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Electron-transfer photochemistry of organic amides and imides

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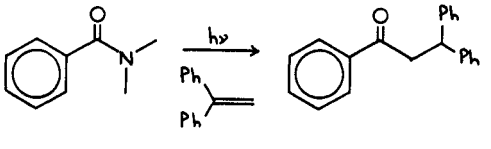
ABSTRACT

The wider variety of photochemical reactions observed for cyclic dicarboximides, rather than for carboxamides, is associated in part with the possibility of reaction pathways involving initial electron transfer. Such pathways are not favourable for thio analogues of the imides. Simple dipeptides and tripeptides, however, do give products on photolysis that are most readily accommodated in a mechanism that starts with excited state electron transfer to the amide group. This is exemplified for a number of dipeptides and for triglycine, with evidence from product arrays that sequential electron transfer is one route to products for the tripeptide.

Compounds containing a ketone chromophore have played an important role in the growth of organic photochemistry as a major sub-discipline of chemistry. There is a diverse range of reactions associated with the excited states of this class of compound, and they are quite readily amenable to both chemical and physical investigation. Significant reaction types include the cleavage, hydrogen-abstraction and cycloaddition reactions of saturated or aromatic ketones (ref.1), and the fascinating array of rearrangements exhibited by acyclic or cyclic enones and dienones (ref.2). The pre-eminence of ketones amongst organic carbonyl compounds is reflected not only in academic studies, but also in practical applications: aromatic ketones are the most widely used class of organic photoactive compound in ultraviolet/visible-sensitive imaging formulations or radiation-cured coatings (ref.3).

Against this background, the photochemical reactions of other types of carbonyl compound appear much less varied (ref.4). For saturated or aromatic carboxylic acids and their derivatives, alpha-cleavage is one of the few reaction processes that is widely reported (e.g. 1) (ref.5). Photochemical reactivity in unsaturated analogues is either much diminished or involves reaction in which the carbonyl group plays an incidental role: it may serve to extend the wavelength of absorption into a more readily accessible spectral region, or it may provide the means by which rapid intersystem crossing is achieved, but it remains unchanged in the overall chemical reaction.



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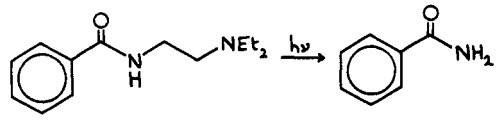

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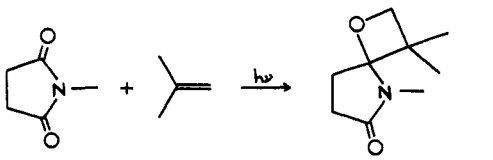
We are interested in the photochemistry of carbonyl compounds in which there is a nitrogen atom adjacent to the C=O group, particularly carboxamides and dicarboximides. Although alpha-cleavage products are formed from some amides, many saturated amides or benzamides are relatively inert photochemically. Several years ago we examined (ref.6) the photochemical behaviour of aromatic amides with a 2-diethylaminoethyl substituent on the nitrogen atom (2). They undergo a Norrish type 2 cleavage reaction, and the quantum yields, although quite low, are 15 to 40 times higher than for amides without the amino substituent (e.g. $PhCONHCH_2CH_2Ph$, $\phi = 0.0004$).

This behaviour parallels what is seen for analogous benzoate esters (ref.7); the inefficiency has two causes, namely the (π,π^*) nature of the lowest excited state, and an unfavourable alignment of orbitals in preferred conformations of an intermediate biradical, and the introduction of an amino substituent helps to overcome the first of these by providing an electron-transfer pathway to the biradical that is not dependent on the electronic nature of the excited state. A similar pattern of behaviour has been noted in dialkylaminoalkyl ketones also (ref.8), and the general mechanistic conclusion is that a compound with a good electron-donor group on a substituent chain can react by an electron-transfer route that has the potential to be more efficient than a process relying on direct hydrogen-atom transfer.

The incorporation of a second carbonyl group adjacent to the nitrogen atom of an amide makes a considerable difference to the electronic properties and photochemistry, and the photochemical reactions of dicarboximides are quite fascinating (ref.9). Over the past 10 to 15 years there have been sustained contributions in the area from Professor Kanaoka's group in Japan, and from Professor Mazzocchi's group at the University of Maryland, as well as from our group. Saturated cyclic dicarboximides undergo a Paterno-Büchi cycloaddition with alkenes (3) (ref.10), and N-substituted compounds give products resulting from hydrogen abstraction and cyclisation, to form either a new 4-membered ring compound that is transformed to a medium-ring ketolactam (4) (ref.11), or a new 5-membered ring product (5) (ref.12).



