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Substituent Effects on Amine Cation Radical Acidity. Regiocontrol of β -(Aminoethyl)cyclohexenone Photocyclizations

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Ion radicals serve as key intermediates in a variety of SET photochemical, electrochemical, and biochemical redox processes. A number of recent studies¹⁻⁷ have focused on synthetic and mechanistic problems related to the chemistry of amine cation radicals. One of the more interesting issues has been the acidity of these reactive intermediates.¹⁻⁵ The rates of α -deprotonation^{4,5,8} and pK_a values^{4,5} of amine cation radicals have been measured. Lewis and his co-workers¹ in their study of SET-promoted, tertiary amine photoadditions to stilbene have probed the effects of substituents on the kinetic acidity of these ion radical intermediates. Lewis's efforts led to an interesting relative acidity scale in which the rates of α -deprotonation appear to be governed by stereoelectronic/steric factors.¹

Our efforts focusing on the development of synthetically useful SET photochemical reactions of amine-enone systems have provided us with an opportunity to investigate the problem of amine cation radical acidity. Our efforts in this area were designed to determine the factors affecting the chemo- and regioselectivities of photocyclization reactions of β -(aminoethyl)cyclohexenones of general structure **1** (Scheme I). More importantly, the distribution of products obtained from photocyclization of **1**, which proceeds via the intermediacy of zwitterionic diradical **2**, will reflect the effects of substituents (R_1 vs R_2) on the kinetic acidity of amine cation radicals. In this communication, we report the results of these efforts, which suggest that factors in addition to those discussed earlier by Lewis¹ are also influential in determining the effect of substituents on the acidities of amine cation radicals.

The β -(aminoethyl)cyclohexenones **1** used in this study were prepared by use of routes beginning with 3-(2'-aminoethyl)anisole and involving sequential Birch reduction, N-alkylations, and hydrolysis.⁹ Photocyclization reactions of these substances were promoted by direct irradiation ($\lambda > 320$ nm) of CH_3OH and CH_3CN solutions. Photoproducts (Table I) were separated by column chromatography and characterized via spectroscopic

Scheme I

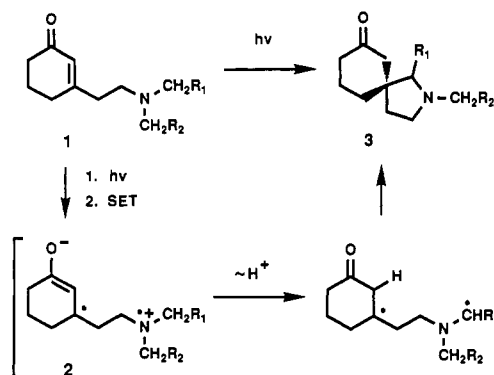


Table I. Product Distributions from Photoreactions of Silyl Amino Cyclohexenones **1** in MeCN and MeOH

reactant (1)		product (3)		% yield ^a MeCN (MeOH)
R_1	R_2	R_1	R_2	
H	CH ₃	H	CH ₃	24 (17)
		CH ₃	H	34 (17) ^b
		Ph	CH=CH ₂	12 (22) ^b
Ph	CH=CH ₂	CH=CH ₂	Ph	25 (66) ^b
		Ph	C≡CH	6 (19) ^b
Ph	C≡CH	C≡CH	Ph	24 (38) ^b
		Ph	CO ₂ CH ₃	23 (44) ^b
Ph	CO ₂ CH ₃	CO ₂ CH ₃	Ph	12 (28) ^b
		Ph	Si(CH ₃) ₃	65 (0) ^b
Ph	Si(CH ₃) ₃	H	Ph	0 (71)
		H	H	0 (72)
H	Si(CH ₃) ₃	Si(CH ₃) ₃	H	76 (0) ^b
H	CH=CH ₂	CH=CH ₂	H	69 (79) ^b
H	C≡CH	C≡CH	H	59 (79) ^b

^a Yields based on recovered starting cyclohexenone. ^b Mixture of α - R_1 and β - R_1 stereoisomers.

methods.⁹ To insure that the ratios of products in each case were both accurately determined and reflective of the relative efficiencies for product formation, NMR¹⁰ and GLC methods were used (both in selected cases) to assay crude photolysates produced by both low- and high-conversion irradiations.

