Photocyclization of α-Keto Amides in Homogeneous Solution and Aqueous Cyclodextrin Media. The Role of Zwitterions and Diradicals in Photoinduced Electron Transfer Reactions

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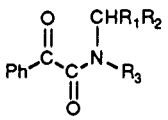
Abstract: A mechanistic investigation of the photoreaction of the N,N-disubstituted benzoyl amides, PhCOCONR′R″ **1–4** (**1**: R′ = C_2H_5, R″ = Ph; **2**: R′ = R″ = C_2H_5; **3**: R′ = R″ = CH_2Ph; **4**: R′ = R″ = *i*-C_3H_7), in homogeneous solutions (water, methanol) and aqueous cyclodextrin is reported. The chief photoproducts, oxazolidin-4-ones, 3-hydroxyazetidin-2-ones, mandelamides, and carbonyl compounds, can all be accounted for by a mechanism involving single electron transfer quenching of the "ketone" excited state with the amide serving as an electron donor. The first quenching product, a zwitterion $\mathbf{Z}_1$, undergoes rapid and irreversible decay to a diradical, **D**, and a second zwitterion, $\mathbf{Z}_2$, by a sequence of proton transfer followed by a second intramolecular electron transfer. Formation of the observed products can be accounted for by decay or interception of **D** or $\mathbf{Z}_2$. Although **D** and $\mathbf{Z}_2$ appear to be resonance contributors to a single structure, calculations suggest that their relative importance varies greatly with configuration, such that a "planar" structure is predominantly zwitterionic while partially or largely twisted structures should be predominantly diradical. The application of this principle leads to a consistent interpretation of the varied product distribution that occurs as substituents on the amide and the reaction medium are varied.

Introduction

The photochemistry of α-keto amides (α-oxo amides) has been the subject of several investigations; although irradiation of these compounds can lead to a variety of products, in a number of cases direct photolysis leads to a moderate to good yield of heterocyclic products (chiefly oxazolidinones and azetidinones) which are otherwise synthetically difficult to obtain. While most of the studies reported thus far have focused on synthetic or preparative aspects of keto amide photochemistry,[1,2a] the several mechanistic possibilities for reaction merit deeper investigation. The lowest excited states are quite clearly associated with the ketone carbonyl; the neighboring amide functionality could serve variously as a source of H-atoms, electrons, or protons with reaction leading to a number of different reactive intermediates including biradicals and zwitterions. Previous studies[2] have suggested that reactions leading to the abovementioned heterocycles proceed via processes closely related to Norrish type II photoelimination of ketones.

In this paper we report a study of the photoreactivity of a series of N,N-disubstituted α-oxo amides **1–4** and the deuterated derivatives **1**-d_1, **2**-d_1, and **3**-d_1 in homogeneous solution and microheterogeneous media (cyclodextrin (CD) complexes). The



	R_1	R_2	R_3
1	H	CH_3	Ph
2	H	CH_3	C_2H_5
3	H	Ph	CH_2Ph
4	CH_3	CH_3	$CH(CH_3)_2$
1-d_1	D	CH_3	Ph
2-d_1	D	CH_3	C_2H_5
3-d_1	D	Ph	CH_2Ph

results reported indicate that the reactivity of these α-oxo amides is initiated by a single electron transfer quenching of the ketone excited state in which the amide serves as an electron donor. The overall chemical outcome of the electron-transfer quenching is shown to be determined by substituents and the microenvironment, which in turn govern the interconversion and decay of zwitterionic and diradical intermediates which are formed from the initial zwitterion.

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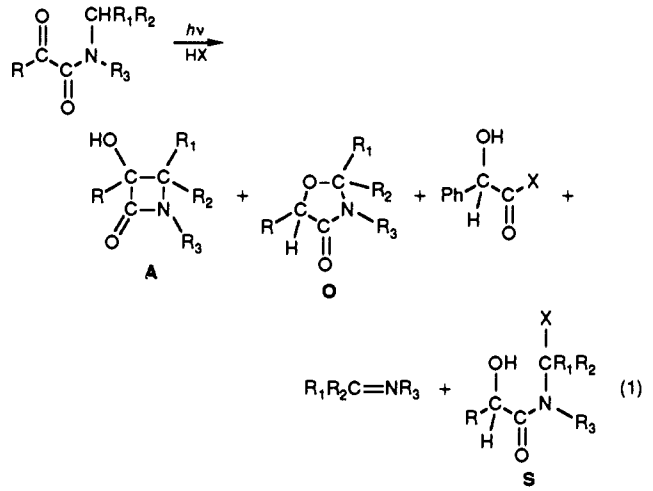
Results

Absorption spectra of various benzoyl amides show a prominent π–π* transition centered near 260 nm. This transition exhibits a modest red shift with an increase in solvent polarity. For all of the amides used in this study there is no detectable fluorescence, and the photoreactions are not readily quenchable. Laser flash photolysis of **1** and **2** in aqueous solution shows no transients longer lived than 5 ns. Photolyses described in this paper generally involve activation via the long-wavelength transition at the wavelength near 300 nm.

Previous studies[1,2] have shown that direct photolysis of α-oxo amides can lead to a variety of cyclization and fragmentation products (eq 1):



(1)

In the present study, we found that irradiation of α-oxo amides **1–4** leads to predominantly the cyclization products, substituted oxazolidin-4-ones (**O**), and 3-hydroxyazetidin-2-ones (**A**). However, photolysis of **3** and **4** at low pH produces substantial amounts

(1) (a) Henry-Logan, K. R.; Chen, C. G. *Tetrahedron Lett.* **1973**, 1103. (b) Zehavi, U. *J. Org. Chem.* **1977**, *42*, 2821. (c) Akermark, B.; Johanson, N. G.; Sjorberg, B. *Tetrahedron Lett.* **1969**, 371. (d) Johanson, N. G.; Sjorberg, B.; Akermark, B. *Acta Chem. Scand., Ser. B* **1976**, *B30*, 383.

(2) (a) Aoyama, H.; Hasegawa, T.; Watabe, M.; Shiraishi, H.; Omote, Y. *J. Org. Chem.* **1978**, *43*, 419. (b) Aoyama, H.; Hasegawa, T.; Omote, Y. *J. Am. Chem. Soc.* **1979**, *101*, 5343. (c) Aoyama, H.; Sakamoto, M.; Omote, Y. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1357. (d) Aoyama, H.; Sakamoto, M.; Kuwabara, K.; Yoshida, K.; Omote, Y. *J. Am. Chem. Soc.* **1983**, *105*, 1958.

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Table I. Disappearance Quantum Yields (Φ_D), Photoproduct Quantum Yields (Φ_i), and Chemical Yields (θ_i) in Homogeneous Media[a]

amide, solvent	Φ_D	Φ_O	(θ_O)	Φ_A	(θ_A)	Φ_M	(θ_M)	Φ_C	(θ_C)
1, methanol	0.016	0.008	(0.50)	<0.001	(0.0)[b]				
1, water	0.019	0.011	(0.58)			0.002	(0.11)	nd[c]	
2, methanol	0.28	0.28	(1.00)						
2, water	0.28	0.24	(0.86)						
3, methanol (met.)	0.28	<0.01	(<0.04)	0.27	(0.96)				
3, met.–water, pH 1[d]	0.47			0.09	(0.20)	0.32	(0.68)	0.33	(0.69)
3, met.–water	0.30	0.07	(0.23)	0.20	(0.67)				
3, met.–water, pH 13[e]	0.28	0.11	(0.40)	0.15	(0.54)				
4, methanol	0.29	0.19	(0.62)	0.09	(0.31)				
4, water, pH 1	0.30	0.04	(0.13)	0.06	(0.20)	0.12	(0.40)	nd	
4, water	0.27	0.16	(0.60)	0.07	(0.26)				
4, water, pH 13	0.25	0.14	(0.56)	0.06	(0.24)				

[a] All quantum yields were determined at 22 ± 2 °C. Estimated error 10%. [b] Trace. [c] Not detected. [d] Methanol–water (1:1), 0.1 M in HCl. [e] Methanol–water (1:1), 0.1 M in KOH.

Table II. Isotope Effects and Deuterium Incorporation in the Oxazolidin-4-ones[a]

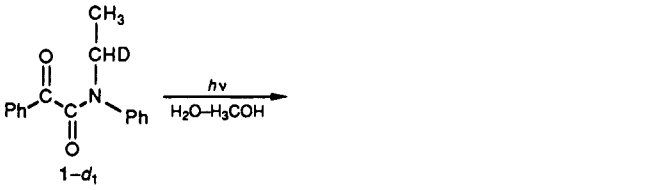
amide	solvent	Φ_D	Φ_O	F_{O2D}[b]	F_{O5D}[c]	Φ_A	F_{A4D}[d]	k_H/k_D
1-d_1	H_2O–H_3COH, (1:1)	0.018	0.010	0.51 ± 0.04	0.00			1.04 ± 0.08
1	H_2O–H_3COH, (1:1)	0.019	0.011					
1	D_2O–D_3COD, (1:1)	0.019	0.011		1.00			
2-d_1	H_2O	0.27	0.24	0.27 ± 0.02	0.00			1.12 ± 0.07
2	H_2O	0.28	0.24					
2	D_2O	0.28	0.25		1.00			
2	H_2O–D_2O, (1:1)	0.28	0.25		0.130 ± 0.006			6.7 ± 0.3
3-d_1	H_2O–H_3COH, (1:1)	0.27	0.07	nd[e]		0.20	0.26 ± 0.02	1.08 ± 0.08
3	H_2O–H_3COH, (1:1)	0.30	0.07			0.20		

