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Chiral Photocages Based on Phthalimide Photochemistry

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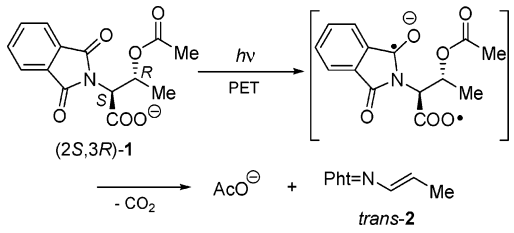
The quest for new efficient caging groups is an active area of research in bio-organic chemistry.[1] More specifically, photoremovable protecting groups (PRPGs) constitute a powerful tool for the masking of potentially bioactive molecules in biological media, controlling the release of the molecule in space and time. Besides the biological applications of these phototriggers (in neurobiology, physiology, biochemistry),[2] they have been applied in multistep organic syntheses as conventional protecting groups,[3] in combinatorial chemistry, solid-phase syntheses, and for the preparation of DNA microarrays using photolithographic techniques.[4] Beyond the widely used *ortho*-nitrobenzyl photocage, which suffers from several disadvantages,[5] a number of PRPGs have been developed,[4,6] many of them based in photoinduced electron transfer (PET) processes.[5] Recently, a new kind of PRPG has been described based on the PET-initiated photochemical decarboxylation of ketoprofen,[7] which allows a rapid and efficient photorelease of alcohols and carboxylic acids. The interest on this kind of photodecarboxylation processes as a basis for PRPG systems is increasing.[8] Motivated by previous studies on the PET decarboxylation photoreactions of the *N*-phthaloylated derivatives of the natural amino acids serine and threonine,[9] we present a novel methodology, which introduces chirality in the area of photocaged systems.

The 3-(2-phthalimido-propionate)-yl PRPG has several advantages that make it especially appropriate for biological applications: The caged systems are soluble in aqueous solutions (phosphate buffer at pH $\approx$ 7.0 was used for the irradiations) and no organic cosolvent is needed. The major photoproduct, an *N*-alkenylphthalimide, is expected to exhibit low toxicity/reactivity, compared with the nitroso- compounds arising from *ortho*-nitrobenzyl PRPGs.[5] The photorelease process is rapid and quantum-efficient. Finally, as a new feature, the introduction of chirality in the photocaged system allows the study of stereodifferentiation processes involving the release of the caged molecule. Enantioselective photoreactions in biological chiral environments or in the presence of biomolecules have been described.[10] When involving chiral triplet states, photophysical evidence for the stereodifferentiation has been obtained as well.[11] In the context of PRPGs, chiral photocages could provide a method for the selective liberation of the masked molecule when a specific (active) conformation of the photocage is favored by the chiral environment.

Apart from the case of interaction with a chiral environment, stereodifferentiation processes in the photochemistry of diastereomers are known.[12] In this context, we tested the diastereoselective photorelease from derivatives of 2-phthalimido-3-hydroxybutyric acid, which include a second stereogenic center. The proof of principle is given here for photocaged acetate, although synthetic routes for new photocages are currently being explored (see below).

First, we synthesized compound (2*S*,3*R*)-**1**, derived from natural threonine, possessing a *threo*-configuration. As depicted in Scheme 1, the photorelease of acetate involves the loss of a molecule of CO_2, initiated by a PET process from the carboxylate to the electronically excited phthalimide chromophore. In the photoreaction of (2*S*,3*R*)-**1**, the alkenylphthalimide *trans*-**2** was detected as the sole photoproduct.

Scheme 1



The photocleavage of this PRPG was accomplished by irradiation into the 300 nm absorption band. The high absorbance of the phthalimide chromophore ($\epsilon_{300} \approx 2 \times 10^3$ mol^{-1} cm^{-1}) is similar to that of simple nitrobenzyl derivatives at the same wavelength. Moreover, the phthalimide absorption properties can be tuned: for example, 4,5-dimethoxy substituted phthalimides shift their absorption band ca. 50 nm to the red.[13] Although the absorptivity of the unsubstituted phthalimides at 350 nm is low ($\epsilon_{350} \approx 8$ mol^{-1} cm^{-1}), the photocleavage is also possible (at lower rates) when irradiated with 350 nm light (see Supporting Information, SI).

During the irradiation of (2*S*,3*R*)-**1**, the diminution of the UV absorption in both bands of the phthalimide was observed in the spectra recorded from 5×10^{-5} M solutions at different times. At higher concentrations (10^{-2} M), used for general in vitro irradiations, a precipitate is formed, composed by the coproduced poorly soluble alkenylphthalimide. The insolubilization of the byproduct also prevents it from competing for the absorption of light and from being photoisomerized.

