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Photochemistry of N-Phthaloyl Derivatives of Electron-Donor-Substituted Amino Acids

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Abstract:

The *hydroxy* substituted amino acids threonine and serine have been investigated concerning their photochemical behaviour when activated as N-phthaloyl substrates. The methyl esters **1a** and **2a** solely underwent cleavage of the central C-C single bond to give the glycine derivative **3** and an aldehyde fragment. C-unprotected threonine derivative **1b** is converted into a series of products the composition of which depends on solvent polarity and on the electronic state.
Three reaction modes were detected for the N-phthaloyl derivatives of the *aryl* substituted amino acids phenylalanine, tyrosine, and dihydroxyphenylalanine (DOPA): (**A**) decarboxylation (only for **12a**), (**B**) ß-fragmentation, and (**C**) ring enlargement reaction. Processes **B** and **C** are initiated by photo electron transfer (PET), as the solvent dependence revealed. The DOPA derivatives **14a** and **14b** are the most prominent examples due to their exclusive **PET** reactivity leading to type **C** products (**18a,b**) with high diastereoselectivity (90:10). PET results from the first excited singlet states of **12** and **13**, whereas for compounds **14** the corresponding triplet states are involved. The correlation between photochemical reactivity and the fluorescence decay data for compounds **12a,b** and **15** is discussed.

INTRODUCTION

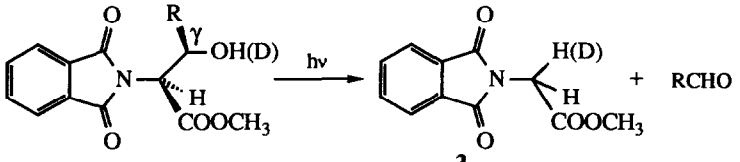
The chemistry of electronically excited phthalimides is dictated by hydrogen and/or electron transfer reactions.[3,4] When substituted with electron donating substituents in the side chain, these substrates represent flexible intramolecular donor-acceptor couples[5] suitable for the study of the distance and energy dependence of photo electron transfer (PET) processes. N-Phthaloyl derivatives of α-amino acids are ideal model substrates due their large structural variety. The

known phototransformations of N-phthaloyl activated amino acid derivatives can be classified by two principal ways of primary action following electronic excitation: H-transfer from γ,δ, or ε-positions[6] or electron transfer from an appropriate donor position which could be a sulfur[7], oxygen[8], or amino[9] substituent in the side chain of the amino acid. In this communication we describe photo electron transfer (PET) initiated processes for the oxygen substituted amino acids threonine and serine and for the aryl substituted amino acids phenylalanine, tyrosine, and dihydroxyphenylalanine (DOPA).

RESULTS

Threonine and Serine (Hydroxy activated amino acids)

When these amino acids (Thr, Ser) were protected against photodecarboxylation[10] by means of their methyl esters, irradiation of the threonine substrate (2S,3R)-**1a** as well as of the serine derivative (2S)-**2a** in acetone or acetonitrile exclusively led to cleavage of the central C-C bond with formation of N-phthaloyl glycine **3** and the corresponding aldehydes acetaldehyde and formaldehyde, respectively (Scheme 1). Use of the O-deuterated starting materials led to α-deuterated **3** in *racemic* form.[11] This cleavage reaction is most probably initiated by PET from the hydroxyl group towards the excited imide moiety followed by intramolecular proton transfer and aldehyde elimination.[12] No products deriving from γ-hydrogen abstraction could be detected in contrast to the results reported by Saito et al. on the photoreaction of structurally comparable N-phthaloyl alkyl hydroperoxides.[13]



1a (R=Me)
2a (R=H)

3

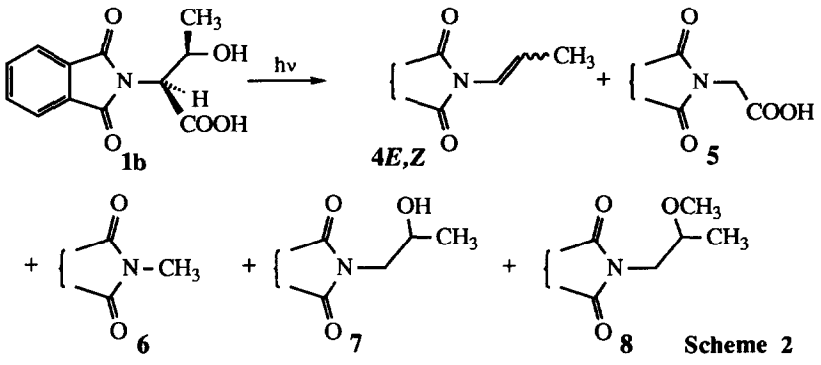
Scheme 1

The C-unprotected amino acid derivatives **1b** and **2b**[14] now offered *two* possible sites of electron donor functionalities: the carboxyl and the hydroxyl group. As already reported for the N-phthaloyl derivatives of methionine[7] a selectivity dependence should also be expected for threonine and serine concerning solvent polarity and the multiplicity of the electronically excited state. In Table 1 the results are shown for the photolysis of N-phthaloyl threonine **1b** (Scheme 2).

