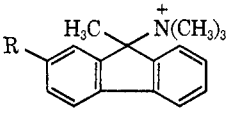
A Reactant-Like Transition State for a Concerted E2 Process[1]

Sir:

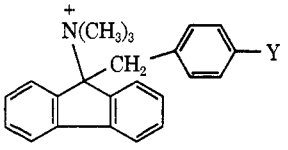
In a recent study[2] on the reaction of 2-substituted 9-methylfluorene-9-trimethylammonium ions (I) with



I

ethoxide ion in ethanol at 40° the magnitude of the Hammett ρ and the variation in the magnitude of k^H/k^D with Hammett σ values of the substituents (R) were considered to support the conclusion that at the transition state the proton was more than one-half transferred to base. Indeed, when R was bromo the hydrogen–deuterium isotope effect was 6.17 at 40° suggesting a symmetrical transition state with the proton approximately one-half transferred.

Accordingly, it was reasoned that an increase in the "acidity" of the β hydrogens might lead to a more reactant-like transition state with the proton less than one-half transferred to base. A series of 9-(4-substituted-benzyl)fluorene-9-trimethylammonium ions (II)



II

was synthesized and the hydrogen–deuterium isotope effects for reaction of these salts with ethoxide in ethanol at 60°, together with the Hammett ρ value for the reaction, are shown in Table I.

Table I. Hydrogen–Deuterium Isotope Effects and the Hammett ρ Value for Reaction of 9-(4-Substituted-benzyl)fluorene-9-trimethylammonium Ions with Ethoxide in Ethanol at 60°

Substituent (Y)	$k_2 \times 10^4$ [a]	k^H/k^D	ρ
OCH_3	8.74	5.91 ± 0.09	
CH_3	11.5	5.75 ± 0.10	
H	16.6	5.61 ± 0.08	+1.33
Cl	34.5	5.34 ± 0.08	
Br	38.1	5.10 ± 0.07	
CF_3	132	4.15 ± 0.12	

[a] In l. mol^{-1} sec^{-1}.

The mechanism of the reaction of the 9-(4-substituted-benzyl)fluorene-9-trimethylammonium salts with ethoxide in ethanol was shown to be the normal concerted E2 process by using deuterium tracer techniques.[3] The rate measurements were carried out under pseudo-first-order conditions by measuring olefin formation spectrophotometrically. In all cases, the olefin was obtained in 100 ± 0.5% yield for the undeuterated substrates and in a yield >90% for the β-d_2 salts. The pseudo-first-order rate constant for elimination from the deuterated compounds was calculated from the expression $k_{overall}$[OD(found)/OD(calcd)]. Excellent Hammett plots were obtained for both the undeuterated and deuterated salts when log k/k_0 was plotted against σ^-.

It is of interest to compare the rate constants for reaction of ethoxide with unsubstituted II, Y = H, and with unsubstituted I, R = H, *i.e.*, $k = 1.66 \times 10^{-3}$ at 60° and 1.49×10^{-3} at 40°, respectively. If one takes into account the temperature difference it is noted that the reaction of II, where the β hydrogen is considerably more "acidic," is appreciably slower than for the 9-methyl substrate I. A possible explanation for this difference in rate is that there is a greater steric hindrance to the attack of base at the β carbon of II rather than at the comparable carbon of I. Dreiding stereomodels suggest that the reaction of II probably proceeds *via* an anti elimination with a dihedral angle of 180° rather than a syn elimination.

It is generally accepted that the magnitude of the primary hydrogen–deuterium isotope effect is low when the degree of proton transfer from carbon to the abstracting base is small or extensive and that the maximum effect is observed when the transition state is symmetric, *i.e.*, the proton is equidistant from carbon and base.[4,5] Since it is expected, for a particular reaction series, that the variation in a para substituent, for example in II, which results in an increase in reaction rate would lead to less extensive proton transfer to base,[6,7] then it is predicted that for increasing electron-withdrawing ability of the substituent the magnitude of k^H/k^D should *increase* if the proton is more than one-half transferred but *decrease* if proton transfer has not reached the symmetrical situation.

It can be seen, therefore, that the hydrogen–deuterium results in Table I are consistent with a transition state where the proton is less than one-half transferred. For such a transition state the small observed positive Hammett ρ value of +1.33 is consistent. To our knowledge, this is the first example of an E2 reaction where the degree of proton transfer has not reached the symmetric situation. For all other systems studied[2,8-10] the magnitude of k^H/k^D increased with electron-withdrawing substituents indicating a transition state with extensive proton transfer.