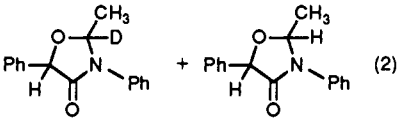
[a] Quantum yields were determined at 22 ± 2 °C. Estimated error 10%. [b] Fraction of the total oxazolidin-4-one quantum yield that corresponds to the 2-d_1-oxazolidin-4-one. Estimated by ^{1}H NMR spectroscopy. [c] Fraction of the total oxazolidin-4-one quantum yield that corresponds to the 5-d_1-oxazolidin-4-one. Estimated by ^{1}H NMR spectroscopy. [d] Fraction of the total azetidin-2-one that corresponds to the 4-d_1-azetidin-2-one. Estimated by ^{1}H NMR spectroscopy. [e] Not determined.

of mandelamides (**M**) and carbonyl products (**C**), both products arising from **S** (X = OH).[3]

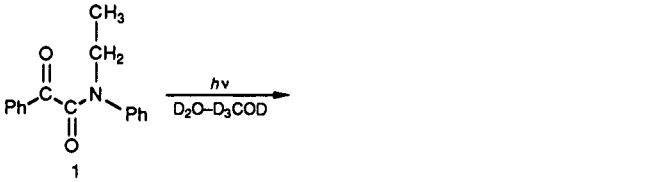
Disappearance (Φ_D) and photoproduct quantum yields (Φ_i) for amides **1–4** are listed in Table I. The chemical yields for product formation, $\theta_i = \Phi_i/\Phi_D$, can also be found in the same table. Although the structural variation in these four amides appears relatively small, there are some interesting contrasts in reactivity. The *N*-ethyl-*N*-phenyl derivative **1** shows relatively inefficient (<2%) reactions. In both water and methanol, the 5-membered cyclized oxazolidin-4-one is the predominant product (60% yield) with only small amounts of mandelamides being detected (11%). In contrast, the *N*,*N*-dialkyl amides **2–4** show much higher quantum yields for reaction (25–50%), with the diethyl amide **2** producing exclusively the oxazolidin-4-one (86%) and the dibenzyl derivative **3** producing predominantly the azetidin-2-one (67%). In the cases of **3** and **4**, the product distribution was found to be strongly pH dependent. The yield of azetidin-2-ones is maximal near neutral pH, while a basic medium slightly favors the formation of oxazolidin-4-ones. Mandelamides and carbonyl compounds are produced in equal efficiencies as the chief products in strongly acidic (pH 1) solutions.

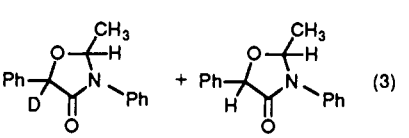
Deuterated derivatives, **1**-d_1, **2**-d_1, and **3**-d_1, were also investigated as was the photolysis of **1** and **2** in deuterated solvents (Table II). The photolysis of monodeuterated α-oxo amides leads to a very small decrease in the overall quantum efficiency for reaction in each case and to virtually no change in the distribution of products. For photolysis of monodeuterated **1**-d_1, in which the oxazolidin-4-one could be derived equally on a statistical basis from migration of a hydrogen or deuterium, the cyclic product obtained in protium solvents has 0.51 D per molecule at the 2-position (**O2D**, eq 2). This indicates a nearly equal probability of hydrogen vs deuterium "migration" with the migrating hydrogen "washed out" via exchange with solvent protons. This is confirmed by the finding that irradiation of undeuterated **1** in deuterated solvents leads to net incorporation of one deuterium at C-5 (**O5D**, eq 3).





51% **O2D** 49% (2)

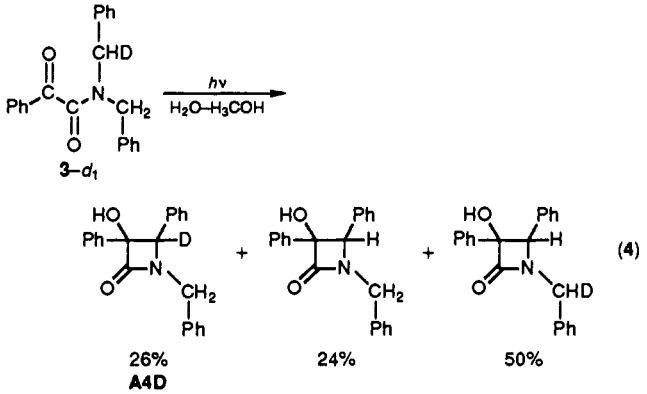




100% **O5D** 0% (3)

Photolysis of monodeuterated **3**-d_1 in protic solvents leads to 0.26 D per molecule at the 4-position of the azetidin-2-one (**A4D**, eq 4) and to 0.50 D per molecule in the methylene of the *N*-benzyl. Again, these results show little selectivity for H(D) transfer. A similar result was obtained for the formation of oxazolidin-4-one from the photolysis of monodeuterated **2**-d_1 in protic solvents; 27% of the total oxazolidin-4-one produced was deuterated at the 2-position (**O2D**), 23% was unlabeled, and the remaining 50% showed incorporation of a D atom in the methylene of the *N*-ethyl.

(3) The oxazolidinones (**O**) and azetidinones (**A**) produced in these reactions are thermally stable at pH 7. Other investigations[2c] also indicate that oxazolidinones are stable in acid (10% sulfuric acid in ethanol), ruling out the possibility that mandelamides and carbonyl products arise from hydrolysis of **O**.



As was the case with **1**, irradiation of undeuterated **2** in deuterated solvents leads to incorporation of 1 D per molecule at the C-5 of the oxazolidin-4-one (**O5D**). Irradiation of unlabeled **2** in a 1:1 H_2O–D_2O mixture leads to relatively low (0.13 D per molecule) incorporation of deuterium in the resulting oxazolidin-4-one, from which an isotope effect for H/D incorporation of 6.7 is determined. It was found that no deuterium is incorporated in the recovered starting material following photolysis of **1** or **3** in deuterated solvents; this indicates that intermediates capable of D/H exchange with solvent do not decay via return to the starting material for either α-oxo amide.

Cyclodextrin Complexes of Benzoyl Amides. α-Oxo amides **1**, **2**, and **4** are sparingly soluble in pure water; **3** is water insoluble. All four of these amides form complexes when added to aqueous solutions of β-cyclodextrin or γ-cyclodextrin. Unfortunately, even though dibenzyl amide **3** can be initially solubilized in an aqueous solution of γ-cyclodextrin, the complex slowly precipitates out making a systematic study of its properties impossible. The absorption spectra of cyclodextrin complexes of **1**, **2**, and **4** are characterized by a decrease in the extinction coefficient between 270 and 290 nm when they are compared to the absorption spectra of the aqueous amides. In contrast, the β-cyclodextrin complex of **3** is characterized by a small increase in the extinction coefficient around 280 nm when the spectrum is compared to the amide's absorption in methanol–water (1:1). Excepting the amide **1**–γ-CD complex, complex formation is also accompanied by the appearance of an isosbestic point around 245 nm.

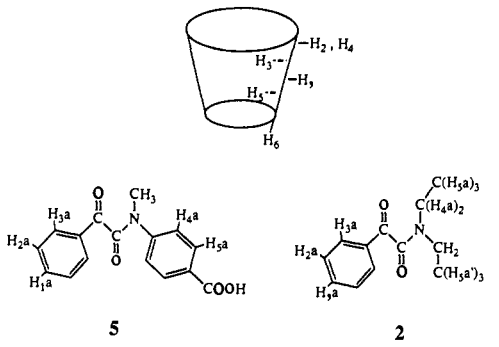
In the case of *N*-ethyl-*N*-phenyl amide **1**, the complex formed with both cyclodextrins was precipitated by addition of **1** to a saturated aqueous solution of either cyclodextrin. The complex precipitates as a white solid, which is soluble in an excess of water; the solid can also be dissolved in DMSO-d_6, and the relative host to guest concentrations can be estimated by ^{1}H NMR spectroscopy. The molar ratio of amide **1** to β- or γ-cyclodextrin was calculated by integration of the NMR signals; the measured values were 1:0.92 and 1:0.96 for **1**–β-cyclodextrin and **1**–γ-cyclodextrin, respectively.

Although the spectroscopic changes in the UV are small, they can be reliably used to measure the dissociation constants (K_d) for amides **1**, **2**, and **4** according to the Bender approach.[4] The value of K_d for **3** cannot be readily measured since the α-oxo amide is water insoluble; however, **3** is directly solubilized by β-cyclodextrin quantitatively as the cyclodextrin complex. Values for K_d are listed in Table III. These values are in the same range as a number of other aromatic "guests" which have been previously shown to associate with cyclodextrin by inclusion in the interior of the cyclodextrin torus.[5] While **1** and **2** form slightly more stable complexes with β- than with γ-cyclodextrin, the reverse is the case for amide **4**.

(4) (a) VanEtten, G.; Clowes, J.; Sebastian, F.; Bender, M. *J. Am. Chem. Soc.* **1967**, *89*, 3252. (b) Hui, Y.; Winkle, J. R.; Whitten, D. G. *J. Phys. Chem.* **1983**, *87*, 23.

(5) (a) Cramer, F.; Saenger, W.; Spatz, H. *J. Am. Chem. Soc.* **1967**, *89*, 14. (b) Dasaratha Reddy, G.; Jayasree, B.; Ramamurthy, V. *J. Org. Chem.* **1987**, *52*, 3107. (c) Demarco, P. V.; Thakkar, A. L. *J. Chem. Soc., Chem. Commun.* **1970**, 2. (d) Yakamoto, Y.; Inoue, Y. *J. Carbohydr. Chem.* **1989**, *8*, 29 and references cited therein.