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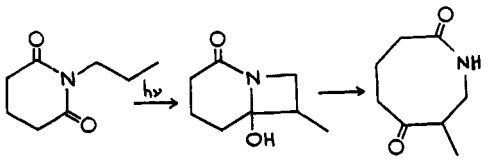

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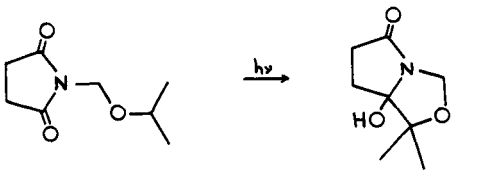

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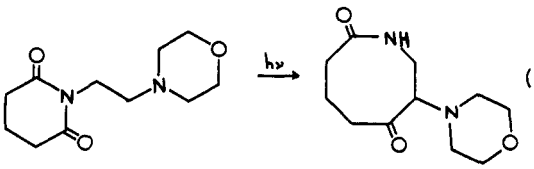

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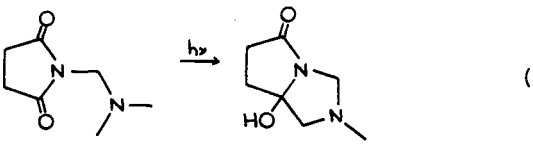

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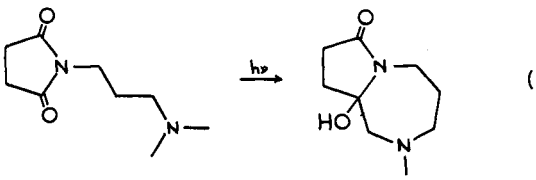

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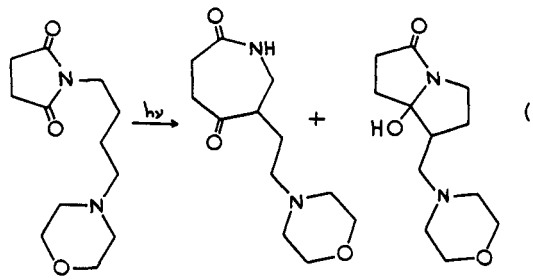

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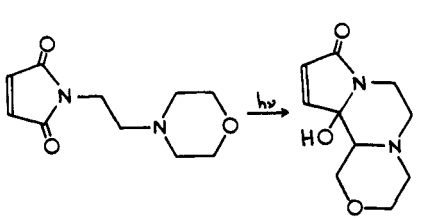
The electronic nature of the reactive excited state is not easy to characterise, but the reactions are "typical" of the (n,π^*) chemistry of saturated ketones. Succinimides and glutarimides with a dialkylaminoalkyl substituent behave in a similar way (6,7), but although reaction at a more remote site takes place with a 3-(dimethylaminopropyl) compound (8), products from a 4-(morpholinobutyl) derivative (9) arise from attack at unactivated C-H positions not adjacent to nitrogen (ref.13).

Aromatic imides (e.g. phthalimides) and unsaturated imides (e.g. maleimides) give different patterns of products. Maleimides carrying 2-dialkylaminoethyl groups lead to reaction at the C-H position remote from the imide (10; compare 6) (ref.13), as do related phthalimides (ref.14). For phthalimides in which there is a longer chain separating the imide and amine nitrogen atoms, similar behaviour is observed, so that medium- or large-ring products may be formed (11) (ref.15). Higher chemical efficiencies result when the substituent is methylthio (MeS) rather than dimethylamino (Me_2N), and rings up to 38 atoms in size have been produced (ref.16). In accounting for such reaction patterns, it is difficult to avoid the conclusion that there must be a high degree of electron transfer, followed by a subsequent proton transfer within a species whose geometry is strongly influenced by the attraction of oppositely charged radical-ion species. The observed differences between saturated and unsaturated imides probably reflect the involvement of a more direct hydrogen-atom transfer in the mechanism for the saturated compounds.