Table 1. Photolysis of **1b** - product composition

entry	solvent[a]	conditions	conversion (%)[b]	**4** (%)[b,c]	**5** (%)[b]	**6** (%)[b]	**7** (%)[b]
1	acetone	pyrex	82	88 (0.69)	6	-	6
2	acetone	quartz	100	86 (0.65)	6	2	6
3	acetonitrile	pyrex	100	68 (0.94)	15	12	5
4	acetonitrile	quartz	100	64 (1.00)	2	32	2
5	acetonitrile	pyrex/BP[d]	100	92 (0.80)	-	8	-
6	benzene	pyrex	60	61 (0.91)	13	19	6
7	benzene	pyrex/10% H_2O	100	51 (0.82)	6	25	15
8	methanol	pyrex	100	-	-	35	40[e]
9	water	pyrex	100	-	-	55	45

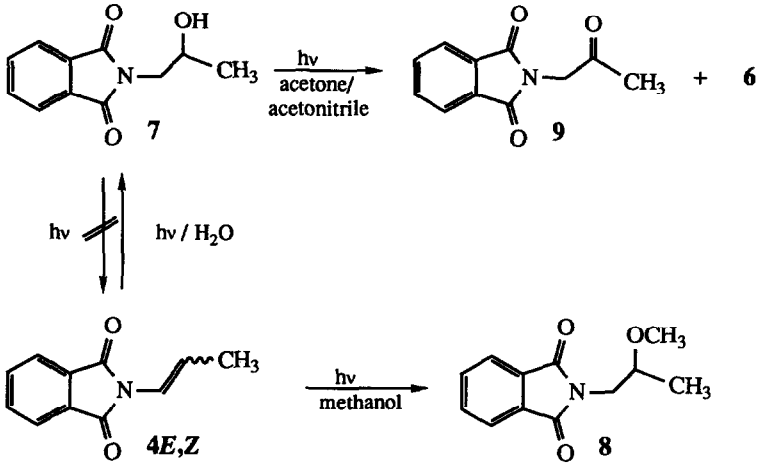
[a] 0.01 M solution of **1b** / 13°C / 3000 Å lamps / 24 h / N_2 / RPR-208 Rayonet photoreactor; [b] ^1H NMR (200 MHz) normalized to 100%; [c] values in parentheses refer to the **4E/4Z**-ratio; [d] 0.004 M solution of benzophenone (BP); [e] additionally 25% of **8** formed.



Scheme 2

The diastereomeric N-propenyl compounds[15] **4E** and **4Z** are the dominant products deriving from the triplet pathway (solvent sensitized as for entry 1,2 or benzophenone-sensitized as for entry 5). The **4E/4Z**-ratio in the benzophenone case, however, clearly differs from the acetone photolysis, indicating the possibility of secondary photochemical isomerization. An additional amount of ca. 30% of N-phthaloyl glycine **5** and the corresponding photodecarboxylation product **6** resulted in acetonitrile (entry 3,4) and benzene (entry 6) as products of the singlet pathway. Low-conversion photolysis clearly showed that **6** is a secondary product formed from **5**. Compound **7** is the precursor neither to **6** nor to the diastereomeric alkenes **4E** and **4Z**. To prove this, independently synthesized **7** was subjected to prolonged irradiation under conditions

identical to entry 1 or 3. After 4 d besides 32% of **6** also a dehydration product **9**[16,17] was formed in 30% (in acetone) and 60% (in acetonitrile), respectively (Scheme 3). **9** could in no case been identified in the product mixture when **1b** was irradiated. Consequently, **4E** and **4Z** are products of an one-photon process. Whether a biradical intermediate, following decarboxylation, is involved in this process or a Grob type fragmentation is induced with concomitant extrusion of carbon dioxide and a hydroxyl radical, has not been clarified yet.[18] The mechanistic scheme is even complicated by the fact that **7** and **8** could also (for **8** even exclusively) be generated *via* secondary photochemical addition of water and methanol, respectively, to the N-propenyl phthalimides **4E** and **4Z**.



Scheme 3

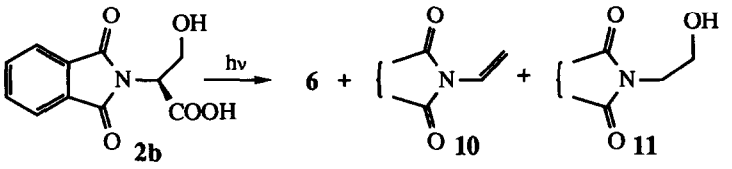
The serine derivative **2b**, the photochemistry of which has already been mentioned by Kanaoka and coworkers[10], behaved in a less complicate way (Scheme 4). In aprotic solvents N-vinyl phthalimide **10** is formed as major product. Under triplet sensitization conditions (Table 2, entry 1), formaldeyde elimination with subsequent decarboxylation leading to product **6** could not be observed.[19] This process becomes more important when direct excitation was applied (entry 2-4). In protic solvents again the (formal) photodecarboxylation product **11** dominates. Independently it was be shown, that **10** under photolytic conditions (e.g. entry 5) rapidly adds water with formation of **11**.