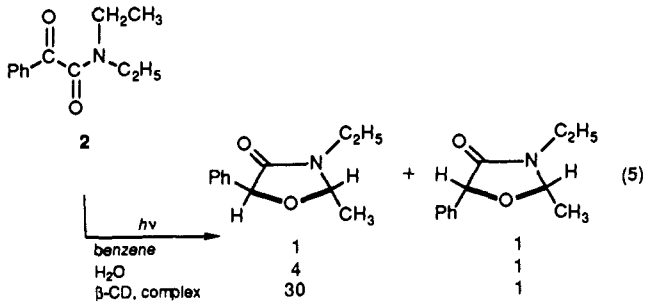
Scheme I



Amides **2** and **5** (Scheme I) are sufficiently soluble in water so that both the amide and cyclodextrin complexes can be investigated by ^{1}H NMR spectroscopy. The extrapolated changes in chemical shifts for protons of both cyclodextrin and the amide that occur upon complete complexation are reported in Table IV. Although all of the cyclodextrin protons are shifted upfield to various extents, the inner protons (H_3, H_5, and H_6) show the largest shifts while the outer protons (H_1, H_2, and H_4) are relatively unaffected. These upfield shifts of the β- and γ-cyclodextrin protons provide evidence for the inclusion of the guest molecule into the hydrophobic cavity of cyclodextrin.[5] Further support for the inclusion phenomenon was obtained from the changes in the chemical shift for the amide protons. Even though these changes are less easy to interpret, they can be used for drawing some qualitative conclusions regarding the structure of the complexes.

Incorporation of amides **1**–**4** into the complexes with the cyclodextrin modifies their photochemistry; Table III lists the quantum efficiencies for various photoprocesses for completely complexed amides **1**–**4**. Although overall the same products were obtained for the amides in the presence and absence of the cyclodextrins, some significant differences in distribution occur which are dependent on both the particular amide studied and the cyclodextrin. For example, for *N*-ethyl-*N*-phenyl derivative **1**, which shows the lowest reactivity of the four amides investigated, reactivity is further attenuated upon complexation with both cyclodextrins, and the attenuation is most significant for γ-cyclodextrin. As in the case of photolysis in homogeneous solution, no deuterium incorporation was observed in recovered starting oxo amide **1** upon photolysis of the **1**–β-CD complex in D_2O. For diethyl amide **2** there is a slight attenuation in reactivity for both cyclodextrins; however, the reduction is somewhat greater for β-cyclodextrin than for γ-cyclodextrin. In sharp contrast, the reactivity of the dibenzyl amide **3** is enhanced upon formation of the complex with β-cyclodextrin both in neutral and acidic solutions. Along with the enhanced reactivity is an increase in the selectivity of forming the azetidin-2-one. For the diisopropyl oxo amide **4**, a small decrease in photoreactivity for the β-cyclodextrin complex is observed, while the γ-cyclodextrin complex exhibits a moderately increased reactivity. Again, complexation of the α-oxo amide elevates the yield of the azetidin-2-one.

The cyclic products obtained from photolysis of amides **2** and **3** exist as diastereomers, and the individual diastereomers can be readily analyzed from their different chemical shifts in ^{1}H NMR spectra. Table V reports the isomer distribution obtained from photolysis of **2** and **3** in different media. The dominant oxazolidin-2-one obtained from photolysis of **2** is distributed roughly equally between the two diastereomers when the photolysis is carried out in benzene (eq 5). In contrast, a nearly 4:1 selectivity favoring the trans is obtained in water. The reaction is even more diastereomer selective when carried out in the cyclodextrin complexes, particularly so for the β-cyclodextrin complex where nearly complete selectivity in favor of trans is observed. Interestingly, somewhat of a reversal occurs with the azetidin-2-one produced upon photolysis of the dibenzyl amide **3**. In this case, relatively high selectivity favoring the *trans*-azetidin-2-one (**t-3A**) is observed in benzene, but this reactivity decreases in the series: benzene, methanol, methanol–water. A preference for trans is observed



(5)

for photolysis in the β-cyclodextrin complex compared to methanol–water.

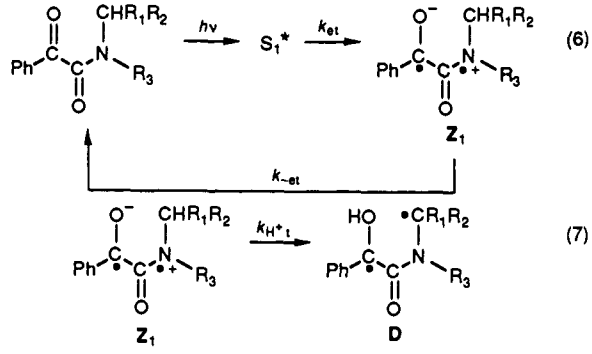
Discussion

Excited-State Quenching in α-Oxo Amides. For several substituted ketones it is possible that net hydrogen atom transfer by the excited carbonyl can occur either by direct atom abstraction or in two steps: electron transfer followed by proton transfer. The latter "charge-transfer" path was first evident for photoreduction via amine donors, which exhibit orders of magnitude higher excited state quenching reactivity than would be anticipated for simple hydrogen sources.[6] Aromatic ketones bearing γ abstractable hydrogens generally undergo a Norrish type II reaction from their n–π* triplet state.[7] However, for amino ketones, the excited carbonyl interacts with the amino group, and electron transfer from the nitrogen to the carbonyl occurs prior to the hydrogen shift. In contrast to the direct hydrogen abstraction reactions, photochemical hydrogen transfer to carbonyl oxygen mediated by the charge-transfer pathway occurs even if the lowest triplet excited state of the ketone is the otherwise unreactive π–π* state.[8]

Acylation of amines raises the ionization potential of the n electrons on N, and the corresponding amides should be less effective photoreducing agents.[8,9] Nevertheless, the amide nitrogen can behave as an electron donor in photoinduced electron transfer reactions. Clear indications of an electron transfer from an amide nitrogen to an excited ketone carbonyl were reported in studies of the photochemistry of β-oxo amides.[10] β-Oxo amides undergo photocyclization through either an unquenchable singlet-state electron-transfer process followed by δ-proton abstraction or via a quencher-sensitive n–π* triplet state δ-hydrogen abstraction. Both mechanisms operate together, but the relative weight of the contributing mechanisms depends on the solvent polarity and, surprisingly, on the number of methyl substituents on the 2-position of the keto amide.

It has been shown that the deuterium isotope effect on the γ-hydrogen abstraction generally provides useful evidence in distinguishing between the direct and the two-step hydrogen-transfer mechanisms.[8,11] Comparative photolysis of deuterated and undeuterated α-oxo amides **1**, **2**, and **3** shows a very small decrease in the overall quantum efficiencies coupled with relatively little (<5%) H/D selectivity in the intramolecular H(D) transfer to form the oxazolidin-4-one or 3-hydroxyazetidin-2-one. From these experiments, a very small but positive isotope effect can be calculated (Table II). These values are substantially smaller than those reported for γ-hydrogen transfer in the Norrish type H reactions,[7] but their magnitude is comparable to the relatively small kinetic deuterium isotope effect reported for the inter- or intramolecular reduction of ketones by electron donors.[6,8,11]

Since the α-oxo amides are virtually nonfluorescent, their photolysis is unquenchable, and they yield no transients detectable by nanosecond laser spectroscopy, it is difficult to specify which excited state is the product precursor. However, the observations that the closely related β-oxo amides can react from the singlet excited state, the lack of α-oxo amide transients persisting on the nanosecond time scale, and the relatively high quantum efficiencies for product formation suggest an intramolecular singlet-quenching process producing very short-lived intermediates may be the most reasonable. Hence, from the lack of a large kinetic isotope effect and the above-indicated short time scale of the reaction, we suggest the intervention of an intermediate produced via electron transfer from the amide nitrogen to the excited carbonyl to form an ion pair or zwitterion $\mathbf{Z}_1$ (eq 6). Transfer of a proton from the *N*-alkyl

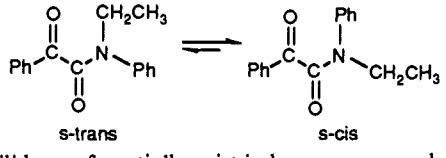


(6)

(7)

group to the ketyl radical followed by electron reorganization would produce the same 1,4-diradical (D) as would be obtained by direct hydrogen abstraction (eq 7). Proton transfer occurring in $\mathbf{Z}_1$ should be highly favorable, since the zwitterionic character of this intermediate should enhance both the nucleophilicity of the carbonyl oxygen and the electrophilicity of the proton α to the nitrogen. A small activation energy for this process could account for the low observed isotope effect. The failure of deuterated solvents to lead to deuterium incorporation in the recovered starting material indicates that the diradical formation is thermodynamically irreversible. Thus, assuming a high efficiency for the forward electron transfer, the limit in the reaction efficiency is probably due to competition between the two decay paths for $\mathbf{Z}_1$, back electron transfer (k_{-et}) and proton transfer (k_{H^+1}), to generate D. Fast intramolecular reverse electron transfer in $\mathbf{Z}_1$ should regenerate the ground-state α-oxo amide and account for the less than unit quantum yield.

The relatively small disappearance quantum yield for the *N*-ethyl-*N*-phenyl oxo amide **1** can be attributed to an unfavorable geometry for the γ-proton transfer. Amide **1** can exist either as the s-cis or the s-trans conformer, arising from the asymmetry of the substitution on the nitrogen (eq 8). It has been shown that



(8)

α-oxo anilides preferentially exist in homogeneous solution in the s-cis rotational conformer.[2b] The ^{1}H NMR spectrum of this amide recorded in fully deuterated methanol–water (1:1) shows the presence of both conformers; the major isomer is s-cis (92 ± 1%) and the minor isomer s-trans (8 ± 3%). Since proton abstraction by the ketyl oxygen occurring from the s-cis structure requires rotation about the C–N bond, back electron transfer in $\mathbf{Z}_1$ should dominate, making the net overall reactivity of the major isomer very small. However, the s-trans conformer should be reactive. From the disappearance quantum yield for amide **1** (Table I) and assuming that only about 8% of the total amide is in the appropriate reactive s-trans conformation, a quantum efficiency for the s-trans isomer around 0.25 ± 0.1 can be estimated. This value is in close agreement with the observed disappearance quantum yields for the other α-oxo amides, suggesting that a common mechanism, with similar rate constants for the difference processes,

(6) (a) Cohen, S.; Chao, H. *J. Am. Chem. Soc.* **1968**, *90*, 165. (b) Cohen, S.; Stein, N.; Chao, H. *J. Am. Chem. Soc.* **1968**, *90*, 521. (c) Davidson, R. S.; Lambeth, P. F. *Chem. Commun.* **1968**, 511.