The data accumulated in Table I reveal several interesting trends. Firstly, products lacking the TMS group are formed exclusively in photoreactions of the *N*-(trimethylsilyl)methyl-substituted amino enones in CH_3OH . This chemoselectivity, observed in our earlier studies,^{2b,d} is due to the decreased basicity of enone radical anions in protic solvents owing to H-bonding interactions and the rapid rate of cation radical desilylation. Secondly, deuterium isotope effects, measured by internal comparisons with the *N*-CH₃-*N*-CD₃ and the *N*-CD₃Ph-*N*-CH₂CO₂CH₃ analogues of **1**, show a marked solvent dependence (e.g., k_D/k_H for **1**-(CD₃CH₃) is 5.1 in CH_3CN and 2.4 in CH_3OH and for **1**-(CD₂Ph,CH₂CO₂CH₃) is 6.5 in CH_3CN and 2.2 in CH_3OH).¹¹

The third and most significant observation relates to substituent effects on kinetic acidities of amine cation radicals. The relative rates of proton transfer between the cation and anion radical centers in intermediate **2** govern the spirocyclic ketone product distributions from reactions of **1**. Consequently, product ratios can be transformed into per-hydrogen relative kinetic acidities. These are listed in Table II along with data derived by Lewis¹ from studies of amine-stilbene photoadditions. Significant differences exist between these series. For example, alkyl substitution decreases the rate of proton transfer in the amine-stilbene ion

(10) The NOE technique was used to maximize the accuracy of ¹³C NMR integrations for product analysis.

(11) The CH_3CN values are consistent with those found by Dinnocenzo (ref 4) in quinuclidine deprotonations of di-*p*-anisylmethylammonium hexafluoroarsenate deprotonations ($k_D/k_H = 6-7.7$ in CH_3CN at 15.1 °C). The magnitude of the isotope effect was found in that work to be directly proportional to the base strength of the quinuclindines.

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(9) The synthetic sequences used in this work as well as the spectroscopic and physical data for all new substances and pure photoproducts will be reported in a full paper on this subject.

Table II. Relative Kinetic Acidity for

$$\text{>N}^+\text{CH}_2\text{R} \xrightarrow{-\text{H}^+} \text{>N}^+\dot{\text{C}}\text{HR}$$

R	this work		Lewis' work ¹	$E_{1/2}(+)^1$ Me ₂ NCH ₂ R (MeCN) (V vs SCE)	BDE H-CH ₂ R (kcal/mol)	calcd rel ^d pK _a values
	CH ₃ CN	CH ₃ OH	CH ₃ CN			
H	0.01 ^b	0.01 ^b	1.1	0.76	104 ¹⁴	+16
CH ₃	0.02 ^b	0.02 ^b	0.5	—	98 ¹⁴	—
Si(CH ₃) ₃	0.1 ^{a,b}	—	—	—	99 ¹⁵ (97) ¹⁶	—
CO ₂ CH ₃	0.5 ^c	0.6 ^c	2.3	0.96	91 ¹⁷	+3
Ph	1.0 ^c	1.0 ^c	1.0	0.90	85 ¹⁴ (88) ¹⁸	+1
CH=CH ₂	1.9 ^c	3.0 ^c	0.5	0.92	85 ¹⁴	-1
C≡CH	3.9 ^c	2.0 ^c	ca. 1.11	1.23	89 ¹⁹	-3

^a A lower limit based upon product detectability. ^b Comparisons are possible between H and CH₃, but only upper limits are possible in comparisons with others. ^c Comparisons are possible between CO₂CH₃, Ph, CH=CH₂, and C≡CH, but only lower limits are possible in comparisons with others. ^d Calculated by using the equation in ref 13a following conversion of $E_{1/2}(+)$ vs SCE to vs NHE (add 0.24 V) and using model hydrocarbon RCH₂-H BDE values. The calculated pK_a values are listed relative to R = Ph and should not be considered as absolute.

radical pair while the opposite effect is observed in the amino enone system. Also, the kinetic acidities at benzylic and methyl centers are the same in the former process whereas the current studies suggest that the Ph group more greatly enhances amine cation radical acidities.