Table 2. Photolysis of **2b** - product composition

entry	solvent[a]	conversion (%)[b]	**10** (%)[b]	**6** (%)[b]	**11** (%)[b]
1	acetone	60	74	-	26
2	acetonitrile	100	83	8	9
3	benzene	100	76	12	12
4	methanol	100	-	38	62
5	water	100	-	-	100

[a] 0.01 M solution of **2b** / pyrex / 13°C / 24 h / RPR-208 Rayonet photoreactor;

[b] ^{1}H NMR normalized to 100%;



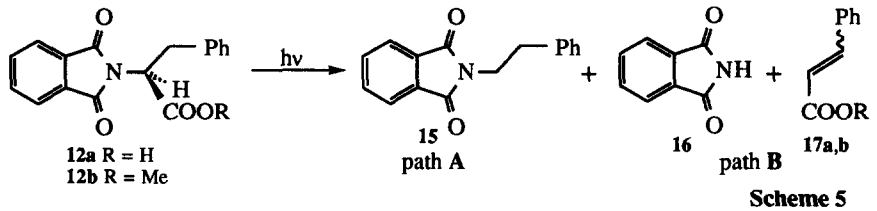
Scheme 4

In summary the following mechanistic conclusions can be drawn: both carboxy as well as hydroxy site of threonine and serine could be activated *via* electronically excited phthalimides. Probably both activation paths are initiated by PET. Whereas PET from the hydroxyl group is favoured in the singlet case (and for the methyl esters **1a** and **2a** where carboxy activation is unproductive), in the triplet case PET from the carboxyl group with subsequent carbon dioxide and water elimination is preferred. Solvent polarity has its influences on the conversion rate, however, not pronounced on the product composition (again indicating a competition between PET-pathways). Protic solvents alter the product composition as a result of partial photochemical addition of solvent molecules towards the primarily formed fragmentation products.

Phenylalanine, Tyrosine, and DOPA (Aryl activated amino acids)

As already described, amino acids with electron-donating substituents in the side chain constitute donor-acceptor couples which could be used for the study of energy and distance dependence of PET processes. A major disadvantage of oxygen as well as sulfur substituted amino acids is the constant oxidation potential of the donor functionality which could not be altered by *substitution* tricks. ß-Aryl substituted amino acids such as phenylalanine (Phe), tyrosine (Tyr), and dihydroxyphenylalanine (DOPA) are much more useful for the study of PET processes.

The C-unprotected phenylalanine **12a** has already been reported to undergo exclusively photodecarboxylation (path A) when irradiated in acetone (triplet sensitization - entry 1 in Table 3) or benzene.[6] The methyl ester **12b** is photostable under these conditions.



12a R = H
12b R = Me

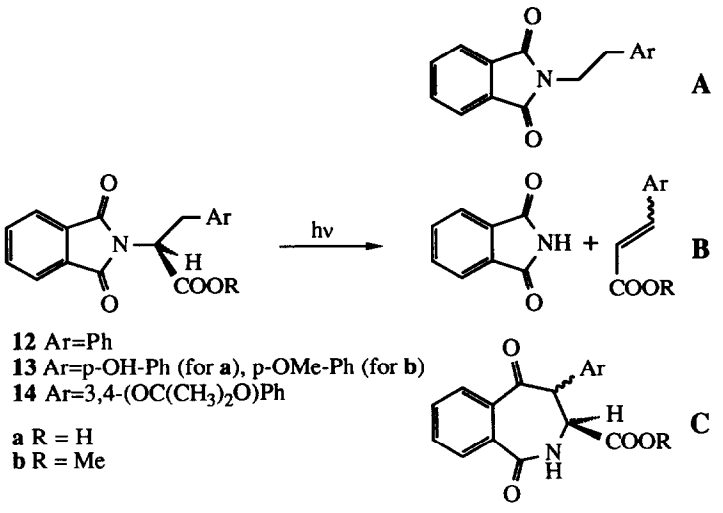
Scheme 5

Table 3. Photolysis of **12a,b**, **13a,b** and **14a,b**: product composition

entry	substrate	solvent[a]	time	conversion (%)[b]	A (%)[b]	B (%)[b,c]	C (%)[b,d]
1	**12a**	acetone	1d	100	100	-	-
2	**12a**	acetonitrile	1d	100	80	20	-
3	**13a**	acetone	1d	80	-	65	35
4	**14a**	acetone	0.5d	80	-	-	100 (89:11)
5	**12b**	acetone	1d	10[e]	-	-	-
6	**12b**	acetonitrile	2d	100	-	100	-
7	**13b**	acetone	1d	75	-	90	10
8	**13b**	acetonitrile	1d	10[e]	-	-	-
9	**14b**	acetone	1d	100	-	-	100 (90:10)
10	**14b**	acetonitrile	2.5d	35	-	-	100 (90:10)

[a] 0.05 M solution of **12-14** / 20°C / 3000 Å / N_2 / RPR-208 Rayonet photoreactor; [b] ^{1}H NMR (250 MHz) normalized to 100%; [c] ca. 1:1 trans/cis mixture of α,ß-unsaturated acids; [d] values in parentheses refer to the trans/cis-ratio; [e] exclusively decomposition.