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Table III. Disappearance Quantum Yields (Φ_D), Photoproduct Quantum Yields (Φ_i), and Chemical Yields (θ_i) in Cyclodextrin Media[a]

medium	$K_d \times 10^3$ (M)[b]	Φ_D	Φ_O	(θ_O)	Φ_A	(θ_A)	Φ_M	(θ_M)	Φ_C	(θ_C)
1-water		0.019	0.011	(0.58)			0.002	(0.11)	nd[c]	
1-β-CD	2.86	0.005	0.002	(0.40)			<0.0001		nd	
1-γ-CD	2.94	<0.001	<0.001				<0.0001		nd	
2-water		0.28	0.24	(0.86)						
2-β-CD	2.84	0.18	0.18	(1.00)						
2-γ-CD	5.20	0.24	0.22	(0.92)						
3-met.-water pH 1[d]	*e*	0.47			0.09	(0.19)	0.32	(0.68)	0.33	(0.70)
3-β-CD, pH 1		0.60			0.17	(0.28)	0.36	(0.60)	0.38	(0.63)
3-met.-water		0.30	0.07	(0.23)	0.20	(0.67)				
3-β-CD		0.64	0.03	(0.05)	0.56	(0.88)				
4-water, pH 1		0.30	0.04	(0.13)	0.06	(0.20)	0.12	(0.40)	nd	
4-β-CD, pH 1		0.24	0.03	(0.13)	0.07	(0.29)	0.08	(0.40)	nd	
4-water		0.27	0.16	(0.60)	0.07	(0.26)			nd	
4-β-CD	4.89	0.24	0.13	(0.50)	0.12	(0.50)			nd	
4-γ-CD	1.16	0.35	0.17	(0.50)	0.17	(0.50)			nd	

[a] Quantum yields were determined at 22 ± 2 °C. Estimated error 10%. Disappearance and photoproduct quantum yields for the cyclodextrin complexes of α-oxo amides **1**, **2**, and **4** are extrapolated values to infinite concentration of CD. In the case of amide **3**, 100% complexation is assumed. [b] Dissociation constant for the aqueous complex. Values were estimated by UV-vis spectroscopy. [c] Not detected. [d] Methanol-water (1:1), 0.1 M in HCl. [e] Since amide **3** is water insoluble, K_d cannot be measured; however, **3** can be directly solubilized in β-CD (1×10^{-2} M) as the complex.

is operating despite the nature of the *N*-alkyl substituents.

From the photophysical data and by reasonable analogy with intermolecular reactivity, we can infer that the reaction involves rapid excited-state quenching via electron transfer to form $\mathbf{Z}_1$ and subsequent, also rapid, proton transfer to yield D as the primary steps of the photoreaction.[12]

(12) An estimation of the thermodynamics for the intramolecular electron-transfer process generating $\mathbf{Z}_1$ can be obtained from spectroscopic and electrochemical data. The free energy change for photoinduced electron transfer (ΔG^*) between an excited carbonyl acceptor and a ground-state amide donor at finite separation R_c in a medium of dielectric constant ϵ can be estimated using equation 16[13]

$$\Delta G^* = F(E_{ox} - E_{red}) - E_{00} - (e^2/\epsilon R_c) \qquad (16)$$

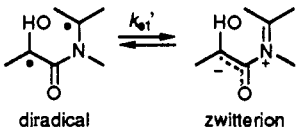
where E_{00} is the energy of the zero-zero transition of the excited state of the acceptor and E_{ox} and E_{red} are respectively the first one-electron oxidation potential of the donor and the first one-electron reduction potential of the acceptor in the solvent under consideration. Electrochemical measurements were made for α-oxo amides **1**, **2**, and **3** in acetonitrile solution at a glassy carbon electrode. All of the amides studied showed identical behavior. Reduction and especially oxidation of the amides were found to be largely irreversible, indicating that secondary reactions are significant on the time scale of the electrochemical experiments. In the presence of such complications, the apparent oxidation potential is shifted anodically and reduction potential cathodically with respect to the actual reversible values. It has been shown,[14] however, that the deviations seldom exceed 0.1 V, and the redox potential can be deduced from the anodic and cathodic peak potentials. Under these considerations, reduction for all of the α-oxo amides occurs around −1.6 ± 0.1 V vs SCE and oxidation at 2.1 ± 0.1 V vs the same reference electrode. It must be noted that the measured oxidation potentials for these α-oxo amides are appreciably more anodic than it should be anticipated for tertiary amides (around +1.5 V[15]). On the other hand, the reduction potentials are also shifted, now cathodically, from the expected value for a benzoyl group (E_{red} = −1.36 V vs SCE in water-ethanol (3:2) for 3-phenyl-3-oxo-acetanilide,[16] a β-oxo amide). These "shifts" suggest a strong inductive interaction or intramolecular ground-state charge-transfer formation between the donor and the acceptor residues of the molecules.[17] The energy of the 0-0 singlet transition was estimated from the fine structure of the n-π* transition observed in methanol-water (4:1) glass at 77 K. The E_{00} values for amides **1** and **3** correspond to an energy of 78 kcal/mol, which is in close agreement with the reported value of 79 kcal/mol for pyruvamide.[18] MMX mechanics calculations suggest an R_c distance (the separation between the oxygen carbonyl and the amide N) around 3.2 Å. Hence, from eq 16, E_{ox}, E_{red}, E_{00}, and R_c, a free energy change (ΔG^*) of about +0.2 ± 0.2 eV/mol (in acetonitrile) can be calculated. This estimate suggests an endergonic photoinduced intramolecular electron transfer reaction. However, if the potentials of the separate "components" of the α-oxo amides (a benzoyl acceptor group and a tertiary amide donor) are considered, and assuming the same value for E_{00} and R_c, a ΔG^* value around −0.5 eV/mol (indicating an exergonic reaction) can be estimated. Since all experimental evidence presented above indicates a facile photoinduced intramolecular quenching in α-oxo amides, we speculate that the unexpected "shifts" observed in the redox potentials of **1**-**3** somehow lead to an underestimation of ΔG^*. However, if these "shifts" are believed to correspond to a partial charge-transfer interaction in the ground state, besides the unfavorable ΔG^* calculated from eq 1, no barrier should exist for the photoinduced intramolecular electron transfer. Although the lifetimes of the singlet excited state charge transfer (CT) complexes are known to be exceptionally short, unexpectedly fast rates for proton-transfer reactions through excitation of CT complexes have been reported.[19]

Table IV. Cyclodextrin-α-Oxo Amide Complexes: Changes in ^{1}H NMR Spectra Upon Formation of Host-Guest Complexes[a]

	Δδ (ppm)[b]		Δδ (ppm)	
	5-β-CD	**5**-γ-CD	**2**-β-CD	**2**-γ-CD
	CD Protons			
H_1	−0.06	−0.02	0.00	−0.01
H_2	−0.02	−0.02	−0.02	−0.01
H_3	−0.30	−0.26	−0.14	−0.15
H_4	−0.06	−0.04	−0.02	0.00
H_5	−0.42	−0.28	−0.30	−0.16
H_6	−0.16	−0.04	−0.13	−0.15
	Amide Protons			
H_1a	0.04	0.00	0.12	0.11
H_2a	0.06	0.00	0.04	0.06
H_3a	0.04	−0.06	−0.12	−0.06
H_4a	0.07	−0.20	−0.03	−0.02
H_5a	0.20	−0.09	0.12	0.01
H_5'a			0.17	0.01

[a] All experiments were carried out in D_2O at room temperature. [b] $\Delta\delta = \delta_{complex} - \delta_{free}$.

Photolysis Intermediates and Reaction Products. Since it is difficult to rationalize the formation of the oxazolidin-4-one (**O**) and methanol adduct product (**S**, X = OCH_3, eq 1) directly from a 1,4-diradical, Aoyama et al.[2d] have proposed a zwitterion structure as the reaction precursor (eq 9).[20] Usually the energy



diradical zwitterion (9)

(13) Rehm, D.; Weller, A. *Ber. Bunsen-Ges. Phys. Chem.* **1969**, *73*, 834.
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(15) Ross, S. D.; Finkelstein, M.; Rudd, E. J. In *Anodic Oxidations*; Academic Press: New York, 1975; p 223.
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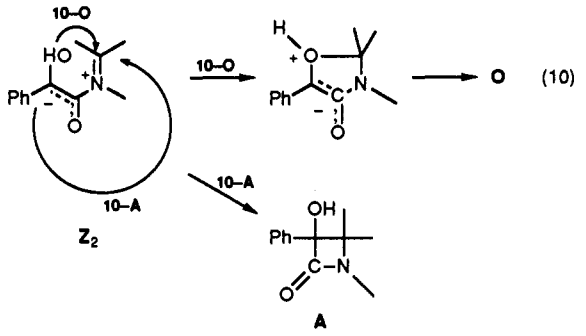
(18) Larson, D. B.; Arnet, J. F.; Seliskar, C. J.; McGlynn, S. P. *J. Am. Chem. Soc.* **1974**, *96*, 3370.
(19) Jones, G., II In *Photoinduced Electron Transfer*; Elsevier: New York, 1988; p 238.
(20) The 1,4-diradical and the zwitterion are resonance forms if nuclear configurations are identical. Therefore, the α-oxo amide reaction intermediate must be represented by a linear combination of covalent (diradical) and zwitterionic terms. The relative weights of the contributing structures are determined by the substituents, the environmental effects, and the actual molecular geometry.[20a] However, when the contribution of the diradical structure is much larger than that of the zwitterionic one, we can regard the species as a "pure" diradical (**D**), whereas the species can be seen as a "pure" zwitterion ($\mathbf{Z}_2$) in the reverse case (vide supra).