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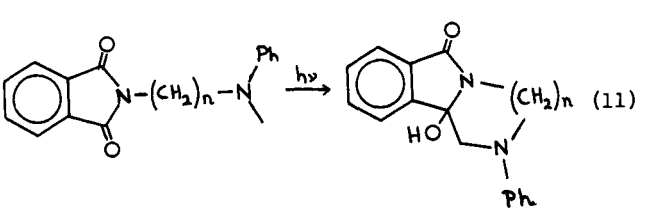

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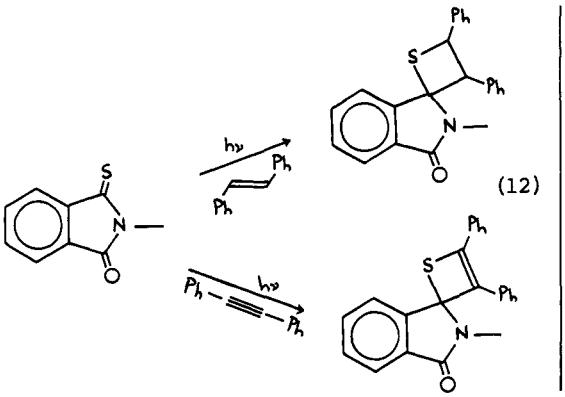
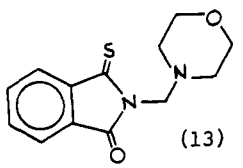
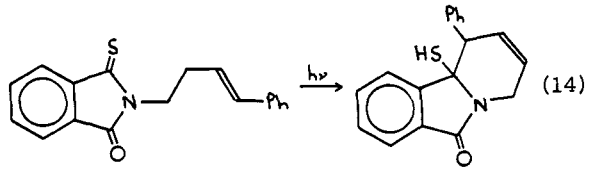
Electron transfer and charged intermediates also play a part in the photochemical addition reactions of aromatic imides with alkenes, as evidenced by the incorporation of alcohol solvents into products; much of this work has been reported by Mazzocchi (ref. 17).

The differences between saturated and unsaturated imides, associated with a fairly even balance in the factors governing electron-transfer processes, was one reason for our interest in the photochemistry of thiocarbonyl analogues. Thiomides also had the attraction of being coloured, so offering a range of visible-wavelength photochemistry, and their study was part of a general growing interest in the photoreactions of organic sulfur compounds. Both saturated and unsaturated thioimides (12) (ref.18) and dithioimides (ref.19) behave like thioketones, especially in their photocycloaddition reactions with alkenes or alkynes. Compounds whose structure might facilitate electron transfer/proton transfer processes (e.g. 13) (ref.18) are found to be relatively photostable (ref. 20).



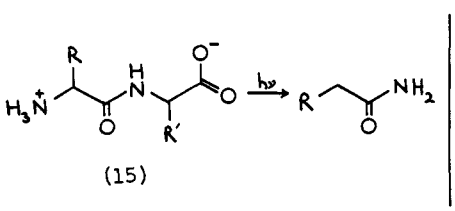


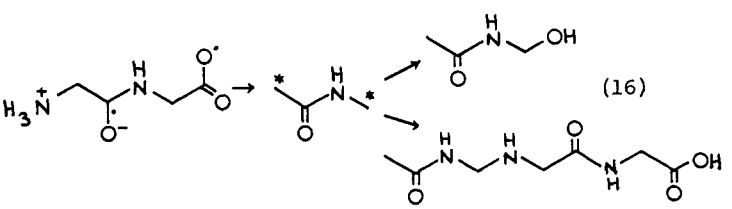


The rationalisation of this behaviour is that the lower excited state energy of the thiocarbonyl compounds is the major factor in reducing the efficiency of electron transfer as compared with analogous carbonyl compounds. Hydrogen abstraction can still occur in appropriately substituted thioimides (14) (ref.21), as it does in thioketones (ref.22).

With the benefit of hindsight, it is possible to rationalise this excursion into imide and thioimide photochemistry as a series of studies which demonstrated that a carbonyl group adjacent to nitrogen is capable of taking part in photo-induced electron-transfer processes. In a different context it has long been established that electron transfer is a facile process in certain polyamides, namely the proteins involved in biological electron-transport mechanisms. A question of current debate in such systems is how the initial step of light absorption by an associated side-chain or other group is translated into electron loss or gain at a remote site. Is the transport pathway provided by the non-amide groups or the amide backbone? A number of recent studies (ref.23) have taken carefully designed model compounds with several reactive groups and 'spacer' groups, to demonstrate that through-space interactions do indeed occur between such reactive groups. We set out several years ago to study simple dipeptides and tripeptides, with the object of searching for chemical evidence relating to the effectiveness of an amide group in an electron-transfer process. Such simple models are far removed from proteins, and at best they offer a guide to the behaviour of a carboxyl end fragment, but they are more amenable than more complex models to a qualitative and quantitative product study. Some earlier studies had been reported (ref.24), especially by Meybeck (ref.25), that provided qualitative (often chromatographic) evidence for selected products; we hoped to confirm and quantify the results, and to provide a fuller account of the fate of the peptides.