The exact source or sources of these differences are not obvious.¹² Lewis has proposed that the alkyl substituent effects have a steric/stereoelectronic origin, i.e., deprotonation occurs along a line parallel with the half-vacant p_N orbital and more rapidly at the less substituted α-carbon. Steric factors alone might also be important in governing orientation of and, thus, deprotonation rates between partners in the stilbene-amine ion radical pair. However, why these factors would be less important in the amino enone system is not clear. Electronics should also play a major role in controlling amine cation radical acidities. The treatment of Arnold¹³ suggests that the pK_a values of these intermediates

should be governed by the amine oxidation potentials and the α-CH bond dissociation energies (see Table II). Indeed, the relative kinetic acidities of amine cation radicals determined by analysis of our results closely parallel the relative pK_a values, estimated by using Arnold's method (Table II). These studies have provided a new view of how substituents can affect the rates of deprotonation of amine cation radical intermediates.

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Site-Specific Bond Cleavage Leading to Hydrogen Atom Production in the Photolysis of 2-Iodopropane

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Selective bond cleavage continues to be a topic of considerable interest in photochemical studies on small molecules.^{1,2} Recently, attempts to understand and influence photolysis reactions that involve competing H and D atom channels in HOD³⁻⁵ and HC₂D⁶ have produced notable results. These interesting experiments focus on understanding and/or controlling the H versus D competition that occurs with respect to bond cleavage at a particular reactive site. In related but somewhat different experiments, we demonstrate how H and D atoms can be used as labels to investigate photolysis involving competition between chemically distinct reactive sites. The question is not whether H or D is formed. Rather, H and D are used as labels to determine at which site bond cleavage occurs.

When 2-iodopropane is photolyzed with 193- or 248-nm excimer laser radiation under collisionless conditions, we observe substantial H atom production. Presumably, the C-I bond is broken initially; thus the remaining radical has chemically distinct carbon atoms that can be labeled initially by using selectively deuterated 2-iodopropane. As a result, "site-specific" atomic hydrogen gen-

(12) (a) A referee has suggested that the differences might relate to the degrees of C-H bond breaking in the deprotonation transition states. Thus, the extent to which radical stabilizing substituents control kinetic acidities in these processes would be increased when the transition states for deprotonation occur later. It is noteworthy that the d-isotope effects found for the enone-amine reactions (ca. 5-6) in MeCN are much larger than those observed¹ (ca. 1.5) for the stilbene-amine system in MeCN. This perhaps reflects later C-H bond cleavage transition states in the former processes. However, it should be noted that small d-isotope effects (ca. 2.3) are associated with the amine-enone reactions in MeOH, yet the deprotonation selectivities are nearly the same as for the reactions occurring in MeCN. (b) Other results which may or may not relate to relative acidities of amine cation radicals are found in electrochemical studies; cf.: Smith, P. J.; Mann, C. K. *J. Org. Chem.* **1969**, *34*, 1821. Lindsay-Smith, J. R.; Masheder, P. J. *Chem. Soc., Perkin Trans. 2* **1976**, 47. Palasz, P.; Utley, J. H. P.; Hardstone, J. D. *J. Chem. Soc., Perkin Trans. 2* **1984**, 807. Shono, T.; Toda, T.; Oshino, N. *J. Am. Chem. Soc.* **1982**, *104*, 2639. Shono, T.; Hamaguchi, H.; Matsumura, Y. *J. Am. Chem. Soc.* **1975**, *97*, 4264. Fuchigami, T.; Nakagawa, Y.; Nonaka, T. *J. Org. Chem.* **1987**, *52*, 5489.

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