Elimination Reactions of *N*-(2-(*p*-Nitrophenyl)ethyl)alkylammonium Ions by an E1cB Mechanism

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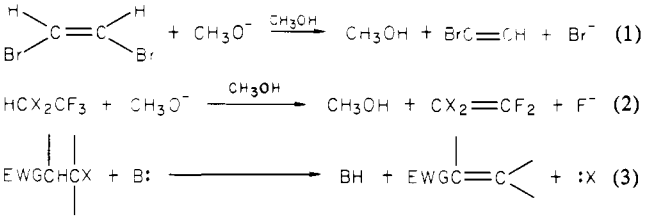
Abstract: Elimination reactions of *N*-(2-(*p*-nitrophenyl)ethyl)quinuclidinium and (2-(*p*-nitrophenyl)ethyl)trimethylammonium ions catalyzed by hydroxide ion and buffer bases undergo a change in rate-determining step from an $(E1cB)_1$ to an $(E1cB)_R$ mechanism with increasing buffer concentration in aqueous solution. Exchange of labeled ^2H or ^3H with solvent was shown for the quinuclidine and trimethylamine derivatives in the presence of buffers. Large inverse solvent deuterium isotope effects on the initial rate confirm the E1cB mechanism with leaving group expulsion partly or entirely rate determining under the same conditions. The dependence of log k on the pK of the leaving quinuclidine gives $\beta_1^{lg} = -0.17$ for k_1 (proton abstraction), $\beta_p = 0.47$ for k_{-1}/k_2 (partitioning of the intermediate zwitterion), and $\beta_{lg} = -0.64$ for k_1k_2/k_{-1} (rate-determining expulsion of the leaving group). The ratio k_2/k_{-1} increases from 10 to 59 with increasing ethanol concentration up to 40% as the result of an increase in the rate of amine expulsion from the zwitterionic intermediate in the presence of organic cosolvents; k_2/k_{-1} also increases with increasing temperature. Rate constants for elimination of 2-(*p*-nitrophenyl)ethyl halides increase with increasing leaving ability of the halide, consistent with a concerted E2 mechanism for all but the fluoride derivative.

Base-induced alkene-forming elimination reactions fall mechanistically into two principal categories: the concerted E2 mechanism and the stepwise E1cB scheme with its irreversible, reversible, and ion-pair variations (Scheme I).[1-5] The distinctions between the E1cB variants depend, respectively, on whether alkene formation occurs from an irreversibly formed carbanion, a reversibly formed carbanion, or from an intermediate complex containing the carbanion and the conjugate acid of the base. It may be noted here that the $(E1cB)_{ip}$ mechanism is the reverse of the preassociation mechanism for nucleophilic addition.[6]

Bordwell[3] has argued that although the E2 mechanism is the path followed by ordinary, nonactivated alkyl compounds, the E1cB mechanism may be more common than generally supposed. Textbooks pay considerable attention to the E2 mechanism and the evidence from which it was developed, but the E1cB path is frequently ignored (except in disguise as a retro-Michael addition).[7] Nevertheless it is clear that the combination of sufficient carbanion stabilization at C-β and a poorly nucleofugic leaving group favors the stepwise E1cB mechanism.[3,8]

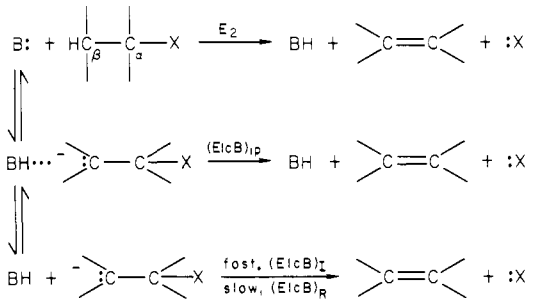
The first clearcut demonstrations of the carbanion mechanism appear to be those reported by Miller[9] (eq 1) and Hine[10] (eq 2).



The most prominent examples are the "activated" eliminations, a group of synthetically important reactions well exemplified by alkene formation from Mannich bases and similar compounds (eq 3), where EWG may be an acyl group[8b] or another electron-withdrawing group such as O_2N-, RSO_2-, $RSO-$, $N{\equiv}C-$, Ph_3P^+-, Me_3N^+-, Me_2S^+-, etc., while X has been $-OCH_3$, $-OPh$, $-NR_2$, $-{}^+NR_3$, and others.[3,11,12] In this context we note again that these eliminations are as a class the reverse of Michael additions, many of which have been shown to use a stepwise mechanism.[13]

Less common E1cB reactions include the base-promoted formation of ketenes from some esters[14] and amides[14d] under certain conditions. The substrates used in these studies were all activated by the presence of *two* EWG's at C-β. Similarly, Douglas and

Scheme I



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(2) More O'Ferrall, R. A. In "The Chemistry of the Carbon-Halogen Bond", Part 2; Patai, S., Ed.; Wiley-Interscience: New York, 1973.
(3) (a) Bordwell, F. G. *Acc. Chem. Res.* **1970**, *3*, 281-290. (b) Bordwell, F. G. *Ibid.* **1972**, *5*, 374-381. (c) Bordwell, F. G.; Vestling, M. M.; Yee, K. C. *J. Am. Chem. Soc.* **1970**, *92*, 5950-5955. A fourth variant in which the intermediate is rapidly generated in larger than steady-state concentration is noted here: the (E1cB) anion mechanism.
(4) Classifications of carbanion elimination mechanisms are given by: (a) Banthorpe, D. V. "Elimination Reactions"; Elsevier: New York, 1963, Chapter 4. (b) McLennan, D. J. *Q. Rev., Chem. Soc.* **1967**, *21*, 490-506. (c) Rappoport, Z. *Tetrahedron Lett.* **1968**, 3601-3604. (d) Bunnett, J. F. *Surv. Prog. Chem.* **1969**, *5*, 53-93.
(5) Hughes and co-workers (Hughes, E. D.; Ingold, C. K. *J. Chem. Soc.* **1933**, 523-526. Hughes, E. D.; Ingold, C. K.; Patel, C. S. *Ibid.* **1933**, 526-530) originated the E1cB mechanism.
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(12) The Ramberg-Bäcklund reaction and the Favorskii rearrangement are reactions that involve γ eliminations in systems activated by an EWG. Bordwell[3a] has summarized the arguments in favor of stepwise, carbanion mechanisms for these reactions.