Table V. Isomer Distribution Obtained Upon Photolysis of **2** and **3** in Different Media

	2		**3**				
solvent	$F_{trans\text{-}O2}$[a]	$F_{cis\text{-}O2}$[b]	$F_{trans\text{-}3A}$[c]	$\theta_{t\text{-}3A}$[d]	$\theta_{O3} + \theta_{3M}$	$F_{cis\text{-}3A}$[e]	$\theta_{c\text{-}3A}$[f]
benzene	0.50	0.50	0.89	0.89	0.00	0.11	0.11
methanol			0.85	0.81	0.04	0.15	0.14
water	0.81	0.19					
water, pH 13	0.63	0.37					
met.–water, pH 1[g]			0.37	0.07	0.68	0.63	0.12
met.–water			0.78	0.52	0.23	0.22	0.15
met.–water, pH 13[h]			0.72	0.39	0.40	0.28	0.15
β-CD, complex, pH 1[i]			0.43	0.12	0.60	0.57	0.15
β-CD, complex	0.97(±)[j]	0.03(±)	0.87	0.84	0.05	0.13	0.11
γ-CD, complex	0.82	0.18					

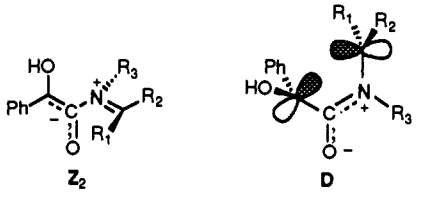
[a] Fraction of the total yield of 3-ethyl-2-methyl-5-phenyloxazolidin-4-one (**O2**) that corresponds to the trans isomer. Estimated by ^{1}H NMR spectroscopy. [b] Fraction of *cis*-oxazolidin-4-one. [c] Fraction of the total 3,4-diphenyl-1-benzyl-3-hydroxyazetidin-2-one (**3A**) that corresponds to the trans isomer. Estimated by high-pressure liquid chromatography. [d] Chemical yield for *trans*-**3A**; $\theta_{t\text{-}3A} = \theta_{3A}$ (Table I or Table III) × $F_{trans\text{-}3A}$. [e] Fraction of *cis*-azetidin-2-one. [f] Chemical yield for *cis*-**3A**. [g] Methanol–water (1:1), 0.1 M in HCl. [h] Methanol–water (1:1), 0.1 M in KOH. [i] Fractions for the isomer distribution obtained upon photolysis of amide **2** and **3** CD complexes are extrapolated values to infinite concentration of the cyclodextrins. [j] Oxazolidin-4-one (**O2**) recovered upon photolysis of the aqueous **2**–CD complex did not show optical activity.

of singlet diradicals lies below the energy of the corresponding zwitterions.[21] However, in this particular case a planar zwitterion would be stabilized by conjugation and could become the ground state of the system. All of the products formed upon photolysis of **1–4** can be satisfactorily explained in terms of this zwitterion intermediate (eq 10). However, interpretation of the stereochemistry and relative product efficiencies in the cyclodextrin media suggest a closer evaluation of this mechanism, especially in the analysis of the different factors that control the D → $\mathbf{Z_2}$ transformation.

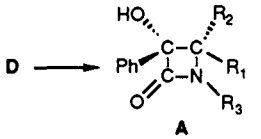


(10)

From basic considerations, it can be anticipated that D and $\mathbf{Z_2}$ must exist as two quite different molecular conformations. Stabilization of the zwitterionic structure requires an extended conjugation through p atomic orbitals; thus the preferred $\mathbf{Z_2}$ molecular conformation should be planar or nearly planar. Below are shown the more stable gas-phase conformations for D and $\mathbf{Z_2}$ predicted by MMX molecular mechanics calculations.



The preferred zwitterion geometry seems to be one where the plane that contains the hydroxyl group, the anionic carbon, and the carbonyl group is slightly twisted from the plane defined by the *N*-alkyl group and the N=C bond. Molecular models suggest that this structure is quite reasonable since, in contrast to the fully planar structures proposed for similar zwitterions,[2d,22] this conformation simultaneously involves maximum conjugation and minimum steric hindrance. On the other hand, for any "disorderly" molecular geometry the zwitterion state should be strongly destabilized because effective conjugation is not possible. Hence, in a partially or fully twisted molecular arrangement, the diradical is presumed to become the ground state. Above is also shown the MMX predicted preferred 1,4-diradical (D) geometry. The amide bond is still planar. The p orbital on the ketyl radical carbon is nearly orthogonal to the amide function, while the p orbital on the carbon α to the N is partially twisted from this same plane. This and similar molecular arrangements in which conjugation between the radical centers, the N, and the carbonyl group is restricted can be also characterized as diradicals. On the basis of the above analysis and in analogy with similar examples where the molecular geometry sharply determines the diradical or zwitterion character of a ground-state molecule,[20a,23] we assume that D and $\mathbf{Z_2}$ exist as two different *conformers* in which the intramolecular electronic distribution (the diradical-like or zwitterion-like character) is controlled by the molecular geometry (eq 11).[24]



(11)

Although the azetidin-2-one (**A**) can be envisioned as being formed from either D or $\mathbf{Z_2}$ from electronic considerations, it is clear that the transition state for forming the 4-membered ring must involve severe distortions from the stabilized $\mathbf{Z_2}$ geometry. Therefore, it is reasonable to infer that this product is preferentially formed from the less-planar D intermediate (eq 11). From a mechanistic point of view, cyclization of D yielding azetidin-2-one should be quite similar to the azetidin-3-ol formation upon photolysis of α-amido ketones[8,9] or α-amino ketones.[27] It is worth emphasizing that in these latter examples, the azetidinol must be formed from a 1,4-diradical since the existence of a relatively stable zwitterion structure in these cases is not possible. On the other hand, oxazolidin-4-ones (**O**), mandelamides (**M**), and carbonyl compounds (**C**) can be formed from the zwitterion ($\mathbf{Z_2}$)[2d] (eqs 12–15).

(21) (a) Salem, L.; Rowland, C. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 92. (b) Dauben, W. G.; Salem, L.; Turro, N. J. *Acc. Chem. Res.* **1975**, *8*, 41.

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(24) Interestingly, the D → $\mathbf{Z_2}$ process resembles the interconversion between the "normal" singlet excited state and the twisted intramolecular charge-transfer (TCIT) state responsible for the dual fluorescence of (*N*,*N*-dimethylamino)benzonitrile and related molecules.[25] These two emissions result from two conformationally distinct excited singlet states: the "normal" emission from a planar state and the TCIT emission from a twisted structure. Interconversion between these species is believed to occur through a simple twist of the phenyl–N bond.[26]

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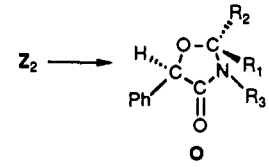
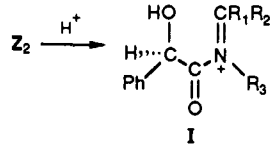
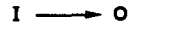


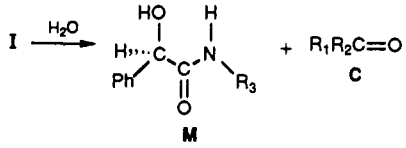
(12)



(13)



(14)



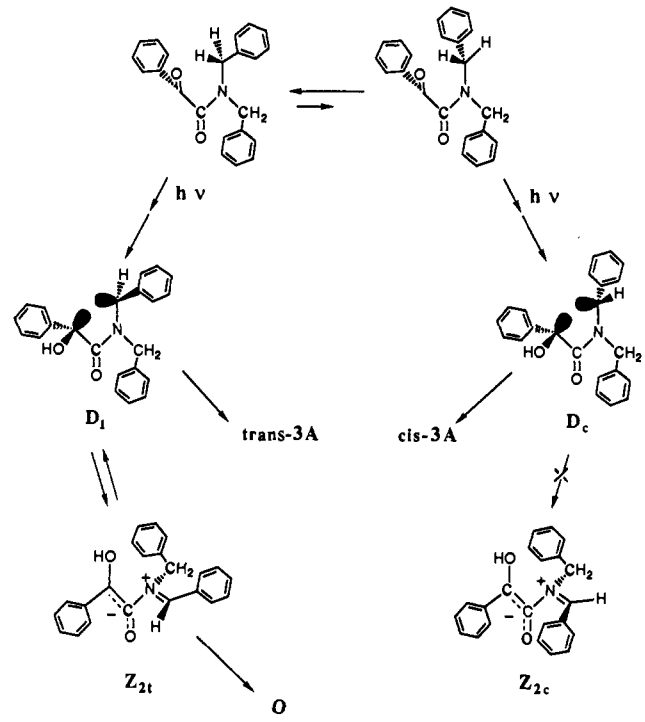
(15)

The process converting D → Z_2 (eq 9) can be seen as a conformational change coupled with intramolecular electron reorganization. For any initial D conformation in either homogeneous solution or host, it is possible to have distortions occurring driven to either minimize the intramolecular steric repulsions or to achieve maximum p orbital overlap. However, since charge stabilization is not possible in a molecular geometry like D, achievement of the transition-state geometry must require nuclear rearrangement before an incipient charge separation occurs. Hence, the activation energy for the D → Z_2 process could reflect the steric hindrance arising from the distorted transition-state geometry. Small substituents on the amide N and polar solvents should favor the D → Z_2 conversion.

