed after PET decarboxylation. When using the ‘more flexible’ substrates 76b and 76c, the yields for the macrocycles 77b and 77c became acceptable (57% and 68%) (Scheme 30).

Increasing the chain length of the N-terminal spacer to C11 additionally leads to an increase in cyclization efficiency as was shown for the two examples 76d and 76e. It is remarkable that the substrate with the longest and most flexible spacer between donor and acceptor gave the highest yield of cyclization product (77e, 80%). Even the trans-1,4-cyclohexane-linked dipeptide 76f gave the macrocycle 77f in
excellent yields (comparable with the directly connected donor-acceptor pair 67).
It was this series of experiments in combination with the results obtained for the variation of the counterion (vide supra) which led to the idea of a ground-state intramolecular stabilization, similar to template effects in other macrocyclization reactions. An alternative concept involves a long-lived excited phthalimide triplet, however, does not explain the high tendency for intramolecular reaction with essentially no intermolecular electron-transfer competition. Another hint for the role of ground-state stabilization came from the fact, that the ‘real’ dipeptides 78 (Pht = Gly-Gly) and 79 (Pht = Gly-Glu) were unreactive under the given reaction conditions, i.e., did neither give cyclization nor redox reactivity. It is highly probable that the same effect which makes the α-decarboxylation exceedingly effective (80) also deactivates the glycine-linked dipeptides (81) (Scheme 31).

5. Conclusion and Perspectives

For a confirmed photochemist it is a banality to describe the two lowest excited singlet and triplet states as ‘electronic isomers’ of the ground state. These ‘isomers’ exhibit, nearly always, distinct differences in reactivity, chemo-, regio-, and stereo-selectivity. It might be, however, worthwhile to recall these properties when developing new applications for synthetic organic chemistry. In the last six years, we have developed a number of useful transformations in the phthalimide series. These transformations allow to synthesize photochemically elimination, ring-expansion, cyclization, cyclodaddition as well as fragmentation products. Spin selectivity is pronounced for many reactions, i.e., singlet states preferentially gave (highly stereo-selective) products deriving from homolytic CH activation, whereas triplets preferentially gave PET-initiated products. Tuning the electronic properties of these ‘electronic isomers’ allows to improve efficiency and selectivity which will lead to more effective photochemical processes in the future. Interesting heterocyclic target families, we are currently concentrating on chiral mitosene derivatives, pyrrolizindines, benzazepines, and pyrroloisoindolines.

I thank the Grammaticakis-Neumann prize committee for providing the opportunity to present our recent results at the 1997 meeting of the Swiss Society of Photochemistry and Photophysics in Lausanne.

I especially acknowledge the (intellectual) support from Prof. W. Adam (University Würzburg) and Prof. D. Sreebch (ETH-Zürich) in the fields of organic photochemistry and organic synthesis. Secondly, I acknowledge the excellent (experimental) support by my coworkers mentioned in the references. Thirdly, I acknowledge the (financial) support given by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, the Bayer AG, Degussa AG, and Merck KGaA.

Received: April 17, 1998