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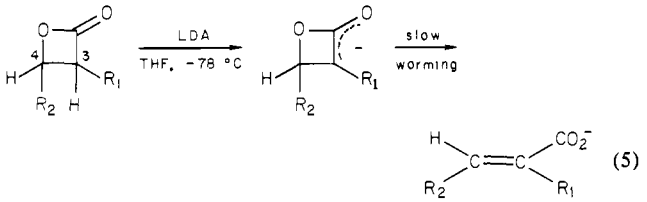
Table I. Variety of Probes Used To Study $ArC_\beta H_2C_\alpha H_2$-lg + :B → BH + $ArCH{=}CH_2$ + :lg–Representative Results[1,2,40a,44]

probe	representative results	ref
ring substitution	Hammett Rho = +2.1 to +4.4	1, 2, 26, 37
leaving group effects	element effect: 1 > Br > Cl > F; $\beta_{lg} = (\partial \log k/\partial pK_{lg})$ is usually positive	26, 37a, 37c, 43b, this work; 24, 26, 37f, 38, this work
effect of base strength	$\beta = (\partial \log k/\partial pK_{BH}) = 0.48$–1.10	24, 26, 39
kinetic hydrogen isotope effects	$1°$, k_H/k_D = 2.6–8.8; $1I°(\alpha)$, k_H/k_D = 1.017–1.09; $1I°(\beta)$, k_H/k_T = 0.97–1.20; $1I°$(lg), $-N(CD_3)_x(CH_3)_{3-x}$, x = 1–3, k_H/k_D = 1.05–1.12; $1I^S$(solvent), k_{OD^-}/k_{OH^-} = 1.30–1.79	1, 2, 24, 36b, 37g, 40, this work; 38a, 40a, 41; 31, 35; 42; 24, 43
heavy atom isotope effects	N(lg), k_{14}/k_{15} = 1.0088–1.0137; 1.024; S(lg), k_{32}/k_{34} = 1.0011–1.0074; C(α), k_{12}/k_{14} = 1.026; 1.08; C(β), k_{12}/k_{14} = 1.015–1.03	38a,b, 40a, 44, 45; 31; 46; 35; 34; 47
stereochemistry	>95% anti elimination	48
isotopic hydrogen exchange at C-β	absent; present	33, 45a, 49; 25, this work

Yaggi have reported that the alkaline hydrolysis of thioacetoacetates, including *S*-acetoacetyl coenzyme A, involves the E1cB formation of a ketene intermediate.[15] Williams and Douglas have reviewed the occurrence of these "elimination–addition" mechanisms for acyl transfer reactions.[16] The same stepwise elimination–addition sequence also occurs in the saponification and aminolysis of aryl phenylmethanesulfonates (via sulfenes) provided the leaving group is poor enough (eq 4).[17] An unusual intra-

$$PhCH_2SO_2OAr + OH^- \rightleftharpoons H_2O + ArO^- + PhCH{=}SO_2 \rightarrow \text{products} \quad (4)$$

molecular elimination (eq 5) has been shown to be stepwise.[18] The ring-opening step is retarded by the orthogonality of the enolate π orbital and the C-4–O σ orbital.



(5)

Most pertinent to the work described in this report is the potential for β-aryl groups to promote the carbanion mechanism by carbanion stabilization. More O'Ferrall and Slae have shown that 9-fluorenylmethanol yields dibenzofulvene by the E1cB mechanism.[8c] Similarly, the fluorenyl group activates 9-((dimethylamino)methyl)fluorene toward the E1cB elimination of dimethylamine.[19] McLennan and co-workers have carried out extensive studies of the base-induced dehydrochlorinations of 1,1-diaryl-2,2,2-trichloroethanes (DDT's) and 1,1-diaryl-2,2-dichloroethanes (DDD's). They have concluded that the DDT's use the E1cB mechanism[20] but that the DDD's (except for the *p*-nitro derivative) use the E2 mechanism.[21] Koch and Dahlberg have argued on the basis of anomalous hydrogen isotope effects on Arrhenius parameters that the alkoxide-promoted dehydrohalogenations of $PhCHBrCH_2Br$ and of some $ArCHXCF_2X'$ (X = Cl, Br; X' = F, Cl, Br) in alcohol solvents proceed by the $(E1cB)_{ip}$ mechanism.[22] Their demonstration that isotopic hydrogen substitution at C-β changes the α-chlorine kinetic isotope effect provides evidence that $PhCHClCH_2Cl$ uses the $(E1cB)_{ip}$ mechanism.[23]

The present work comprises part of an investigation of the elimination reactions of 2-arylethyl compounds (eq 6).[24-26] In

$$ArCH_2CH_2X + :B \rightarrow BH + ArCH{=}CH_2 + :X \quad (6)$$

the history of mechanistic studies of base-induced eliminations, these substances have played a particularly prominent role.[1,2] A large number of variables can be investigated. Table I lists these variables together with representative results. A thorough discussion of some of the experiments appears below. The generally accepted picture that has emerged is that reaction 6 proceeds by the E2 mechanism, but with increasingly carbanion-like transition states as ring substituents are made more electron attracting and as the leaving group is made poorer: the variable E2 transition state theory.[1-3,27-30]

However, in 1933 Hughes, Ingold, and Patel considered it possible that (2-(*p*-nitrophenyl)ethyl)trimethylammonium ions (**7**, 4-NPT^+) decompose in water by the E1cB mechanism.[5] Their evidence was that the reaction is slower in 0.5 M HCl than in water. This fact was explained according to the steady-state rate law for the stepwise path: reprotonation of the intermediate zwitterion by acid inhibits alkene production. The evidence was not considered conclusive and is made still less certain by a later observation that catalysis by hydroxide ions persists down at least to pH 4.6.[31] Thus, Hughes and Ingold did not really know the