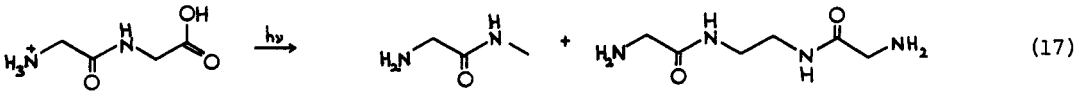
The simplest dipeptide, glycylglycine (15; R,R'=H), on photolysis in aqueous solution at 254 nm gives carbon dioxide, ammonia and acetamide (ref.26) in chemical yields between 50 and 90%. The measured yield of acetamide varies with the thermal treatment of the solution after photolysis and is maximum after heating to 100°C for a short period or if the analysis is performed by gas chromatography. Two thermally labile precursors were identified (16), one fully characterised as N-hydroxymethylacetamide, and the other thought to be an N-methylacetamide substituted with a glycylglycyl group; the latter compound breaks down readily to give acetamide, formaldehyde and glycylglycine, and the structure is consistent with the n.m.r. spectra of solutions containing the material (ref.27).





A mechanism that rationalises these major products starts with electron transfer from the carboxylate group to the amide in the excited state of the peptide. This is followed by loss of ammonia from the ammonio-substituted amide radical anion, and loss of carbon dioxide from the carboxylate radical. The biradical/zwitterion so formed can undergo addition of water to give N-hydroxymethylacetamide, or addition of glycylglycine, or hydrogen abstraction to form acetamide directly. Terminal deamination has been established as a major step in the reaction of electrons with aliphatic oligopeptides in aqueous solution (ref.28), and this lends support to the proposal that an amide radical anion plays a role in the relatively specific photolysis that we observe for dipeptides.

Minor products from the photolysis of glycylglycine include N-acetylglycine and bis(acetamido)methane ($CH_3CONHCH_2NHCOCH_3$). When the photolysis is carried out in acidified solution (pH 1-2), ammonia and acetamide formation is suppressed, and the major products (17; R=H) are carbon dioxide (75%), N,N-diglycylethane-1,2-diamine (50%), and glycine N-methylamide (30%). This different array of products most likely arises from an initial alpha cleavage adjacent to the carboxyl group, and the products attributable to electron transfer are not formed when the good electron-donor group (carboxylate anion) is no longer available at low pH.



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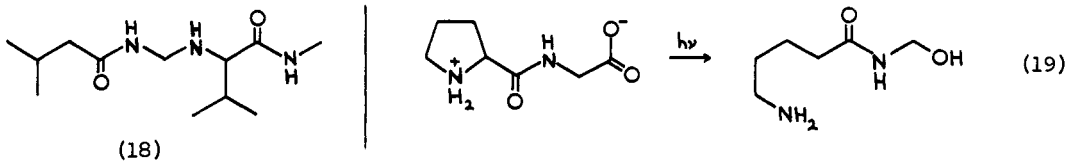


(18) (19)

Two dipeptides with additional alkyl groups, alanylglycine (15; R=Me, R'=H) and valylglycine (15; R=Pr^i, R'=H), were found to give similar patterns of products in aqueous solution, and also in acidic solution (cf. 17). Of particular interest is the isolation and characterisation of a compound (18) that represents an additional type of labile intermediate, decomposing on heating into isovaleramide, formaldehyde, and valine N-methylamide. The results fully support the mechanistic hypothesis that was formulated for the glycylglycine results.

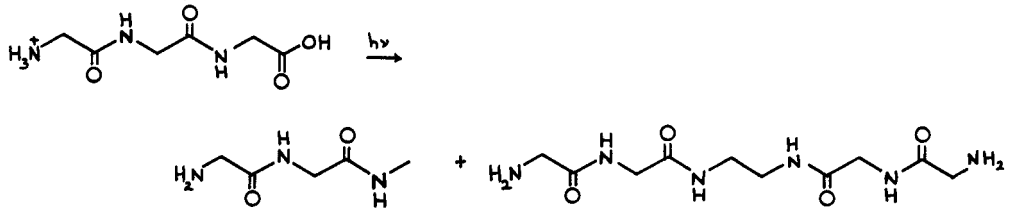
For glycylglycine we measured a quantum yield for reaction of (0.44 ± 0.11) at 254 nm; the error range reflects in part the very low value for the absorption coefficient at this wavelength. This quantum yield value is remarkably high and represents a highly quantum efficient process not previously suggested for peptides. The implication is that reverse electron transfer is not efficient (perhaps in these model systems the loss of ammonia occurs simultaneously with electron transfer), and in a more general context, the amide group is capable of acting as a relay in electron-transfer processes.