In the case of α-oxo amides **1** and **2**, intramolecular bond rotations involved in the D → Z_2 process must be facilitated by the relatively small *N*-ethyl substituents. The high efficiency of **1** and **2** for yielding oxazolidin-4-one (Table I) is consistent with facile and effectively irreversible formation of the zwitterion. In contrast, a considerable barrier for the D → Z_2 transformation for the bulky substituted amides **3** and **4** should be expected. The relatively high efficiencies of these α-oxo amides for yielding azetidin-2-ones can be attributed to generation of azetidin-2-one and zwitterion formation as two competitive pathways from D. Azetidin-2-one formation should not require a large diradical distortion, so that intramolecular diradical cyclization competes with zwitterion formation and the 4-membered product is obtained.[28]

The product distribution and the stereochemistry of the azetidin-2-one produced upon photolysis of dibenzyl oxo amide **3** under different experimental conditions suggest that **D** and Z_2 can behave as equilibrated species (D ⇄ Z_2) (Scheme II). As is shown in Table V, the chemical yield (θ_i) for the *trans*-azetidin-2-one (**t-3A**) decreases (or increases) to the same extent that the oxazolidin-4-one (or mandelamide) formation becomes more (or less) efficient. It must be noted that the D ⇄ Z_2 equilibrium should only be important in those cases where the difference in stability between D and Z_2 is small. This seems to be the case for amides **3** and **4**. Steric repulsion among the bulky substituents destabilizes the semiplanar zwitterionic structure, decreasing the energy gap between the diradical and the zwitterion. In the case of amides **1** and **2**, a low barrier for the D → Z_2 process and a relatively high Z_2 stability satisfactorily explain the large oxazolidin-4-one yields.

Scheme II



Oxazolidin-4-ones are probably produced either by direct cyclization of Z_2 or by cyclization of the iminium ion, I (eqs 13 and 15). In neutral or acidic media, Z_2 protonation should quantitatively produce I (eq 13). Intramolecular cyclization and hydrolysis of I, yielding oxazolidin-4-one or mandelamide, respectively, should be two competitive and highly pH sensitive decays of the iminium ion (eqs 14 and 15). However, in aprotic or basic media, direct cyclization of Z_2 should mainly account for oxazolidin-4-one formation. The large isotope effect measured for deuterium incorporation in the oxazolidin-4-one (**O2**, Table II) suggests that I is not formed in basic media. This isotope effect value is consistent with a relatively low zwitterion basicity, as is expected for an enolate ion. Furthermore, the lack of mandelamide formation at pH 13 is consistent with deprotonation of Z_2 in basic media. An increased oxygen nucleophilicity for the attack on the C–N double bond should favor cyclization over hydrolysis of the zwitterion.

Modification of Photochemical Reactivity of the α-Oxo Amides by Cyclodextrin Complexation. The effect of introducing cyclodextrin complexation in the photochemistry of α-oxo amides **1–4** (Table III) can be reasonably explained on the basis of two CD effects on the guest: (a) conformational control on the primary stage of the photoreaction (amide + *hν* → D) and (b) modification of the D ⇄ Z_2 equilibrium.

Structure of the Complexes in Aqueous Media. In order to interpret the changes in the photochemical behavior of the α-oxo amides produced by cyclodextrin complexation, a good knowledge of the structure of the complex is essential. Examination of the aromatic substrate induced chemical shift in the ^{1}H NMR spectrum of the CD provides a convenient method for determining

(28) This explanation is also consistent with some well-documented aspects of the photochemistry of the α-oxo amides:[2d] (i) the less hindered α-oxo amides (pyruvamides) mainly yield oxazolidin-4-ones and (ii) introduction of an electron-donating group stabilizing the cationic center in Z_2 increases the oxazolidin-4-one yield at the expense of the azetidin-2-one yield. The reverse is true for an electron-withdrawing group destabilizing the zwitterion.

(29) Note that $\theta_{t\text{-}3A} + \theta_{3O} + \theta_{3M}$ is almost solvent independent, suggesting that these three products are connected by the same or equilibrated intermediates. On the other hand, the efficiency for *cis*-azetidin-2-one formation is nearly constant, suggesting that the *cis*-azetidine precursor does not interact with the medium. These results can be tentatively explained by considering that two different diradicals can be produced by **3** depending on which of the benzylic protons is abstracted (Scheme II). Fast intramolecular cyclization in D_t and D_c, competing with diradical interconversion, should yield *trans*- and *cis*-azetidin-2-one, respectively. Molecular electron rearrangement occurring in D_t may also produce Z_{2t}. Protonation (or deprotonation at pH 13) of Z_{2t} "traps" the ionic intermediate, increasing the oxazolidin-4-one (or mandelamide) yield at the expense of the *trans*-azetidin-2-one formation. In contrast, even though formation of Z_{2c} from D_c seems likely, molecular models suggest that the intramolecular bond rotations involved in this process should be highly obstructed by the phenyl substituents. Hence, this D_c should mainly collapse into *cis*-azetidin-2-one. Generation of two different diradicals in the photolysis of α-oxo amide **3** supposes that the two benzylic protons are not equivalent; this can be most reasonably attributed to the population of two different ground-state oxo amide conformations.

the direction of substrate penetration in the cavity.[30] If an aromatic nucleus enters the CD cavity, protons H_3, H_5, and H_6 of CD are expected to be shielded since they will be in the magnetic shielding region of the aromatic π-cloud. For all four studied CD complexes (Table IV), protons H_3, H_5, and H_6 are shifted upfield while H_1, H_2, and H_4 are relatively unaffected, supporting the contention that complexation occurs at the interior of the CD torus. In the particular case of amides **5** and **2** complexed with β-CD, the fact that H_5 and H_6 show large upfield shifts could be interpreted as a deep and vertical penetration of the aromatic probe via the wider end of the cavity.[31] In contrast, the γ-CD complexes show a relatively small induced shift on H_6, suggesting a shallow penetration (or a fast exchange) of the guest. This is also consistent with the relatively large shift observed on H_3.

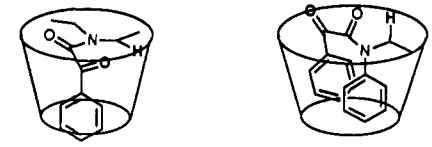
On the other hand, at least two major CD-induced effects on the protons of the guest can be anticipated: (i) Upon complexation, the guest should perceive a change in microenvironment. The CD cavity should behave as a rigid "solvent cage"; hence, the presence of the CD oxygens arranged in a structured pattern on the CD wall must specifically affect the chemical shifts of some of the protons of the probe. (ii) The restricted shape and size of the CD cavity should constrain the guest and could stabilize conformations that are less favored in free solution. A change in the conformation of the guest could be, in principle, detected by ^1H NMR spectroscopy.

The observed downfield shifts ($\Delta\delta > 0$) for amide **5** protons in the β-CD complex (Table IV) are consistent with a deshielding effect due to the exposure of the amide to the hydroxylic oxygens on C_2, C_4, and C_6 of the CD. On the other hand, since a CD-induced shielding effect on the protons of the guest is not expected, the upfield shift ($\Delta\delta < 0$) observed on the amide **5** protons in the γ-CD complex should correspond to a change in the molecular geometry of the amide upon complexation. These shifts could be attributed to the structure where both amide **5** rings are within the CD cavity. In this case, the intramolecular shielding ring currents can partially cancel the deshielding effect of the CD oxygens. This complex structure is consistent with the known preference of γ-CD (vs β-CD) for including 1,3-diaromatic systems in a "U" conformation.[32]

In accord with the existence of only one aromatic ring in diethyl amide **2**, the induced changes in the chemical shifts in both CD complexes follow the same trend, only differing in the magnitude of the effect (Table IV). Interestingly, the terminal methyl protons of the *N*-ethyl groups (H_{5a} and $H_{5a'}$) are strongly affected in the complex between **2** and β-CD, but essentially unshifted in the complex between **2** and γ-CD. Since these downfield shifts can be attributed to the deshielding effect of the hydroxylic oxygens on C_2 and C_4, this observation shows that the wider CD cavity forms a looser complex. The observed upfield shifts in H_{3a} and H_{4a} are more difficult to explain. Inspection of CPK space-filling models showed that both protons should be very sensitive to a change in the amide conformation since they are located near the narrow shielding/deshielding cone defined by the carbonyl groups of the α-oxo amide. Hence, these induced chemical shifts could be tentatively attributed to a change in the distance (angle) between these H_{3a} and H_{4a} protons and the carbonyls.

From the available ^1H NMR evidence and the concurrent changes in the UV absorption spectrum produced upon complexation of the α-oxo amides, it seems most reasonable to conclude that complex formation between amides **1**, **2**, **3**, and **4** and β-CD, as well as **2** and **4** and γ-CD, involves penetration of the benzoyl aromatic ring in the CD cavity (Scheme III, a). On the other hand, although the structural variation between α-oxo amide **5** and **1** is large, we assume for the amide **1**–γ-CD complex that both aromatic rings are also included in the γ-CD cavity (Scheme III, b).

Scheme III



a b

Conformational Control Effect. The need for a conformationally flexible hydrophobic molecular probe to expose the minimum area to the aqueous phase ("hydrophobic effect") constrains the guest in the finite cavity of the CD. This effect can result in the favoring of some specific conformations coupled with a restriction in the free rotational motion of the guest (conformational control effect).[4b,31,33] Generally, cyclodextrin encapsulation can force the guest to react from a particular "frozen" molecular geometry. Hence, suppression of some normal excited-state decays can occur, resulting in an alteration of the photobehavior of the included guest.