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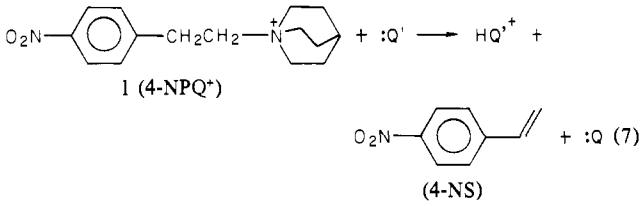
rate of the uncatalyzed reaction.[32]

A number of subsequent experiments with isotopically labeled 4-NPT$^+$ ions seemed to rule out the E1cB path even for this substrate. Hodnett and Flynn found no incorporation of tritium into the substrate from tritiated water during elimination (100 °C, pH 7, HPO_4^{2-} buffer).[33] Hodnett and Sparapany measured a leaving group nitrogen isotope effect ($^{14}N/^{15}N$, 100 °C, pH 6) of 1.024.[31] This value exceeds half the theoretical maximum effect. We may compare this result with that of Grout, McLennan, and Spackman who found a chlorine leaving group isotope effect of unity for the dehydrochlorination of *p*-nitroDDD, a substrate considered by these authors to use the $(E1cB)_I$ mechanism.[21c] Hodnett and Dunn reported an α-carbon isotope effect ($^{12}C/^{14}C$, 100 °C, pH 7) of 1.078,[34] while Simon and Müllhofer had measured the same effect as 1.026.[35] The results are ca. 50% and 20%, respectively, of the maximum value (calculated for complete formation of the double bond). Despite the difficulty of these experiments, the results clearly imply that leaving group departure occurs during the rate-controlling step and that a free carbanion intermediate is not reversibly formed. This interpretation excludes the $(E1cB)_R$ and $(E1cB)_I$ mechanisms for 4-NPT$^+$ and requires that the $(E1cB)_{Ip}$ intermediate, $LOH\cdots{}^-CH(Ar)CH_2NMe_3^+$, has a lifetime too short to incorporate covalent tritium at C-β but long enough that leaving group departure be activation controlled and rate limiting. A simpler rationalization is the E2 mechanism, and this mechanism has been assumed for 2-arylethyl substrates to this day.[36]

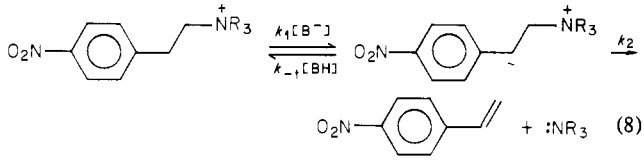
Recently, Alunni and Jencks studied the reversible elimination reactions of *N*-(2-(*p*-nitrophenyl)ethyl)quinuclidinium ions (**1**, 4-NPQ$^+$) catalyzed by substituted quinuclidine buffers.[24] In the elimination direction (eq 7), plots of k_{exp} (s^{-1}) vs. [buffer] at



1 (4-NPQ$^+$) (4-NS)

constant pH showed downward curvature for the most acidic quinuclidinium catalysts. This observation led them to reconsider the E1cB mechanism with step two, leaving group departure, becoming partly controlling at high [buffer]. Experimental difficulties prevented a conclusive demonstration that the buffer curvature signified a change in rate-controlling step.

In this study we show that Hughes and Ingold's conjecture is correct: 4-NPT$^+$ and 4-NPQ$^+$ and other 4-NPQ'$^+$ species produce *p*-nitrostyrene (4-NS) by the E1cB mechanism (eq 8).[25] The



E2 and $(E1cB)_{Ip}$ mechanisms are excluded. The formation of the intermediate zwitterion can be made less or more reversible depending on base strength, buffer concentration, buffer ratio, leaving group ability, solvent composition, and temperature. The experimental criteria used to establish the E1cB path include two classical techniques—isotopic hydrogen exchange and kinetic buffer saturation—as well as two newer techniques: (1) the lack of interaction between the base catalyst and the leaving group ($\partial\beta/\partial pK_{lg} = p_{xy} = 0$)[26] and (2) the observation of large, inverse, [buffer]-sensitive solvent isotope effects.[8c,25] The factors influencing the partitioning ratio for the intermediate, k_{-1}/k_2, are discussed, and an estimate of the lifetime of the zwitterion is made. Also given is an assessment of the extent of leaving group departure at the transition state of step two. A discussion of mechanistic choice in base-induced alkene-forming eliminations is offered.

Experimental Section

Materials. Quinuclidines, their hydrochlorides, *p*-nitrophenethyl bromide, and *p*-nitrostyrene were obtained or prepared and purified as described previously.[24] Glass-distilled water was used throughout. Reagent grade potassium chloride was used directly. Fisher certified standard potassium hydroxide and hydrochloric acid solutions were used as received, but checked periodically. Trimethylamine hydrochloride was recrystallized from ethanol/diethyl ether (3/1, v/v) and dried in vacuo. Acetohydroxamic acid and *N*-hydroxysuccinimide were commercial materials (Aldrich). They were recrystallized from ethyl acetate and dried in vacuo. Commercial 2,4-dinitrochlorobenzene (Eastman) and *p*-nitrophenylacetonitrile (Aldrich) were recrystallized each from 95% ethanol. The nitrile was deuterated at the benzylic position by the method of Hibbert and Long.[50] Three treatments provided ca. 90% deuteration. *p*-Nitrophenethyl chloride was prepared by the method of von Braun and Bartsch,[51] while *p*-nitrophenethyl fluoride was prepared as described by Winey and Thornton.[43b] 1,2-Dibromo-1-(*p*-nitrophenyl)-