Regarding the nature of the active excited state, previous studies on the intermolecular reaction between excited phthalimides and carboxylates[14] pointed out that the electron-transfer process involves the triplet state of the phthalimide. In the case of the PRPG system, which involves an intramolecular PET, we performed parallel irradiations of (2*S*,3*R*)-**1** in buffer solution purged with air and in the presence of triplet sensitizers. Comparing with the reference reaction (deoxygenated buffer solution), we did not observe an appreciable decrease in the formation of *trans*-**2** in the first case, only a small increase in the yield (ca. 6%) when the reaction is sensitized with acetone (300 nm) and an effective sensitization at 350 nm, using 2-carboxybenzophenone as sensitizer (see SI). These observations are compatible with (i) a relatively high quantum yield of intersystem crossing ($\Phi_{ISC} = 0.8$ has been determined for *N*-methylphthalimide),[14] therefore the acetone sensitization being of little noticeable effect at 300 nm, and (ii) an intramolecular electron-transfer faster than the intermolecular quenching of the triplet state by oxygen. A PET process from the singlet state, as in the case of the singlet-state decarboxylations of benzophenone (e.g., ketoprofen)[7] or xanthone chromophores[8] cannot be ruled out, although phthalimide-mediated decarboxylation processes do not

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Table 1. Quantum Yields of Acetate Release and Product Distribution (%) of the Isolated Photoproducts after Irradiation of (2*S*,3*R*)-**1** and **3**

substrate	Φ^b	*trans*-**2**	*cis*-**2**	**4**
(*threo*-)(2*S*,3*R*)-**1**, 300 nm	0.40 ± 0.05	>95		
(*erythro*-) **3**, 300 nm	0.22 ± 0.05	20	65	15
(*threo*-)(2*S*,3*R*)-**1**, 350 nm[c]		>95		
(*erythro*-) **3**, 350 nm[c]		30	40	30

[a] 5×10^{-3} M, buffer solution pH = 7, 120 min, using RPR-3000 Å and 3500 Å lamps in a rayonet housing. [b] Measured at 313 nm, monitoring the formation of **2**. [c] Irradiation times were longer, because of the low absorbance (ca. 8 h).

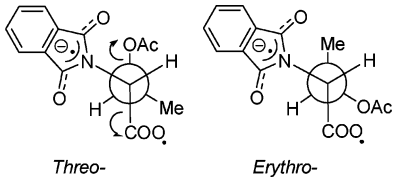
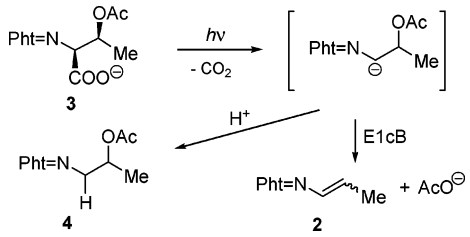


Figure 1. Newman projections of the threo and erythro configurations, depicted in the conformations yielding the lower number of steric repulsions.

Scheme 2

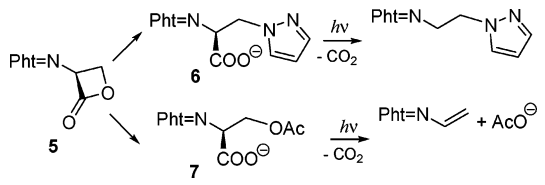


fit into the singlet-state decarboxylation type, which comprises only intramolecular processes greatly influenced by substitution (position) effects.[7,8]

A different process was verified for the diastereomeric photocage with the erythro configuration. When caged acetate **3** was irradiated (Scheme **2**), a mixture of *cis*- and *trans*-propenylphthalimides **2** was observed, along with some 1-phthalimido-2-propanol acetate (**4**), the product of simple decarboxylation.[15] The different distribution of photoproducts after the irradiation of the two diastereoisomers is shown in Table 1. The compounds were also irradiated at 350 nm, showing only marginal wavelength dependence for the reaction of **3**.

A plausible explanation for this behavior stems from geometrical considerations. The Newman projections of both diastereoisomers (Figure 1) show that the threo diastereoisomers can lead to the trans double bond through an antiperiplanar geometrical disposition of −COO• and −OAc leaving groups, which is the preferred situation for an E2 concerted β-elimination. During the formation of the double bond, conjugation with the π-system of the phthalimide and electronic reorganization take place in a concerted fashion. By contrast, in the case of the erythro diastereoisomers, the steric interactions avoid the concerted β-elimination, and an intermediate carbanion is formed after decarboxylation (Scheme 2). This carbanion can be protonated by the aqueous solvent or eliminate acetate via E1cB mechanism, yielding either the cis or the trans double bond.

Scheme 3



A simple and general strategy for chiral caging is the use of the serine-derived β-lactone **5** (Scheme 3) that can be ring-opened by a variety of nucleophiles.[16] The decaging activity depends on the leaving group ability of the molecule thus inserted: For example, caged pyrazole **6** did not lead to the liberation of pyrazole but to the product of simple decarboxylation, as opposed to **7**, which cleanly liberates acetate.

In summary, a new PRPG has been developed, which can be advantageously applied for the caging of carboxylates and similar molecules. This PRPG includes a chiral moiety, derived from natural amino acids. The scope of chiral photocaging has been preliminarily explored by the analysis of a model system.

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Supporting Information Available: Experimental procedures, copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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