The efficiency of the photoreaction (Φ_D) of these α-oxo amides should be mainly controlled by the competition between back electron transfer (k_{-et}) and proton transfer ($k_{H^+_1}$) to generate D, both processes occurring in Z_1 (eqs 6 and 7). The experimental observation that deuterium incorporation was not observed in recovered *N*-ethyl-*N*-phenyl oxo amide **1** upon photolysis of the **1**–β-CD complex in D_2O indicates that, even though capable of H/D exchange, the diradical intermediate formed in this CD complex does not decay via return to the starting oxo amide. This observation suggests that the decrease in the reactivity of amide **1** observed upon complexation with β-CD is due to a CD effect on the primary stage of the photoreaction (amide + $h\nu \rightarrow$ D) rather than to an enhancement of the reverse proton transfer reaction ($Z_1 \rightarrow$ D). Hence, it seems most reasonable to suppose that cyclodextrin complex formation produces a change in the Φ_D value (relative to "free" aqueous solution) by modifying the $k_{H^+_1}/k_{-et}$ rate constant ratio.[34]

From the above analysis of the structure of the complexes the lack of reactivity of the α-oxo amide **1**–γ-CD complex can be explained, assuming that this amide is preferentially included in a "U" conformation (Scheme III, b). Since the short-range intramolecular electron-transfer reactions (k_{et} and k_{-et}, eq 6) should be not largely affected by a change in the molecular geometry of the amide, the suppression of the photoreaction can be mainly attributed to the unfavorable geometry for γ-proton transfer. During the Z_1 lifetime, the CD holds **1** in the U conformation making $k_{H^+_1}$ very small.

These same two factors, CD conformational control on the guest and sensitivity of $k_{H^+_1}$ to the geometry of Z_1, could also explain the photoreactivity of the conformationally more simple complexes. If the magnitudes of the CD-induced NMR chemical shifts on the H_{3a} and H_{4a} protons of diethyl amide **2** are believed to be a measure of the "deformation" of the included α-oxo amide, they correlate with the magnitude of the observed decrease in the photoreaction efficiencies for the β- and γ-CD complexes (Table III). The tightest **2**–β-CD complex is relatively less reactive. In aqueous solution, free bond rotations should facilitate the γ-proton transfer, but encapsulation of **2** in the CD cavity seems to produce

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(34) It has been suggested that the environment of the CD cavity is very similar to that of an alcohol.[35] Therefore, since photolysis of **1**–**4** in methanol produces only a small decrease in the efficiency of the reaction (F_D) compared to those values estimated in water, it seems clear that the sometimes abrupt changes in the reactivity of the amides for the different α-oxo amide–CD complexes cannot be attributed to a simple solvent effect.

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both (i) an unfavorable change in the distance (angle) between H_{4a} and the ketone carbonyl and (ii) a partial immobilization of the probe hindering the bond rotations, leading to a more favorable geometry for proton transfer during the short Z_1 lifetime. Both factors must contribute to reduce the rate for the proton shift ($k_{H^+_1}$) so that the photoreactivity of **2** in the CD complexes is also reduced.

In principle, it is not possible to anticipate whether the geometric arrangement reached by the α-oxo amide in a particular CD complex will favor or disfavor the proton-transfer process. Such a prediction would require the knowledge of the optimum geometry for γ-proton transfer occurring in Z_1, as well as the exact complex structure. However, it is quite possible that the increase or decrease observed in the reaction efficiencies for the other α-oxo amide–CD complexes may also correspond to the CD-imposed conformational changes on the included guests.

Modification of the D ⇄ Z_2 Equilibrium. When a particular mode of decay of a photoreaction intermediate requires a large degree of perturbation via a rotational motion, the rigid wall of the CD can sterically obstruct that reaction pathway.[36] Therefore, since the D ⇄ Z_2 equilibrium involves a conformational change, the CD wall might hinder this transformation by acting as a "physical" barrier.

The experimental observation that oxazolidin-4-one and mandelamide formation (both products arising from Z_2) is not completely supressed by CD complexation of amides **1–4** indicates that the zwitterion intermediate can be formed inside the CD cavity. Hence, complexation must produce only a partial obstruction to the D → Z_2 process.

Therefore, the CD effect enhancing the selectivity of forming azetidin-2-one upon photolysis of the dibenzyl amide **3** and the diisopropyl derivative **4** is better interpreted by assuming that CD encapsulation affects the D ⇄ Z_2 equilibrium rather than the direct D → Z_2 conversion. In contrast to the "disordered" diradical structure, the stabilized Z_2 requires a relatively strict geometry. Thus, the molecular distortions produced by the restrictions imposed by the CD wall coupled with the relatively low polarity of the CD cavity should preferentially destabilize the zwitterionic form. Hence, CD complexation should partially hinder the D → Z_2 conversion but, more importantly, "stimulate" the Z_2 → D process. Combination of these two factors results in a "shift" of the D ⇄ Z_2 equilibrium toward the diradical form. Since azetidin-2-ones are produced directly from D, the enhancement in the efficiency for azetidin-2-one formation can be attributed to an increase of the equilibrium D conformer population compared to free solution. Note that this effect is only important for amides **3** and **4**. Their bulky zwitterions should be particularly destabilized by the constraining forces inside the CD cavity. In the cases of smaller amides **1** and **2**, the product distribution is unaffected since no apparent barrier is imposed by the CD to the D → Z_2 process nor are the relatively smaller zwitterions sterically destabilized by the CD cavity.

A similar enhancement for the formation of the azetidin-2-ones was observed by Ayoama et al. upon solid-state photolysis of inclusion complexes of *N,N*-dialkylpyruvamides with deoxycholic acid (DCA).[37] While the photolysis of *N,N*-dialkylpyruvamides in aprotic solvents of low polarity (benzene) yielded oxazolidin-4-ones as the chief products, irradiation of the solid complexes produces almost exclusively azetidin-4-ones. These authors proposed that the zwitterion intermediate (Z_2), which is severely restricted in the environment provided by the DCA channels, collapses via the formation of azetidinones because these products are sterically smaller than the oxazolidinones.

Summary

In conclusion, the results obtained in this investigation indicate that intramolecular electron-transfer quenching of the ketone excited state to yield the intramolecular anion radical–cation radical zwitterion Z_1 initiates reaction in each case and that this intermediate, through very short-lived, is the precursor of all of the products obtained. A sequence of intramolecular proton transfer to generate D can be followed by a second electron transfer to generate the "even-electron" zwitterion, Z_2. These subsequent intermediates differ in relative stability depending upon substituents and the microenvironment, and their decay or interception accounts for all of the observed products; the product distribution can be further accounted for by evaluating the factors which influenced the relative stability of D and Z_2 and the case of their interconversion. The analysis that has been developed to understand the varied photoreactivity of amides **1–4** should be applicable to developing an understanding (and also a directing) of the reactivity of other keto amides as well as other molecules which can generate similar interconvertible diradical–zwitterion intermediates.

Experimental Section

General. UV–visible spectra were obtained on a Hewlett-Packard 8451A diode array spectrometer. Nuclear magnetic resonance spectra were taken on a General Electric 300-MHz QE-300 NMR.

Synthesis. The α-oxo amides **1–4** were prepared from the benzoylformic acid chloride and the amines, according to literature.[1c,d,38] These amides were characterized by ^{1}H NMR, IR, and mass spectroscopy. Their spectral data are in close agreement with reported values.[2a] Monodeuterated α-oxo amides **1-d_1**–**3-d_1** were synthesized from the deuterated amines. Amines-d_1 were obtained by reduction of the appropriate Schiff base with AlD_4Li.[39]

1-d_1: NMR ($CDCl_3$) δ 1.3 (d, 3 H, methyl), 3.95 (q, 1 H, methylene), 7–8.2 (m, 10 H, aromatics). The mass spectrum exhibits a molecular ion peak at 254.1 mu. **2-d_1**: NMR ($CDCl_3$) δ 1.2 and 1.3 (two asymmetric triplets, 6 H, methyl), 3.25 and 3.6 (two quartets, 3 H, methylenes), 7.5–8.0 (m, 5 H, aromatics); molecular ion peak 206.1 mu. **3-d_1**: NMR ($CDCl_3$) δ 4.3 and 4.65 (two singlets, 3 H, benzylics), 7.2–8.1 (m, 15 H, aromatics); molecular ion peak 330 mu.

Mandelamides **1M**, **3M**, and **4M** were prepared from O-acetyl mandelic acid chloride and the appropriate amine followed by hydrolysis of the ester function. These amides were characterized by ^{1}H NMR and mass spectroscopy.

Irradiation and Identification of the Photoproducts. Argon-degassed water–methanol (1:1) or benzene solutions containing 300 mg of the amides were photolyzed for several hours at 300 nm. Photoproducts were separated by preparative HPLC (10 mm × 25 cm, C-18 cartridge, acetonitrile–water, 1:1) or TLC (silica gel, hexane–ethyl acetate mixtures as eluent). Oxazolidin-4-ones and azetidin-2-ones were identified by comparison of their ^{1}H NMR and mass spectra with literature data. The stereochemical assignments for *trans*- and *cis*-3,4-diphenyl-1-benzyl-3-hydroxyazetidin-2-one (**3A**, Table IV) are based on a low-field singlet (δ 4.78) attributed to the proton bearing C-4 in the *cis*-**3A**, which lies within the deshielding region of the adjacent aryl group on C-3. In the case of *trans*-**3A**, H-4 absorption occurs at δ 4.65 ppm. Similarly, *trans*- and *cis*-3-ethyl-2-methyl-5-phenyloxazolidin-4-one (**O2**, Table IV) can be distinguished on the basis of the absorptions of the proton and the methyl group bearing C-2 of the oxazolidin-4-ones. *trans*-**O2**: δ 1.55 (d, CH_3), 5.52 (q, H-2), *cis*-**O2** δ 1.60 (d, CH_3), 5.40 (q, H-2). Mandelamides (**1M**, **3M**, and **4M**) and benzaldehyde were compared with original samples.