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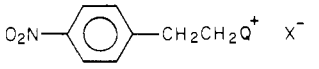
Table II. Properties of *N*-(2-(*p*-Nitrophenyl)ethyl)quinuclidinium Salts



compd	Q (X^-)	mp,[a] deg	apparent M_r	purity,[b] %
1	quinuclidine (Br^-)	217–219 (2-propanol)	345	99.0
2	3-hydroxyquinuclidine (ClO_4^-)	168.5–169.5 (ethanol)	384	98.1
3	1,4-diazabicyclo[2.2.2]octane $(ClO_4^-)_2$	220–224 (95% EtOH)[c]	477	96.8
4	3-chloroquinuclidine (Br^-)	254.5–255 (2-propanol)	371	101.3
5	3-oxoquinuclidine (Br^-)	249–250 (95% EtOH)	355	100
6	4-methyl-1,4-diazabicyclo[2.2.2]octane $(I^-)_2$[d]	229–232 (95% EtOH)	542	~98.0

[a] All the salts decomposed upon melting. [b] By UV analysis (see Experimental Section). Estimated ±1% uncertainty. [c] The melting range depends on the initial bath temperature and the rate of heating. [d] This salt contains a small amount of perchlorate.

ethane was obtained from *p*-nitrostyrene and Br_2/CCl_4.[52] Melting points were in satisfactory agreement with the literature in all cases.

***p*-Nitrophenethyl Iodide.** A solution of 1.0 g (0.0043 mol) of *p*-nitrophenethyl bromide in 5 mL of dry acetone was added to a solution of 2.5 g (0.0167 mol) of sodium iodide in 20 mL of dry acetone. After 1.5 h, the white precipitate of NaBr was filtered and washed with acetone. The acetone solutions were combined and acetone was removed by rotary evaporation. The residue was treated with chloroform and filtered to remove additional NaBr. Evaporation of the chloroform left 1.28 g of pale yellow solid, mp 92–96 °C (quantitative yield). Recrystallization from methanol gave thick needles: mp 96.5–98 °C; ^1H NMR ($CDCl_3$) δ 8.17 (doublet, 2 H, J = 9 Hz), 7.36 (doublet, 2 H, J = 9 Hz), 3.27 (multiplet, 4 H). The compound does not appear to have been described previously.[53] Its identity follows from the method and mild conditions of the synthesis and the NMR spectrum.

(2-(*p*-Nitrophenyl)ethyl-β,β-d_2)trimethylammonium Perchlorate. (*p*-Nitrophenyl)acetonitrile-α,α-d_2 (800 mg, ca. 90% d_2) was reduced with $THF-BH_3$ according to the procedure of Brown and Subba Rao.[54] The resulting (2-(*p*-nitrophenyl)ethyl)ammonium chloride was treated with excess methyl iodide in methanol with the calculated amount of Na_2CO_3 present. After 20 h at room temperature and 1 h of refluxing, the solvent was removed. The dark, semisolid residue was washed with diethyl ether and then dissolved in a small amount of water. The aqueous solution was made acidic with the calculated amount of 70% $HClO_4$ plus a 0.5-mL excess. Reduction of the volume followed by chilling produced 90 mg of fine needles, mp 185–187 °C. The isotopically light salt melts at 189–189.5 °C (ethanol). The 270-MHz NMR spectrum of the heavy salt is identical with that of the light salt (as the iodide; see below) except that the residual β-protons could not be resolved from the bottom of the *N*-methyl resonance and the triplet at δ 3.74 due to the α-protons had collapsed to a singlet. Integration was not precise; we estimate ca. 90% deuterium at the β position.

(2-(*p*-Nitrophenyl)ethyl)trimethylammonium Iodide. Phenethylamine hydrochloride was nitrated with 90% HNO_3 by the method of Goss, Hanhart, and Ingold.[55] The para isomer was isolated by recrystallization of the mixed hydrochlorides from 95% ethanol, mp 205–208.5 °C (lit.[55] mp 209–210 °C). This isomer was methylated as described above to give, in good yield, yellow plates, mp 204.5–205.5 °C. Recrystallization from 95% ethanol raised the melting point to 205.5–206.5 °C. The melting point in the literature has been reported as 195–196 °C,[56] 199 °C,[5] 200–203 °C,[31] and 206 °C.[33,55] We have found it important to obtain the para isomer in good purity prior to methylation. The mixed methiodides are difficult to separate by fractional crystallization; we found that repeated recrystallizations from 95% ethanol raised the melting point of such a mixture as high as 203 °C, but the NMR spectrum showed evidence of at least one other isomer. Treatment of this sample with aqueous KOH produced a non-first-order increase in absorbance at 335 nm, and the "infinity" spectrum was not that of pure *p*-nitrostyrene. For the same reason, the synthesis should not be done by methylating phenethylamine prior to nitration.

Analysis for purity was best accomplished by ultraviolet spectroscopy. A known weight of the salt was treated with 1 M potassium hydroxide and converted to *p*-nitrostyrene (λ_{max} 311 nm (ε 13000)). In this way the (2-(*p*-nitrophenyl)ethyl)trimethylammonium iodide was found to be 101.0% pure. The NMR shifts are reported in Table III.

***N*-(2-(*p*-Nitrophenyl)ethyl)quinuclidinium Salts.** The parent compound and the 3-chloro- and 3-oxoquinuclidinium analogues were available as the bromides from previous work.[24] They were recrystallized several times and analyzed by UV spectroscopy as described above. Melting points and apparent molecular weights (degree of purity) are given in Table II. The other analogues were synthesized by a variation of Alunni's method.[24] The preparation of the 3-hydroxyquinucludinium compound is described in detail. In a small flask were placed 1.00 g (0.0043 mol) of *p*-nitrophenethyl bromide, 2.21 g (0.015 mol) of 3-hydroxyquinuclidine hydrochloride, 0.3 g (0.0075 mol) of NaOH, and 10 mL of methanol. Substitution of the quinuclidine for the bromide proceeds by an elimination–addition mechanism as shown by an increase in the intensity of UV absorption in the regions where *p*-nitrostyrene absorbs strongly but where *p*-nitrophenylethyl species do not. The absorption ascribed to *p*-nitrostyrene subsequently decreases. The proportion of quinuclidine adduct is generally at a maximum (70–90%) after 24 h at room temperature. The salts were precipitated by the addition of 100 mL of diethyl ether. The ether was decanted from the somewhat sticky solid, which was washed several times by addition and decantation of diethyl ether. The solid was then dissolved in the minimum amount of water, the solution cooled, and 1 mL (0.0114 mol) of 70% $HClO_4$ added. The crystals that eventually formed were filtered and recrystallized from hot ethanol to which just enough water was added to effect solution; mp 168.5–169.5 °C, 1.38 g (85%). Properties of this and the other salts are given in Table II. Proton chemical shift assignments are found in Table III.

