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The Reactive Nature of α-Ammonium Distonic Radical Cations

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Abstract. **The enhanced reactivity of α-ammonium distonic radical cations has been shown to derive from a combination of thermodynamic and polar factors. Ab initio calculations demonstrate that an α-ammonio substituent *destabilizes* an alkyl radical, hence increasing the exothermicity of its C-C bond-forming reactions. Secondly, a Hammett study involving cyclization of such radicals has confirmed their electrophilic nature. In this study, a good correlation between the log k_{rel}'s for cyclizations of a series of *p*-substituted N,N-dimethyl-N-(5-aryl-4-pentenyl)methanaminium-1-yl radicals and the σ^+ values of the substituents was obtained ($\rho^+ = -0.29$, $\langle r \rangle = 0.954$).**

In a recent paper we presented laser flash photolysis data and results from competition studies which gave initial insight into the overall reactivity of α-ammonium distonic radical cations in solution.[1] From kinetic studies, including that of the cyclization of radical **4a** (Ar = C_6H_5), we were able to conclude that radicals substituted with an α-ammonio substituent exhibit behavior which is typical of other carbon-based radicals, but that they are somewhat more reactive than analogous hydrocarbon radicals in both their hydrogen abstraction and their cyclization processes.

It was suggested that these greater reactivities derived at least in part from the expected electrophilic character of α-ammoniomethyl radicals, although no direct evidence of electrophilic character was provided. With a large positive σ_p value of 0.82, an α-ammonio substituent would certainly be expected to impart significant electrophilic character to a radical.[2] We wish at this time to report results of a computational study and of a Hammett study which combine to provide insight into the reactive nature of such radicals.

The computational effort was directed at (a) determining the impact of a $(CH_3)_3N^+$ substituent on alkyl radical stability, and (b) determining the relative thermodynamic stability of the distonic radical cation $(CH_3)_3N^+CH_2^{\bullet}$ relative to its conventional counterpart, $[(CH_3)_2NCH_2CH_3]^{\bullet+}$. Previous calculations by Pasto on the effect of the ammonio substituent (NH_3^+) indicated that it destabilizes a methyl radical quite significantly (RSE ~ -4 kcal/mol),[3] whereas Radom's calculations indicated that the parent ammonium distonic radical cation ($NH_3^+CH_2^{\bullet}$) is slightly more stable (~ -1 kcal/mol) than its conventional isomer $[NH_2CH_3]^{\bullet+}$.[4]

Pasto's results for NH_3^+, combined with Bordwell's experimental estimation of a radical destabilization of ~ -5 kcal/mol for the $(CH_3)_3N^+$ substituent,[5] indicate a similar influence on radical stability by these substituents. Our computed evaluation of isodesmic equation 1 (Table 1) is consistent with these earlier estimations:[6,7]

$$(CH_3)_4\overset{+}{N} + (CH_3)_3CH_2^{\bullet} \longrightarrow (CH_3)_3\overset{+}{N}CH_2^{\bullet} + (CH_3)_4C \qquad \text{(Eq. 1)}$$

$$\Delta H^{\circ} = +\,4.6 \text{ kcal/mol}$$

Table 1. Energy of Reaction in Eq. 1 at 298.15 K

Level of Theory	Energy of Reaction, kcal/mol[a]
MP2 / 6-31G*	+ 4.24
MP2 / 6-311G** // MP2 / 6-31G*	+4.40
[QCISD(T) / 6-311G** // MP2 / 6-31G*]′	+ 4.56

[a] Includes zero-point and thermal correction; scaled by 0.9646.

In contrast to the similar effect of NH_3^+ and $(CH_3)_3N^+$ substituents on radical stability, the impact of methyl substituents on distonic versus conventional radical stability turns out to be quite profound, as indicated in Table 2.[6,7] Consistent with Radom's calculations on the parent system, we found that the parent distonic radical cation, **2a**, is slightly more stable than its conventional isomer **1a**. However, methyl-substituted analog **2b** was found to be disfavored by *more than 12 kcal/mol*, relative to its conventional isomer **1b**.

1a, R = H
b, R = CH3

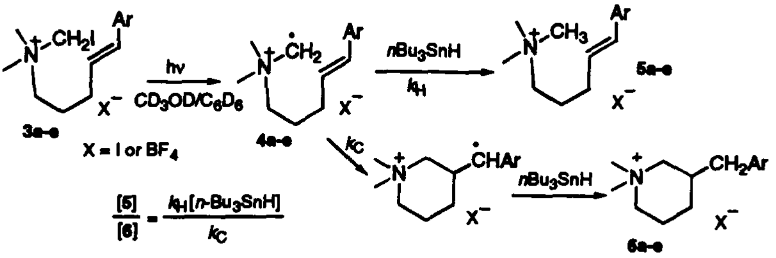
2a, b

Table 2. Isomerization Energies for the Conversion **1** → **2** at 298.15 K

Level of Theory	Isomerization Energy, kcal/mol[a]	
	1a → 2a	**1b → 2b**
MP2 / 6-31G*	- 2.84	+12.32
MP2 / 6-311G** // MP2 / 6-31G*	- 3.93	+11.34
[QCISD(T) / 6-311G** // MP2 / 6-31G*]′	- 0.87	+15.14
QCISD(T) / 6-311G** // MP2 / 6-31G*	- 1.03	-
Expt[b]	≤ -1	-

[a] Includes zero-point and thermal correction; scaled by 0.9646. [b] Reference 8.