Further support for our conclusion comes from the detailed studies on the E2 reaction of 2-arylethyltrimethylammonium ions with base. For this system, the trend in k^H/k^D with para substituent[8] was opposite to that observed in the present study. For the 2-arylethyl salts the proton has been shown to be more than half transferred to base at the transition state from the large secondary k^{OD^-}/k^{OH^-} value of Steffa and Thorn-

(1) Supported by a grant from the National Research Council of Canada.
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ton,[11] 1.79 at 80° for the unsubstituted compound, and the observation of a large positive ρ value of +3.77.[12]

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Tautomerism of the Nucleoside Antibiotic Formycin, as Studied by Carbon-13 Nuclear Magnetic Resonance[1]

Sir:

Tautomerism of the nucleic acid bases has been well studied because of the obvious biological significance. In this communication I wish to report the carbon-13 spectra of several nucleoside antibiotics and related compounds and present evidence for prototropic tautomerization. The carbon-13 spectra of a wide variety of nucleosides have been previously reported.[2] In general all the carbon resonances have exhibited reasonably narrow spectral lines. This is in sharp contrast to the ^{13}C spectra of formycin A (7-amino-3-β-D-ribofuranosyl-1*H*-pyrazolo[4,3-*d*]pyrimidine) and formycin B (1,6-dihydro-3-β-D-ribofuranosyl-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one) shown in Figure 1.[3] Formycin A[4,5] and 8-azaadenosine[6,7] (7-amino-3-β-D-ribofuranosyl-*v*-triazolo[4,5-*d*]pyrimidine) are cytotoxic adenosine analogs while formycin B is a cytotoxic inosine analog. The chemical shifts and line assignments are given in Table I. The assignments are based upon partial decoupling experiments, the previous assignments for the naturally occurring nucleosides,[2] and a comparison of the chemical shifts in the series $\Delta\delta$(adenosine–inosine) and $\Delta\delta$(formycin A–formycin B). The unusual broadening is a function of sample temperature and solvent composition, but it is not particularly sensitive to concentration. In Figure 1 the narrow downfield line is the C2 carbon. The line widths of the other heterocyclic base carbons were 15–30 Hz at 25°. As the temperature was raised the line widths narrowed, and at 90° both the base and the sugar carbons had line widths $\leq$1.5 Hz. The

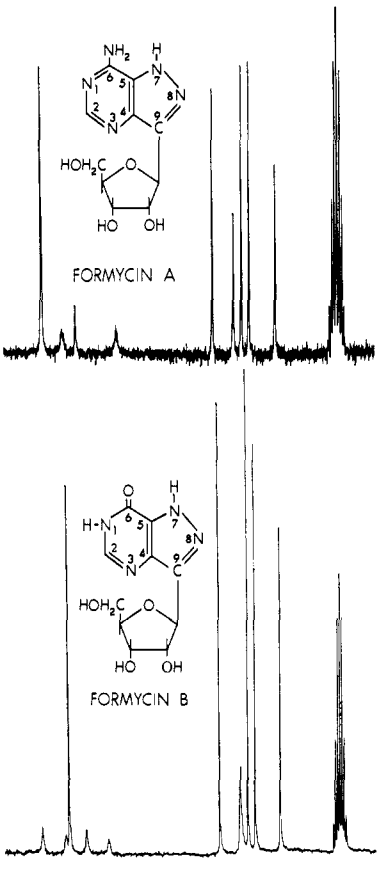

Figure 1.

samples were prepared quickly to minimize the absorption of water. In a separate experiment it was observed that the small amount of water present was due to water of hydration of the formycin samples. The relatively high melting point of DMSO-d_6 prevented us from lowering the temperature to observe the spectra in the "slow exchange" limit. However, the line broadening of base carbons does demonstrate that the formycin molecules are involved in a dynamic equilibrium. Scalar relaxation of the carbons resulting from ^{13}C–^{14}N or ^{13}C–^{1}H coupling can be ruled out as the dominant relaxation process because the line width was relatively independent of concentration in the range where the viscosity was very dependent upon nucleoside concentration. The hydrogen bonding properties of the solvent and the large uncertainties in extracting kinetic and thermodynamic parameters from a detailed analysis of the line shape (when the spectra are only recorded above the coalescence temperature) vitiate the extraction of these parameters from the present experiments.

The ^{13}C spectra of a series of indoles,[8] indazoles, and pyrazoles[9] were also recorded to see if the line broadening would be evidenced in other compounds. The details of this study will be presented separately, but for indole, indazole, and five derivatives of indazole the ^{13}C spectra did not exhibit any significant line broadening under the present experimental conditions. On the other hand, pyrazole and 3-methyl-

(1) Portions of this work were presented at the 13th ENC, May 1972.
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