***N*-Methyl-3-oxoquinuclidinium Iodide.** To a slurry of 1.0 g (0.0062 mol) of 3-oxoquinuclidinium chloride and 0.44 g (0.0032 mol) of K_2CO_3 in 25 mL of methanol was added 8.8 g (0.062 mol) of methyl iodide. The mixture was stirred at room temperature for 3 days. Addition of anhydrous diethyl ether caused precipitation of white solids, which were collected and dissolved in hot ethanol with just enough water to effect solution. Twenty drops of concentrated HI was added. The cooled solution produced hygroscopic white crystals, mp 295–297 °C dec. The material was not completely characterized. In the NMR spectrum, the methyl resonance appears at δ 3.05 (D_2O). That for *N*-methylquinuclidinium ion is at δ 2.99. The UV spectrum in water has a maximum at 281 nm (ε 10.8). For comparison, 3-oxoquinuclidinium ion has λ_{max} at 283 nm (ε 14.4) and cyclohexanone has λ_{max} at 285 nm (hexane, ε 14).[57]

Kinetic Measurements. The decomposition of the (2-(*p*-nitrophenyl)ethyl)ammonium ions to *p*-nitrostyrene was studied with aqueous potassium hydroxide and with aqueous buffers at 25 and 40 °C. The ionic strength in all cases was maintained at 1.00 M with potassium chloride. Slight variations in pH within a buffer series required small (<10%) corrections to the experimental first-order rate constants for the highest [buffer] solutions in a few cases. The appearance of *p*-nitrostyrene was followed spectrophotometrically at 335 nm (ε = 8640) after injection of 10–100 μL of substrate solution into a temperature-equilibrated cuvette containing 2.0–3.0 mL of the buffer or the hydroxide solution. The *p*-nitrophenethyl halides were introduced as ethanol solutions, the final ethanol concentration being 0.3 vol %. Experiments with hydroxide solutions were followed to completion, and pseudo-first-order rate constants were obtained from the slopes of the semilog plots of $A_\infty - A_t$ vs. time. The product was found to be sufficiently stable in dilute alkali to provide accurate A_∞ readings for all but the slowest reactions. In those cases, the A_∞ readings were too small and were optimized by one or two iterations until the first-order plots were linear for >3 half-lives. Reproducibility was <2%.

The eliminations with buffer solutions were too slow to be followed to completion. Initial rates of production of *p*-nitrostyrene were determined by using ca. 10^{-3} M substrate and following the reaction to 1–2%

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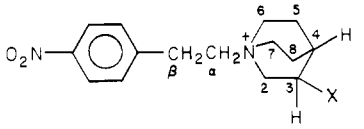
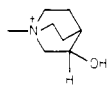
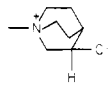
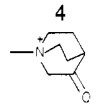
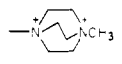
Table III. ^{1}H NMR Chemical Shift Values for (2-(*p*-Nitrophenyl)ethyl)ammonium Ions[a]



ammonium group	β	α	2	3	4	5,8	6,7
 1	3.24	3.46	3.52	2.04	2.23	2.04	3.52
 2	3.27	3.52	3.79	4.37	2.13	2.31, 1.98	3.52
 3	3.29	3.59	3.50	3.24		3.24	3.50
 4	3.27	3.58–3.72	4.09	4.68	2.27	2.52, 2.09	3.58–3.72
 5	3.26	3.52	3.74		2.92	2.21–1.74	3.52
 6	3.36	3.91	4.10	4.10	3.30[b]	4.10	4.10
$-N^+(CH_3)_3$[c] 7	3.40	3.74			*N*-methyl resonance is at δ 3.29		

[a] All spectra were determined at ca. 10^{-2} M in D_2O with a 270-MHz instrument. The shift values are given in ppm downfield from internal DDS. The aromatic ring proton shifts are, in all cases, at δ 7.55 and 8.26 (±0.05 ppm) with J = 8 Hz. [b] This is the chemical shift for the *N*-methyl group. [c] Minch et al.[56] report the spectrum of this compound in Me_2SO-d_6: δ 3.40 (s, $N(CH_3)_3$, 3.53 (s, CH_2N), 3.84 (m, Ar CH_2). It is clear from the spectrum of the β,β-d_2 salt (see Figure 5) that the α-protons are downfield from the β-protons, at least in D_2O.

completion. The linear increase in absorbance at 335 nm with time was divided by $\epsilon_{product}$ and [substrate]$_0$ to obtain experimental first-order rate constants. Reproducibility (≤±5%) was adequate. For reactions with oxyanion bases (OH^-, acetohydroxamate, *N*-hydroxysuccinimidate, carbonate) and with ammonia it was shown that reaction of buffers with the product was too slow to complicate the kinetics. Thus, premature downward curvature of the initial rate plots was neither expected nor observed. With Dabco[24] and trimethylamine buffers, however, less than 0.5% reaction occurred before curvature was observed.