In the Hammett study, a series of *p*-substituted N,N-dimethyl-N-iodomethyl-5-aryl-4-pentenaminium salts (**3a-e**)[9] were utilized in photo-induced free radical chain competition experiments which involved competition between cyclization (k_C) and reduction (k_H) of the intermediate radicals (**4a-e**). For each member of the series, six samples of substrate and *n*-Bu_3SnH in CD_3OD were prepared in sealed NMR tubes, varied only in concentration of the tin hydride. The samples were then irradiated at 33 °C for 45 minutes in a Rayonet reactor and the ratios of **5**:**6** determined by 500 MHz ^1H NMR, using anisole as the internal standard.[10]



The slope of the line obtained from a plot of these ratios versus [*n*-Bu$_3$SnH] gave the ratio of k_H/k_C which then, using the known value[1] for k_H provided the values of k_C which are given in Table 3.

Table 3. **Rate constants for Cyclizations of *p*-substituted N,N-dimethyl-N-(5-aryl-4-pentenyl)methanaminium-1-yl radicals, 4a-e**

Substrate	3b	3c	3a	3d	3e
p-Substituent	CF$_3$	Cl	H	CH$_3$	OCH$_3$
σ^+	0.61	0.11	0	-0.31	-0.78
k_H/k_C	0.35±0.02	0.28±0.01	0.27±0.02	0.22±0.01	0.130±0.006
k_C (x $10^7 s^{-1}$)	2.1±0.3	2.5±0.3	2.6±0.3	3.2±0.5	5.5±0.9

[a] all errors are propagated; [b] yields in all cases were >90%.

The Hammett plot derived from the data in Table 3 is depicted in Figure 1. It can be seen that there is a good correlation of log k_{rel} with σ^+ (ρ^+= - 0.29, <r> = 0.954), whereas neither σ nor $\sigma^\bullet$ were found to correlate well with the data. A good correlation with σ^+ generally is indicative of conjugative interaction of the *p*-substituent with the reaction site, and the - ρ value indicates delocalization to an electron-deficient site. The transition state for cyclization of this highly reactive, electrophilic radical should therefore be early, with significant polarization, but with little radical character developed at the benzylic site (Figure 2).

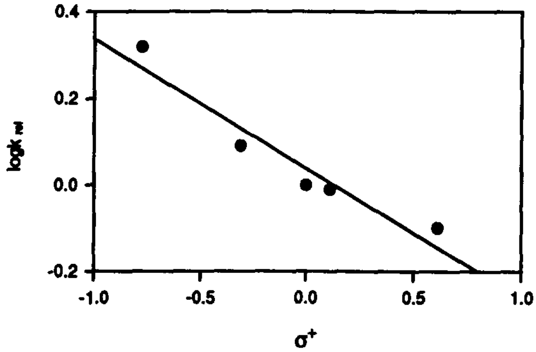


Figure 1. Plot of the log of the rate constants for cyclization of radicals 4 (see Table 3) vs Hammett σ^+ values of the substituents.

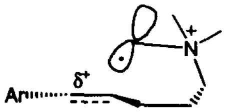


Figure 2. Depiction of the cyclization transition state

Based upon the above computational results and the experimental Hammett results, it can be concluded that the additional reactivity (relative to analogous alkyl radicals) exhibited by α-ammonium distonic radical cations in their cyclization reactions derives from a combination of their inherent thermodynamic instability and their electrophilic character.

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References and Notes

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6. All calculations were performed with the *Gaussian94* program system.[7] Geometry optimizations were performed at the second-order Møller-Plesset level, with vibrational frequencies, zero-point and thermal energy values scaled by 0.9646. All post-Hartree-Fock calculations utilized the frozen-core approach. In all cases, <*S*^2> values were approximately 0.76, indicating only very minor spin contamination. An approximation to the [QCISD(T)/6-311G**] theoretical model, denoted as [QCISD(T)/6-311G**]′ is described by E[QCISD(T)/6-311G**]′≈ E[QCISD(T)/6-311G**] = E[QCISD(T)/6-31G*] + E(MP2/6-311G**) - E(MP2/6-31G*) where the effect of basis set extension is partially taken into account by evaluation at the MP2 level of theory.
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9. Radical precursors, **3a-e**, were mixtures of *E* and *Z* isomers. Control studies indicated no significant kinetic impact resulting from this; indeed NMR examination of reactions terminated after 50% completion indicated that unreacted **3** had been completely isomerized to the *E* isomer under the reaction conditions.
10. All substrates, **3a-e**, and products, **5a-e** and **6a-e**, were fully characterized by ^{1}H and ^{13}C NMR, HRMS, and elemental analyses.

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