When, however, acetonitrile was used as solvent, a relatively slow cleavage reaction leading to phthalimide (**16**) and the diastereomeric methyl cinnamates (**17b**) was observed (entry 6). The corresponding acid **12a** in acetonitrile (entry 2) gave traces of cinnamic acids (**17a**, path A) besides the decarboxylation product **15** (Scheme 5).



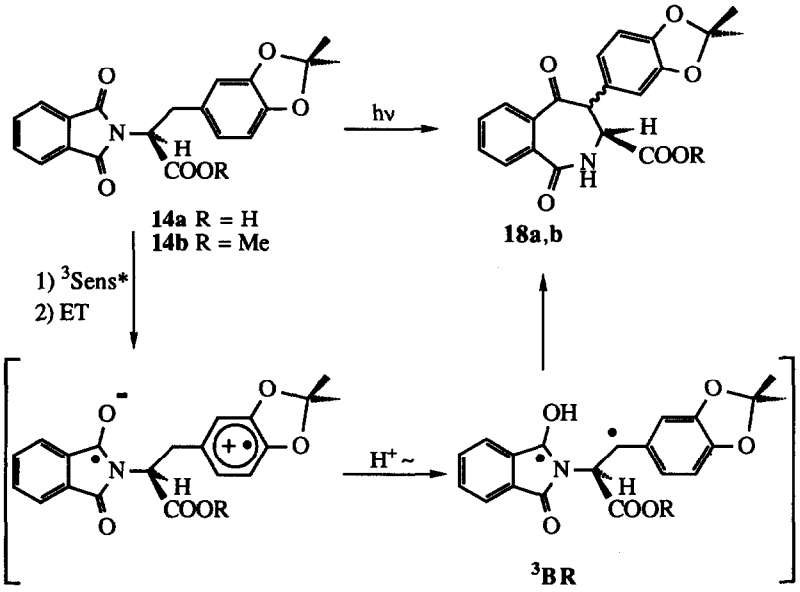
12 Ar=Ph
13 Ar=p-OH-Ph (for **a**), p-OMe-Ph (for **b**)
14 Ar=3,4-(OC(CH$_3$)$_2$O)Ph

a R = H
b R = Me

Scheme 6

These results already indicated the possibility of photochemical induced electron transfer steps leading to a pair of aryl radical cation and phthalimide radical anion. From intermolecular PET reactions of phthalimides with electron-rich arenes it is known that aryl radical cations serve as efficient source of benzylic radicals, i.e. as highly acidic species.[20] The 1,4-biradicals (singlets for entry 2 and 6) formed after proton transfer can efficiently undergo 2,3-bond (Norrish II type) cleavage. PET processes should gain more importance for aryl substituents with lower oxidation potentials. Thus, the tyrosine derivatives[21] **13a,b** yielded the fragmentation products B (entry 3,7) more efficiently than **12b**. Triplet excited **13b** (entry 7) also gave path B products besides ca. 10% of path C products (Norrish II cyclization follwed by ring opening). For the DOPA derivatives (**14a,b** - entries 4,9,10) the product composition completely switched in direction of path C products.[22] The C-unprotected N-phthaloyl DOPA **14a** did not give even traces of decarboxylation products (path A) quite similar to the results obtained for the methionine case.[7] In the latter case a thioether moiety served as efficient electron donor substituent, for **14a** the electron-rich aryl group took over this task. For both cases the product formation is now favored from the triplet excited states. It is obvious that photoinduced electron transfer preceds H-transfer from the benzylic position, otherwise no substantial difference should be observable when going from the phenyl derivative **12b** to the catechol derivative **14b**. Additionally the solvent dependence and the competition between decarboxylation (probably also an electron transfer process) and γ-hydrogen abstraction from the benzylic position reveals that PET operates.

Why, however, are the ring enlargement products **18a,b** formed in the DOPA case (entries 4,9,10) exclusively (Scheme 7) ? Spin state selectivity could give the answer: PET is energetically already feasible from the triplet state of **14a,b**[23] which is approximately 12 kcal lower in energy than the corresponging singlet state.[24] Because of the relatively short singlet lifetimes (*vide infra*) and good ISC quantum yields[25] the reaction pathway *via* triplets becomes more effective for the electron-rich DOPA substrates. If triplet states are involved in these cases, triplet 1,4-biradicals (^{3}BR) are the crucial intermediates following PET and proton transfer. These biradicals cannot directly undergo 2,3-bond cleavage due to an additional spin barrier. This could be the reason for the altered product composition implying that the C-C bond formation step is favored after ISC to the singlet biradical state.