Buffer Association. For buffer series in which $[AcNHO^-]/[AcNHOH] = R < 1.0$ and with the higher buffer concentrations, the plots of k_{obsd} (s^{-1}) vs. $[AcNHO^-]$ for compound **6** showed slight but definite downward curvature. This departure from linearity was almost exactly duplicated with 2,4-dinitrochlorobenzene as the substrate. In the latter reaction, a nucleophilic substitution, step one is taken as rate controlling.[58] This small negative effect may be accounted for by buffer association forming kinetically inactive hydrogen-bonded complexes, $AcHNO^-\cdots HONHAc$.[59] An apparent buffer association constant, K_{assoc}, may be defined (eq 9) in which $[BH]_{ST}$ and $[B^-]_{ST}$ are the stoichiometric

$$K_{assoc} = \frac{[B^-\cdots HB]}{[BH][B^-]} = \frac{([B^-]_{ST} - [B^-])}{([BH]_{ST} - [B^-\cdots HB])([B^-]_{ST} - [B^-\cdots HB])} \quad (9)$$

concentrations of the buffer components and $[B^-]$ represents the concentration of "free" acetohydroxamate ion. The concentration of "free" $AcNHO^-$ was obtained from the curved buffer plot for 2,4-dinitrochlorobenzene by answering the question: what concentration of buffer base, $[B^-] < [B^-]_{ST}$, would provide k_{obsd} (s^{-1}) = $k_{B^-}[B^-]$, in which k_{B^-} is the second-order catalytic coefficient obtained from the linear, low [buffer] region of the plot? The resulting values for $[B^-]$ were used in eq 9 to calculate K_{assoc} = 0.27 M^{-1}. With this value, $[B^-]$ (and [BH]) could be calculated for any other buffer solution. Applied to the data for compound **6** (R = 0.5), the buffer plot could be straightened up to $[AcNHO^-]/[AcNHOH]$ = 0.25 M/0.50 M with only very slight residual negative curvature thereafter. "Free" $[AcNHO^-]$ and [AcNHOH] were calculated for all buffers prior to analysis of the kinetic data.

Solvent Effects. The elimination reactions of compounds **1** and **6** were studied by using acetohydroxamate buffer (R = 1.0, $[B^-]$ = 0–0.2 M) with added ethanol (10–40 vol %, 3–17 mol %) and acetonitrile (10–30 vol %, 4–13 mol %). Stock solutions were prepared by combining the appropriate volume of organic addend, potassium chloride, and aqueous master buffer and diluting to the mark with water. Ionic strength was 1.00 M for all runs. Kinetics were determined as described above. Plots of k_{obsd} (s^{-1}) vs. $[B^-]$ were curved for compound **1** and were analyzed as described below. The same plots for compound **6** were linear for all cases except 40 vol % ethanol. The downward curvature in that case could be rectified by an apparent buffer association constant, K_{assoc} = 2.7 M^{-1}. This correction was also applied to the data for compound **1** in 40 vol % ethanol. Correction for buffer association in more aqueous solvent mixtures proved to be unnecessary due to two factors: lower K_{assoc} values and the use of lower concentrations of buffer components.

In the absence of an empirical relation between measured pH and $[OH^-]$,[24] the intercepts of the linear buffer plots for compound **6** were used, together with experimental values for k_{OH^-}, to evaluate $[OH^-]$ = Intercept/k_{OH^-} for each partly aqueous buffer medium.

Solvent Isotope Effects. The elimination reactions of compounds **1**, **6**, and **7** were examined with acetohydroxamate buffers in D_2O as well as H_2O solutions.[25] For this purpose concentrated master buffers (3.0–3.5 M) having the desired buffer ratio were prepared in mixed H_2O–D_2O solution. Identical aliquots of the master buffer were added to the appropriate weight of potassium chloride and diluted with H_2O or D_2O to make the stock buffer solutions, which were further diluted as required. In the D_2O solutions, exchangeable protium reached 3% at most. For compounds **1** and **6** in H_2O solutions, exchangeable deuterium was ≤3.8%. But for compound **7** in H_2O solution, the exchangeable deuterium was 23% for the most concentrated buffer. Because of the

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Table IV. ElcB Kinetic Parameters for Alkene-Forming Elimination Reactions from p-$NO_2C_6H_4CH_2CH_2X$ Species Induced by KOH and by Acetohydroxamate[a]

X (pK_{XH^+})[b]	$10^3k_{OH^-}$,[c] M^{-1} s^{-1}	$10^5k_{AcNHO^-}$,[d] M^{-1} s^{-1}	k_{AcNHOH}/k_2,[d] M^{-1}	k_2/k_{H_2O}[d]	$10^2k_\infty/[OH^-]$, M^{-1} s^{-1}
 (11.45)	0.77 3.87[e]	1.48 8.80[e]	85 30[e]	10.9 26[e]	0.45 12[e]
1					
 (10.02)	1.11	2.51, 2.70	11.1, 11.5	54, 56	6.0
2					
 (9.22)	2.33	3.57, 3.91	1.6, 1.7	120, 120	59
3					
 (9.03)	2.06	3.97, 3.96	2.6, 2.5	182, 190	41
4					
 (7.5)	(3.72)[f]	5.21, 5.50	1.5, 1.6	850, 875	90
5					
 (3.01)	21.8	37.0 0.26[g] ~0.047[h]	<0.01		
6					
$N(CH_3)_3$ (9.85)	1.50 0.169[i] 5.4[e]	2.70, 2.91 ~17[e]	1.7, 1.8 ~1[e]	290, 280 ~800[e]	42 ~450[e]
7					

[a] In water at 25 °C, ionic strength 1.0 M (KCl). [b] pK values determined at 25 °C and ionic strength 1.0 M (Gresser, M. J.; Jencks, W. P. *J. Am. Chem. Soc.* 1977, *99*, 6963–6970). [c] $[OH^-] = 0.10$ M. [d] The first entries in these columns were calculated from stoichiometric [buffer]. The second entries use "free" [buffer] obtained from an apparent buffer association, $K_{assoc} = 0.27$ M^{-1} (see Experimental Section and Results). Where there is a single entry, no correction was necessary. [e] At 40 °C, ionic strength 1.0 M (KCl). [f] Interpolated from the linear plot of log k_{OH^-} vs. pK_{XH^+}. The experimentally observed value (1.01×10^{-3} M^{-1} s^{-1}) is lower owing to an interaction between OH^- and the oxoquinuclidinium moiety. [g] Induced by N-hydroxysuccinimidate (p$K_a = 5.85$). [h] Induced by cacodylate (p$K_a = 6.3$). [i] Compound 7-β,β-d_2. Activation parameters for compound 1 are: for k_{OH^-}, $\Delta H^\ddagger = 19.4$ kcal/mol, $\Delta S^\ddagger = -7.8$ cal/(mol deg); for k_{AcNHO^-}, $\Delta H^\ddagger = 21.5$ kcal/mol; $\Delta S^\ddagger = -8.6$ cal/(mol deg). The values are based on two temperatures only.