Prolylglycine is different from the other dipeptides studied in not having a free ammonio group that can be eliminated as ammonia. Instead, an analogous reaction results in ring-opening of the pyrrolidine ring, and the product, after loss of carbon dioxide, carries an amine and a hydroxymethylamide group (19); this can be isolated and characterised as a bis(benzyloxycarbonyl) derivative (ref.29). The initial yield of product is around 25%, and heating the photolysed solution results in its conversion to δ-valerolactam. An additional significance in these results arises because there is a high level of prolyl (and hydroxyprolyl) residues in dermal connective tissue, which is known to undergo photodegradation in sunlight-induced skin damage (ref.30). As with the acyclic dipeptides there is a link with radiolytic studies, since electron addition is reported to lead to ring-opening in prolyl peptides (ref.31).

In all of the aliphatic dipeptides discussed so far, the main contribution to absorption at 254 nm comes from the amide group. When one of the constituent amino-acid units has an aromatic side-chain, absorption at this wavelength is much stronger and is associated very largely with the aromatic group. To see how this affects the photochemistry, we irradiated phenylalanylglycine and glycylphenylalanine, and in both cases ammonia and carbon dioxide are produced in reasonable yields, although the chemical yields and the quantum yields are not as high as with the aliphatic dipeptides. The main amide product from phenylalanylglycine, after heating the photolysis solution, is phenylpropanamide ($PhCH_2CH_2CONH_2$), which is analogous to acetamide from glycylglycine. We also find some glycine, and very small quantities of phenylalanine, glycylglycine and diketopiperazine, which had been reported by Meybeck (ref.25).

The main conclusion to be drawn from these results is that absorption of light by an aromatic side-chain group leads in some degree to the same electron-transfer process that operates in aliphatic dipeptides - in effect, the absorbing group acts as a 'relay' for the transfer of an electron. Preliminary work with prolylphenylalanine shows the formation of carbon dioxide and δ-valerolactam, albeit in relatively low yields, and from phenylalanylproline ammonia is formed.

Another key step in testing the generality of the hypothesis that electron transfer occurs readily in the excited states of peptides relates to the possibility of sequential electron transfer along a peptide backbone. The simplest model compound using our approach is triglycine. This undergoes clean photolysis under acid conditions to give (ref.27) carbon dioxide (78%), glycylglycine N-methylamide (70%) and N,N'-di(glycylglycyl)ethane-1,2-diamine (20), presumably by an alpha-cleavage mechanism. The N-methylamide is also formed (73%) at pH 6, but not the substituted diamine; additionally, ammonia (27%) and N-acetylglycine N-methylamide (5%) are amongst the products at the higher pH.



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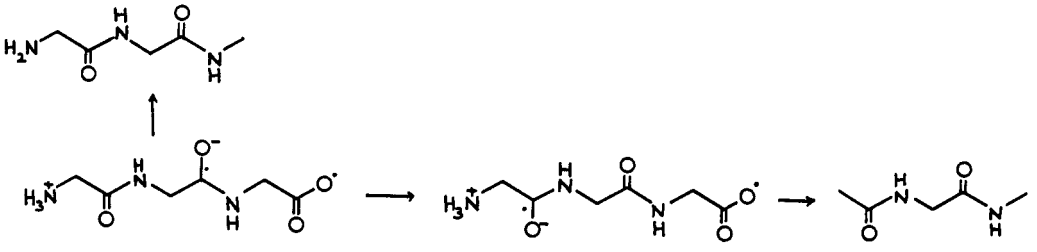
These results are best accommodated by a mechanism (21) in which electron transfer to the first amide group is followed by a divergence in the pathway: about 70% of the intermediate that reacts does so by loss of carbon dioxide and internal proton transfer to yield the decarboxylated product, and about 30% undergoes a second electron transfer to the more remote amide group, which then results in loss of ammonia and formation, in part, of the N-acetyl methylamide.



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These studies raise a number of interesting questions that we are pursuing, such as the role of different conformations in determining the efficiency of sequential electron transfer along a peptide backbone, but they do offer support, based on extensive product analysis, for the involvement of electron-transfer processes in the photochemical reaction pathways of peptides in particular, or amides more generally.

Acknowledgements

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