Scheme 7

Another hint for PET processes already in the phenylalanine cases comes from the fluorescence decay data.[26,27] Wheras in non-polar solvents such as toluene (DK: 2.4) the decay was relatively short (ca. 4 ns) for the Phe derivatives **12a** and **12b** as well as for the decarboxylation product **15** ($\Phi_{Em.} \leq 0.001$, excitation wavelength: 316 nm, see Table 4), the decay time increased in acetonitrile (DK: 36) by a factor of 2.3 for **12a** and of 3.6 for **12b**. This effect was not observed for **15**. A plausible explanation for this is repopulation of the first excited singlet state *via* back electron

transfer from the radical ion pair. This process may lead to an increase in the fluorescence lifetime. Further investigations concerning the luminescence properties and the photochemistry of electron donor substituted phthalimides are in progress.

Table 4. Representative fluorescence decay data of **12a**, **12b**, and **15**

substrate[a]	solvent	lifetime (ns)[b]	substrate[a]	solvent	lifetime (ns)[b]
1a	toluene	3.6	**1a**	acetonitrile	8.4
1b	toluene	6.0	**1b**	acetonitrile	21.3
4	toluene	6.4	**4**	acetonitrile	3.9

[a] 5×10^{-5} M, $\lambda_{Em.}$=390±1 nm; [b] χ^2 =1.27±0.03.

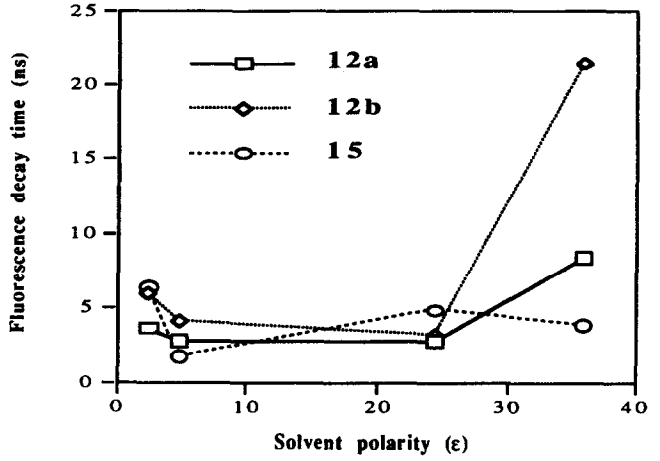
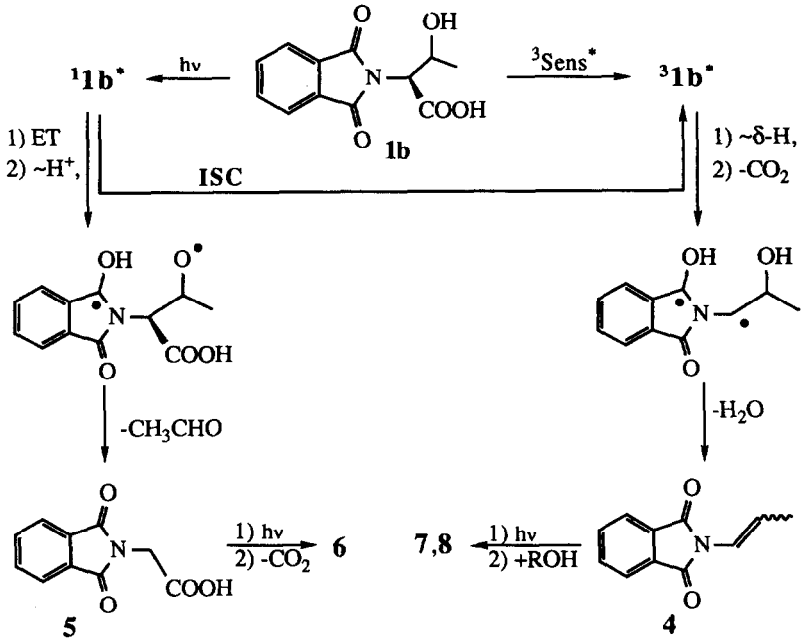


Figure 1. Fluorescence decay of substrates **12a**, **12b**, and **15** in solvents of different polarity (toluene, cyclohexane, methylene chloride, and acetonitrile).

SUMMARY and CONCLUSIONS

Oxygen as well as aryl substituted amino acids constitute versatile substrates for the study of PET processes in phthalimide photochemistry. Three factors influence the reaction mode and selectivity: (i) the donor ability of the side chain substituent, (ii) the solvent polarity, and (iii) the electronic state of the excited phthalimide, i.e. singlet versus triplet selectivity. The fluorescence decay data indicate a relatively fast ISC process, which means that triplet processes do also play an important role in direct photolysis of N-phthaloyl substrates. The sensitized (benzophenone) photoreactions revealed the triplet photochemistry and could therefore serve as experimental tool for the determination of the singlet behaviour. This interplay is shown in Scheme 8 for the

threonine substrate **1b**.