primary kinetic isotope effect on k_{-1} (see Discussion) this isotopic impurity has only a small effect on $k_{obsd}(H_2O)$. With a knowledge of that isotope effect, the small correction was easily estimated. Acetohydroxamate concentrations in the buffer series with $R = 0.5$ were corrected for apparent buffer complexation as described above.[60]

Isotopic Exchange Experiments. Incorporation of isotopic hydrogen into unconverted compounds **1** and **7** was examined with acetohydroxamate buffers by 270-MHz NMR spectroscopy. Compound **1** (10^{-2} M) was allowed to react at 40 °C in D_2O with acetohydroxamate buffer ($R = 0.33$, [AcNDOD] = 0.45 M, [KCl] = 0.85 M). The reaction solution was covered with a layer of *n*-heptane and shaken frequently in order to extract *p*-nitrostyrene as formed. At intervals ca. 0.5 mL of the reaction solution was placed in an NMR tube and refrigerated. Just prior to examination by NMR, 2 drops of 40% $NaOD/D_2O$ were added to each tube, which was then shaken vigorously to extract the quinuclidine product into the heptane layer. Failure to carry out this procedure leaves quinuclidine in the reaction solution (as quinuclidinium ion) where it interferes critically with the spectrum of the unreacted starting material. The NMR spectrum was promptly determined in the aliphatic region. A small portion of the reaction solution was treated at time zero with $CDCl_3$ rather than heptane, and the reaction tube was shaken frequently. After a time corresponding to approximately 17% elimination, the accumulated *p*-nitrostyrene was observed by NMR to be partially (ca. 35%) deuterated at the benzylidene position.

Incorporation of deuterium into compound **7** could not be observed by the technique described above. Instead, compound **7** deuterated at C-β was prepared, and a search for *protium* incorporation was made. The deuterated substrate (10^{-2} M) was allowed to react at 25 °C in H_2O with acetohydroxamate buffer ($R = 0.5$, [AcNHOH] = 1.0 M, [NaCl] = 0.50 M, pH 9.03). At time zero, 1 mL of solution was withdrawn and quenched with 12 drops of 0.2 M methanolic picric acid, and the sparingly soluble (2-(*p*-nitrophenyl)ethyl)trimethylammonium picrate was collected by filtration.[55] At a time corresponding to 42% elimination, the remainder of the reaction solution was quenched with picric acid and the solid collected and washed with anhydrous diethyl ether. The picrates were dissolved into NMR tubes with ca. 60% D_2SO_4–D_2O and the spectra determined in the $CH_2CH_2N^+(CH_3)_3$ region.

Control experiments in which the buffer and the leaving groups were allowed to react with *p*-nitrostyrene showed that under the exchange conditions, at the quenching times, the instantaneous rate of addition is less than the instantaneous elimination rate by a factor of far less than 10^2. Even this estimate exaggerates the amount of styrene that could have returned (with exchange) to reactant because the concentration of styrene used in the calculation is greater than that present at any time prior to the quenching time, and in the case of compound **1**, because the styrene was extracted from the reaction medium as formed.

A single attempt was made to investigate tritium incorporation from tritiated water in the elimination reaction of compound **7**. The compound (1.7×10^{-2} M) was allowed to react with acetohydroxamate buffer ($R = 0.5$, [BH] = 0.90 M, [KCl] = 0.55 M) at room temperature in tritiated water (1.05×10^{11} cpm/equiv). Carbon tetrachloride was added so that *p*-nitrostyrene could be extracted as formed. Technical problems forced the examination of the product rather than the reactant. After 70% elimination, the accumulated *p*-nitrostyrene was isolated as the dibromide.[52] Unlabelled dibromide was added and the mixture recrystallized to constant specific activity. After correction for self-quenching, the specific activity of the product was 2.25×10^9 cpm/mol for a 2.14% incorporation. The likely exchange mechanism gives complex kinetics, and a detailed analysis was not made. The amount of tritium incorporation is reasonable if one assumes the E1cB mechanism with a normal primary kinetic isotope effect on k_{-1}. With a value for k_{-1}/k_2 obtained in ordinary water (see below and Table IV), we can calculate that the observed tritium incorporation requires an isotope effect, $(k_{-1}^H/k_{-1}^T) < 30$, which corresponds to $(k_{-1}^H/k_{-1}^D) < 10$.[61] Our directly measured

(60) For **6** with acetohydroxamate buffers in D_2O, no curvature was observed because of the low buffer concentrations used. A value of $K_{assoc} = 0.27$ M^{-1} was assumed. Its application to the experimental data for **1** and **7** produced improved fits to eq 11–14. Because of the good fits, no further optimization was done.