Flash Photolysis Experiments. A conventional transient absorption apparatus was used. The laser source was a Questek 2000 excimer laser (308 nm, ca. 15 ns, ca. 100 mJ). A pulsed (PRA M-305) Osram XBO-150 W1 xenon arc lamp (Oriel 66060 housing, PRA 302 power supply) was used as the monitoring light source. The monitoring light was passed through an ISA H-2a monochromator and was detected using dynodes of an RCA 4840 photomultiplier tube (PMT). The output from the PMT was monitored with a Nicolet 4094A digital oscilloscope using a Model 4175 plug-in.

Water solutions of α-oxo amides **1** and **2** (3 mL, 2.0×10^{-4} M) were degassed by bubbling with argon for 40 min. No transient absorption could be detected between 320 and 650 nm. Under the same conditions, it was possible to detect the transient bearing the short-lived triplet excited state of valerophenone in an air-equilibrated methanolic solution.

Isotope Effects. Argon-degassed water or water–methanol (1:1) solutions (see Table II) containing 100 mg of the α-oxo amides **1-d_1**, **2-d_1**,

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and **3**-d_1 were photolyzed at 300 nm. Photoproducts were separated by preparative TLC.

The relative concentration ratio of the photoproducts derived from the migration of a hydrogen or deuterium were calculated by ^{1}H NMR. For oxo amides **1**-d_1, k_H/k_D was calculated by integration of the ^{1}H NMR signals bearing hydrogens on C-2 and C-5 of the oxazolidin-4-one. The integration value of the ^{1}H NMR signal due to the protons on C-5 was taken as proportional to the total concentration of the oxazolidin-4-one, and the integration value for the protons on C-2 was taken to be proportional to the concentration of the nondeuterated oxazolidin-4-one. For oxo amide **2**-d_1, the isotope effect was calculated from the integration of the ^{1}H NMR signals for the protons on C-2, C-5, and the *N*-methylene group. For oxo amide **3**-d_1, k_H/k_D was calculated from the integration of the ^{1}H NMR signals for the protons on C-4, the *N*-benzylic protons, and the hydroxy group of the azetidin-2-one. All of the k_H/k_D values shown in Table II are the average of at least three independent experiments for each α-oxo amide-d_1.

Deuterium Incorporation in the Oxazolidin-4-ones. Isotope Effect. Argon-degassed D_2O, D_2O–H_2O (1:1), or D_2O–D_3COD (1:1) solutions (see Table II) containing 100 mg of the α-oxo amides **1**-d_1 and **2**-d_1 were photolyzed at 300 nm. Photoproducts were separated by preparative TLC. Oxazolidin-4-ones **O1** and **O2** obtained under photolysis in a fully deuterated solvent showed complete incorporation of a deuterium atom on C-5 in their ^{1}H NMR spectra.

Photolysis of oxo amide **2** in D_2O–H_2O (1:1) yielded a mixture of the oxazolidin-4-one monodeuterated and nondeuterated at C-5. The primary isotope effect, k_H/k_D, was calculated by integration of the ^{1}H NMR signals for hydrogens on C-2 and C-5. The integration value of the ^{1}H NMR signal due to the protons on C-2 was taken as proportional to the total concentration of the oxazolidin-4-one, and the integration value for the protons on C-5 was taken to be proportional to the concentration of the nondeuterated oxazolidin-4-one. No deuterium incorporation in the oxazolidin-4-ones (**O1** and **O2**) was noted when these cyclic products were dissolved in D_2O and heated for 4 h at 50 °C.

Deuterium Incorporation in α-Oxo Amides. These experiments of deuterium incorporation in the α-oxo amides **1**, **2**, and **3** were carried out in CH_3COD–D_2O (1:1), pH 7, for all three amides and in CH_3COD–D_2O (1:1), pH 1, for amide **3**.

In general, 15 mg of the amide was dissolved in 5 mL of the appropriate solvent and photolyzed at 300 nm. Using the values of the disappearance quantum yield (Table I), the irradiation time was adjusted to keep the number of einsteins absorbed by the sample equal to the initial moles of amide. Under these conditions, on average, the recovered unphotolyzed oxo amide was "hit" by at least one photon. After the required percentage of conversion was reached, the solvent was eliminated and the unconverted amide separated by preparative TLC.

The search for deuterium incorporation in amides **1** and **2** was carried out by ^{1}H NMR. In this case, the ratio of the integration value of the signal bearing the CH_2 and CH_3 groups did not show changes compared with the observed ratio for an unphotolyzed amide sample (2:3). Within the error of the method (5%), no incorporation was observed. In the case of **3**, the search for incorporation of deuterium into the recovered amide was carried out by mass spectroscopy. Within the error of the method (1%), no incorporation was observed.

Molecular mechanics calculations were performed on a Macintosh IIsi with the MMX software supplied by Serena Software, Bloomington, IN.

Cyclodextrin Complexes of α-Oxo Amides. UV Spectral Measurements. Stock amide solutions (0.01 M) were prepared in methylene chloride, and 50-mL portions of these solutions were evaporated under nitrogen in 5-mL flasks. Then, varying concentration cyclodextrin solutions were added, and the resulting solutions were stirred for 8 h. The UV spectra of these solutions were recorded and the optical density changes measured where the maximum shift was noticed (270–280 nm). The stability constants were estimated from the slope and intercept of So/DA versus 1/(CD) plots, where So is the concentration of amide and DA is the observed change in the absorption of the amide upon complexation.

Preparation of the Amide 1–Cyclodextrin Solid Complexes. β-Cyclodextrin (γ-CD) (5 mequiv) was dissolved in 5 mL of distilled water. To this solution was suspended 1 mequiv of **1**, and the mixture was stirred at 40 °C in an oil bath for 7 days. The fine powder was filtered out, washed with cold water, and dried in the vacuum at 50 °C for 10 h. Five milligrams of this solid was dissolved in DMSO-d_6 and a ^{1}H NMR spectrum recorded. Integrations of the resonance signals of the amide and cyclodextrin protons were summed separately. Comparison between the relative theoretical and experimental number of protons allowed the estimation of a molar ratio equal to 1:0.92 and 1:0.96 for amide **1** to β- and γ-cyclodextrin, respectively.

^{1}H NMR Studies. Solutions containing different proportions of guest to host were prepared by stirring 0.5, 1, 2, 3, and 4 mg of the cyclodextrins with 1 mg of amides in 1 mL of D_2O for about 1 h. The ^{1}H NMR spectra of the D_2O solutions of β- and γ-CD and their complexes were recorded. Good linear plots were obtained when the chemical shifts (δ) of the cyclodextrin protons were plotted as a function of the complexation fraction of the CD, α_{CD}. Table IV shows the change in the chemical shifts ($\Delta\delta = \delta_{complexed} - \delta_{free}$) extrapolated to full complexation for each CD proton. In the same experiment, the difference in the chemical shifts of the amide protons was measured as a function of the complexation fraction of the amide, α_A. The changes in the chemical shifts (Δδ) of the amide protons are also shown in Table IV.

The α_{CD} and α_A values for amide **2** and the CDs were calculated using the dissociation constants (Table III). Dissociation constants for amide **5**–β-CD and amide **5**–γ-CD complexes were estimated by the UV technique to be 2.65×10^{-3} and 2.84×10^{-3} M, respectively.

Quantum Yield Determination. Homogeneous and cyclodextrin solutions of the α-oxo amides (3 mL, 1×10^{-4} M in amide) were degassed by bubbling argon for 40 min. All quantum yields were determined in a Quanta-Count (PTI) at 300 ± 20 nm. The actinometer employed was heterocoerdianthrone (R1). Conversion of the starting amide was kept between 5 and 15%. After photolysis, 2 mL of these samples was diluted with 2 mL of acetonitrile, a standard was added, and the resulting solutions were stirred in the dark for 4 h. Since formation of CD complexes with the oxo amides is not observed in acetonitrile–water (1:1), this treatment of the samples guarantees that the photoproducts and the unphotolyzed oxo amide are free before the HPLC analysis (column: Waters Nova-Pak C18, 8 mm × 10 cm cartridge; acetonitrile–water (1:1) or acetonitrile–water (3:2) were used as eluents). The estimated Φ_D and Φ_i values at different concentrations of CD were plotted as a function of the complexation fraction of the amide (α_A). Good linear plots were obtained in all cases. The α_A values were calculated from the dissociation constants (Table III). The Φ_D and Φ_i values reported in Table III for oxo amide **1**, **2**, and **4** CD complexes are extrapolated values to infinite concentration of CD ($\alpha_A = 1$).

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Registry No. 1, 64201-19-0; **1**-d_1, 138835-02-6; **1M**, 138835-13-9; **2**, 34906-86-0; **2**-d_1, 138835-03-7; **2**–β-CD, 138835-10-6; 2-γ-CD, 138835-11-7; *trans*-**O2**, 138835-06-0; *cis*-**O2**, 138835-07-1; **3**, 40991-79-5; **3**-d_1, 138835-04-8; *trans*-**3A**, 138835-05-9; *cis*-**3A**, 87419-13-4; **3M**, 138835-12-8; **3M**–β-CD, 138835-14-0; **O3**, 84711-85-3; **4**, 51804-83-2; **4M**, 51804-81-0; **5**–β-CD, 138835-09-3; **5**–γ-CD, 138855-64-8; **O5D**, 138835-15-1; β-CD, 7585-39-9; γ-CD, 17465-86-0; D_2, 7782-39-0.