Scheme 8

For triplet excited **1b** the decarboxylation / dehydration route is dominating, whereas singlet excited **1b** preferentially undergoes a sequence of electron transfer / proton transfer and fragmentation with formation of acetaldehyde and the glycine derivative **5** which is further photodecarboxylated. The latter route is the only observable when the corresponding methyl ester **1a** is applied.

In case of the aryl substituted amino acids the role of the solvent gets more dominant. The phenylalanine dertivative **12b** gave path B products (Norrish-cleavage) only in acetonitrile, a solvent which favours electron transfer processes, whereas in acetone (lower polarity / triplet sensitization) no photoreaction could be observed. Quite the contrary, the DOPA derivatives **14a** as well as **14b** gave ring enlargement products (path C) much faster in acetone indicating a photo electron transfer process which originates from the triplet excited state (*vide supra*).

In summary the electron-donor-substituted amino acids investigated here are well suited substrates for the investigation of radical as well as electron transfer processes in the photochemistry of phthalimides. Furthermore these compounds which are easily available in enantiomerically pure form could lead to interesting new photoproducts (e.g. the benzazepinediones **18a,b**[28]) in diastereo- and enantiomerically pure form.

EXPERIMENTAL PART

All starting materials (N-phthaloyl amino acids and their corresponding methyl esters **1**, **2**, **12**, **13**, and **14**) were synthesized from enantiomerically pure α-amino acids (Degussa AG, Fluka AG, and Sigma AG) using methods published by Kidd[29], Nefkens[30], and Sheehan[31]. The tyrosine derivative **13b** (PHT=Tyr-OMe) was applied as the methyl ether, the DOPA derivatives **14a** and **14b** (PHT=Dpa-OH and PHT=Dpa-OMe) were applied as their respective acetonides. The photochemical reactions were performed in pyrex vessels (100-250 ml) using a RPR-208 Rayonet© photochemical reactor equipped with 3000Å lamps (approx. 800 W) at 13°C under a nitrogen atmosphere. All solvents used for photoreactions (benzene, acetone, acetonitrile, and methanol) were puriss. p.a. (Fluka). Benzophenone (BP, recryst. twice from diethyl ether) was used as sensitizer. The substrate concentration was varied (see Tables 1-3) from 0.01 to 0.05 M, the triplet sensitizer (BP) concentration was 0.004 M. Analyses of the crude product mixtures were performed using ^1H and ^{13}C NMR spectroscopy. Product mixtures were separated (when necessary) be means of silca gel column chromato-graphy (Merck, 60-230 mesh). Analyses of the purified photoproducts were performed using ^1H and ^{13}C NMR (Bruker AC 200, Bruker AC 250, and Bruker WM 400) spectroscopy, IR (Perkin-Elmer 1420), UV (Hitachi U-3200), and MS (Finnigan MAT 8200) spectroscopy. For fluorescence spectroscopy an Aminco-Bowman Series 2 luminescence spectrometer was used. A time correlated single-photon technique (Edinburgh Instruments, model 199 S) using simultaneous acquisition of fluorescence and excitation (SAFE)[32,33] was employed to determine the fluorescence decay parameters. The excitation and emission wavelength were 316 and 390 nm, respectively. The data were analyzed using a conventional iterative convolution technique described elsewhere[34]. The reported decay times are averages of 4 measurements with fit values of chi-square <1.3.

Standard irradiation procedure
A solution of the substrate (0.01 to 0.05 M) in the appropriate solvent (see Tables 1-3) in a pyrex vessel purged with a constant stream of dry nitrogen was irradiated for the time given in Tables 1-3. After evaporation of the solvent the composition of the crude photoproduct was determined by NMR spectroscopy using characteristic signals of the independently synthesized compounds. Subsequent thin layer chromatography of the crude reactions products led to the analytically pure products.

*Irradiation of the methyl esters of N-phthaloyl threonine and serine (**1a**, **2a**)*
Following the standard procedure, after 72 h irradiation of 245 mg (0.93 mmol) of **1a** in 65 ml of acetonitrile and 2 ml deuterium oxide a total of 90% of crude photoproduct was isolated which was >95% methyl-[2-$^2H_1$]-2-phthalimidoethanoat. After crystallization from methanol/water 35%. mp 110-112°C (112°C [11a]). ^1H-NMR (250 MHz, $CDCl_3$): δ = 3.74 (s, 3H, OCH_3), 4.42 (d, $^1J_{HD}$=2.9 Hz, 1H, NCH(D)), 7.73 (m, 2H, Ar.-H), 7.86 (m, 2H, Ar.-H).
Similar results were obtained with the serine derivative **2a**. Acetaldehyde and formaldehyde were detected in a sealed tube experiment with **1a** and **2a**, respectively.

*Irradiation of N-phthaloyl threonine **1b***
Following the standard procedure, after irradiation of a 0.01 M solution of **1b** in 100 ml of solvent the crude photoproduct was analyzed by ^1H and ^{13}C NMR spectroscopy. Product ratios were determined using characteristic signals of the independently synthesized products.
^1H-NMR (250 MHz, $CDCl_3$) data for: (E)-N-propenylphthalimide (**4*E***): δ = 1.82 (d, *J* = 5.0 Hz, 3H, CH_3), 6.55 (m, 2H, =CH); (Z)-N-propenylphthalimide (**4*Z***): δ = 1.72 (d, *J* = 7.0 Hz, 3H, CH_3), 5.81 (dq, *J* = 7.0, 8.3 Hz 1H, =CH), 6.13 (dq, *J* = 1.7, 8.3 Hz 1H, =CH); 2-phthalimidoacetic acid (**5**): δ = 4.40 (s, 2H, NCH); N-methylphthalimide (**6**): δ = 3.15 (s, 3H,

CH_3); (RS)-2-hydroxypropylphthalimide (**7**): δ = 1.22 (d, *J* = 6.3 Hz, 3H, CH_3), 3.72 (dd, *J* = 4.3, 6.8 Hz, 2H, NCH), 4.08 (m, 1H, OCHCH$_3$); (RS)-2-methoxypropyl-phthalimide (**8**): δ = 1.16 (d, *J* = 5.9 Hz, 3H, CH_3), 3.30 (s, 3H, OCH_3), 3.78 (m, 1H, OCHCH$_3$); 2-oxypropyl-phthalimide (**9**): δ = 2.19 (s, 3H, CH_3), 4.43 (s, 2H, CH_2).

Irradiation of N-phthaloyl serine **2b**
Following the standard procedure, after irradiation of a 0.01 M solution of **2b** in 100 ml of solvent the crude photoproduct was analyzed by ^{1}H and ^{13}C NMR spectroscopy. Product ratios were determined using characteristic signals of the independently synthesized products.
^{1}H-NMR (250 MHz, $CDCl_3$) data for: N-vinylphthalimide (**10**): δ = 5.00 (d, *J* = 9.9 Hz, 1H, =CH), 6.03 (d, *J* = 16.4 Hz, 1H, =CH), 6.83 (d, *J* = 9.9, 16.4 Hz, 1H, =CH); 1-hydroxyethyl-phthalimide (**11**): δ = 3.92 (s, 4H, CH_2).

Irradiation of N-phthaloyl phenylalanine and N-phthaloyl tyrosine (and their corresponding methyl esters) ***12a, 12b, 13a, and 13b.***
Following the standard procedure, after irradiation of a 0.01 M solution of **2b** in 100 ml of solvent the crude photoproduct was analyzed by ^{1}H and ^{13}C NMR spectroscopy. Product ratios were determined using characteristic signals of the independently synthesized products.
Path A products: ^{1}H-NMR (250 MHz, $CDCl_3$) data for N-phenylethylphthalimide (**15**): δ = 2.92 (dd, *J* = 7.6, 7.5 Hz, 2H, CH_2), 3.83 (dd, *J* = 7.6, 7.5 Hz, 2H, CH_2).

Path B products: ^{1}H-NMR (250 MHz, $CDCl_3$) data for N-phthalimide (**16**): δ = 7.68 (s, 4H) ; *E*-cinnamic methyl ester (E-**17a**): δ = 6.32 (d, *J* = 15.0 Hz, 1H, =CH), 6.88 (d, *J* = 15.0 Hz, 1H, =CH); Z-cinnamic methyl ester (Z-**17a**): δ = 5.88 (d, *J* = 11.5 Hz, 1H, =CH), 7.63 (d, *J* = 11.5 Hz, 1H, =CH).
Path C products:
from N-phthaloyl-DOPA (**14a**): mixtures of diastereomers (trans:cis = 89:11):
major diastereomer: (3S,4S)-2,3,4,5-Tetrahydro-4-(3′,4′-dihydroxy)-phenyl-1,5-dioxo-1*H*-benz[c]azepine-3-carboxylate-acetonide (*trans*-**18a**):
^{1}H-NMR (250 MHz, $CDCl_3$): δ = 1.51 (s, 6 H, 2 CH_3), 4.27 (dd, *J* = 4.7, 7.7 Hz, 2 H, CH), 4.48 (d, *J* = 4.7 Hz, 1 H, CHNH), 6.41 - 6.67 (m, 3 H, Ar. - H), 7.48 - 7.73 (m, 4 H, Ar. - H), 8.57 (d, *J* = 7.7 Hz, 1 H, NH).- ^{13}C-NMR (64 MHz, $CDCl_3$): δ = 26.3 (q, 2 C), 56.8 (d), 61.8 (d), 108.8 (d), 109.8 (d), 118.8 (s), 122.4 (d), 128.9 (s) 130.8 (d), 132.9 (d), 133.6 (s), 134.8 (d, 2 C), 137.3 (s), 146.7 (s), 147.6 (s), 169.3 (s), 171.7 (s), 202.7 (s). IR (CCl_4): ν = 3140 (m), 2970 (w), 2880 (w), 2960 (w), 1800 (w), 1780 (m), 1620 (m), 1375 (s), 1090 (s), 990 (vs).
minor diastereomer: (3S,4R)-2,3,4,5-Tetrahydro-4-(3′,4′-dihydroxy)-phenyl-1,5-dioxo-1*H*-benz[c]azepine-3-carboxylate-acetonide (*cis*-**18b**):
^{1}H-NMR (250 MHz, $CDCl_3$): δ = 1.51 (s, 6 H, 2 CH_3), 4.40 (d, *J* = 3.2 Hz, 1 H, CHNH), 4.95 (dd, *J* = 3.2, 6.0 Hz, 1 H, CH), 6.41 - 6.67 (m, 3 H, Ar. - H), 7.48 - 7.73 (m, 4 H, Ar. - H), 8.57 (d, *J* = 6.0 Hz, 1 H, NH).- ^{13}C-NMR (63 MHz, $CDCl_3$): δ = 146.9 (s), 147.2 (s), 167.9 (s), 170.1 (s), 203.3 (s) (separated signals from cis/trans-mixture).

from N-phthaloyl-DOPA methyl ester (**14b**): mixtures of diastereomers (trans:cis = 90:10):
major diastereomer: Methyl-(3S,4S)-2,3,4,5-tetrahydro-4-(3′,4′-dihydroxy)-phenyl-1,5-dioxo-1*H*-benz[c]azepine-3-carboxylate-acetonide (*trans*-**18b**):
^{1}H-NMR (250 MHz, $CDCl_3$): δ = 1.57 (s, 3 H, CH_3), 1.58 (s, 3 H, CH_3), 4.18 (d, *J* = 10.0 Hz, 1 H, CH), 4.56 (dd, *J* = 6.0, 10.0 Hz, 1 H, CHNH), 6.32 - 6.48 (m, 2 H, Ar. - H), 6.57 (d, *J* = 7.8 Hz, 1 H, Ar. -H), 6.92 (d, *J* = 6.0 Hz, 1 H, NH), 7.43 (dd, *J* = 2.0, 7.0 Hz, 1 H, Ar. - H), 7.52 - 7.63 (m, 2 H, Ar. - H), 7.82 (dd, *J* = 2.0, 7.0 Hz, 1 H, Ar. - H).- ^{13}C-NMR

(64 MHz, $CDCl_3$): δ = 26.0 (q, 2 C), 53.0 (q), 58.0 (d), 65.1 (d), 108.1 (d), 108.3 (d), 118.7 (s), 121.4 (d), 128.9 (d) 129.2 (s), 130.0 (d), 131.6 (s), 132.8 (d, 2 C), 137.3 (s), 147.6 (s), 148.2 (s), 169.1 (s), 169.6 (s), 202.3 (s).- IR (CCl_4): ν = 3385 (m), 3080 (w), 3005 (m), 2960 (w), 1740 (s), 1680 (vs), 1500 (s), 1245 (vs), 1230 (s), 985 (m).-

minor diastereomer: Methyl-(3S,4R)-2,3,4,5-tetrahydro-4-(3′,4′-dihydroxy)-phenyl-1,5-dioxo-1*H*-benz[c]azepine-3-carboxylate-acetonide (*cis*-**18b**):

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 1.62 (s, 3 H, CH_3), 1.63 (s, 3 H, CH_3), 4.30 (d, *J* = 3.0 Hz, 1 H, CH), 5.00 (dd, *J* = 3.0, 5.7 Hz, 1 H,CHNH), 6.32 - 6.48 (m, 2 H, Ar. - H), 6.59 (d, *J* = 6.0 Hz, 1 H, Ar. -H), 6.79 (d, *J* = 5.7 Hz, 1 H, NH), 7.43 (m, 1 H, Ar. - H), 7.52 - 7.63 (m, 2 H, Ar. - H), 7.82 (m, 1 H, Ar. - H).- ^{13}C-NMR (64 MHz, $CDCl_3$): δ = 167.9 (s), 168.5 (s), 202.0 (s).- (separated signals from cis/trans-mixture).-

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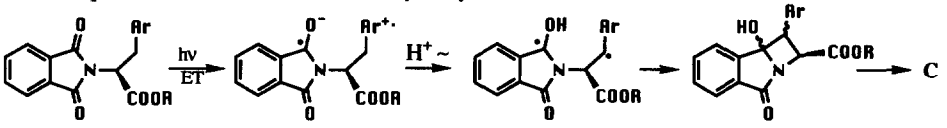
22. A plausible mechanism involves a hydroxyazetidine as instable intermediate:



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