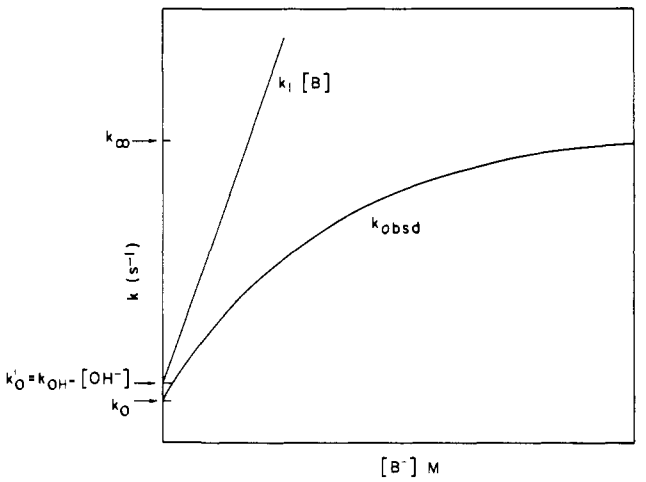


Figure 1. Plot of eq 11 (schematic): the dependence of k_{obsd} (s^{-1}) on [buffer] at constant buffer ratio for the E1cB mechanism.

value for (k_{-1}^H/k_{-1}^D) is 5.7 for protonation of the zwitterion by acetohydroxamic acid.[25]

Analysis of Buffer Curvature. For the E1cB mechanism (eq 8 and 10), application of the steady-state approximation gives eq 11. Useful definitions and equalities include $k_0 = k_{obsd}([buffer] \rightarrow 0) = k_{OH^-}[OH^-]k_2/(k_{H_2O} + k_2)$; $k_0' = k_{OH^-}[OH^-]$; $k_0'/k_0 = (k_{H_2O} + k_2)/k_2 = (k_0' + k_\infty)/k_\infty$; $k_\infty = k_{obsd}([buffer] \rightarrow \infty) = \sum k_1[B^-]k_2/\sum k_{-1}[BH] = k_{OH^-}[OH^-]k_2/k_{H_2O} = Rk_{B^-}(k_2/k_{BH})$; R = buffer ratio = $[B^-]/[BH]$. So defined, k_∞ is a pseudo-first-order constant, dependent on $[OH^-]$, as are k_0 and k_0'.

$$\gtrless CH \underset{k_{-1}[BH]}{\overset{k_1[B^-]}{\rightleftharpoons}} \gtrless C^- \xrightarrow{k_2} \text{products} \qquad (10)$$

$$k_{obsd}\ (s^{-1}) = \frac{\sum k_1[B^-]k_2}{\sum(k_{-1}[BH]) + k_2} = \frac{(k_{OH^-}[OH^-] + k_{B^-}[B^-])k_2}{(k_{H_2O} + k_{BH}[BH]) + k_2} \qquad (11)$$

Equation 11 predicts that k_{obsd} vs. $[B^-]$ at constant R will describe a rectangular hyperbola approaching $k_{obsd} = k_\infty$ at $[B^-] = \infty$. Figure 1 shows such a plot in schematic form.

Whenever buffer curvature is so pronounced that a reliable value for k_∞ can be measured (buffer saturation), evaluation of several kinetic parameters is simplified: values of $\sum k_1[B^-]$ and $\sum k_1[B^-]/k_{obsd}$ may be calculated from eq 12; then eq 12 and 13 are used to obtain k_{B^-} and k_{BH}/k_2. Moreover, k_{H_2O}/k_2 is equivalent to k_0'/k_∞.

$$\sum k_1[B^-] = k_{B^-}[B^-] + k_0' = \frac{k_\infty k_{obsd}}{k_\infty - k_{obsd}} \qquad (12)$$

$$\sum k_1[B^-]/k_{obsd} = (k_{BH}/k_2)[BH] + (k_{H_2O} + k_2)/k_2 \qquad (13)$$

The more common situation was that complete buffer saturation was not attainable ($k_\infty \gg k_0'$) and k_∞ was not directly measurable. In such cases the following procedure was used. From eq 11 and the given definitions may be derived eq 14. Whenever $k_\infty \gg k_0'$, as will be the case when buffer saturation is not observed, it is a good first approximation to let $(k_{H_2O} + k_2)/k_2 = 1.0$ and $k_0 = k_0'$. One may then plot $(k_{obsd} - k_0')/[BH]$ vs. k_{obsd} to obtain preliminary values for (k_{BH}/k_2), k_{B^-}, and (from the abcissal intercept, where $k_{obsd} \rightarrow k_\infty$ as $1/[BH] \rightarrow 0$) a value for k_∞. With a number for k_∞ and the definitions given previously, one may estimate $(k_{H_2O} + k_2)/k_2$ and k_0 and thereby use eq 14 more accurately. Iteration proceeds until k_∞ converges; no more than two iterations were found necessary. Finally, best values for k_{B^-} and k_{BH}/k_2 were found as the slopes of eq 12 and 13.

$$\frac{[(k_{H_2O} + k_2)/k_2](k_{obsd} - k_0)}{[BH]} = -(k_{BH}/k_2)k_{obsd} + Rk_{B^-} \qquad (14)$$

Results

Kinetics and [Buffer] Dependence. The rates of production of *p*-nitrostyrene from six different *N*-(2-(*p*-nitrophenyl)ethyl)-quinuclidinium ions (compounds **1–6**) and from (2-(*p*-nitrophenyl)ethyl)trimethylammonium ion (**7**) were measured in aqueous solution (μ = 1.00 M, KCl) at 25 °C with acetohydroxamate buffers. A few experiments with other buffers and sets with compounds **1** and **7** at 40 °C were also performed. For all compounds except **6** the plots of k_{obsd} (s^{-1}) vs. concentration of acetohydroxamate buffers showed pronounced *but varying* curvature. For this and other reasons (see below under Salt, Medium, and Buffer-Association Effects), we conclude that the curvature is not primarily a consequence of buffer association nor of specific medium or salt effects brought about by varying [buffer] over a wide range. The small amount of curvature induced by these combined environmental effects was assessed from the results for compound **6** and, independently, for the nucleophilic substitution reaction of acetohydroxamate buffers with 2,4-dinitrochlorobenzene. The concentrations of free $AcNHO^-$ and AcNHOH were calculated for each buffer solution from a value of K_{assoc} = 0.27 M^{-1} (eq 9), as described in the Experimental Section. It is these concentrations that were subsequently used in assessing the dependence of the kinetics on [buffer]. The curvature of the resulting plots was almost indistinguishable from that of the original plots obtained with $[buffer]_{ST}$.

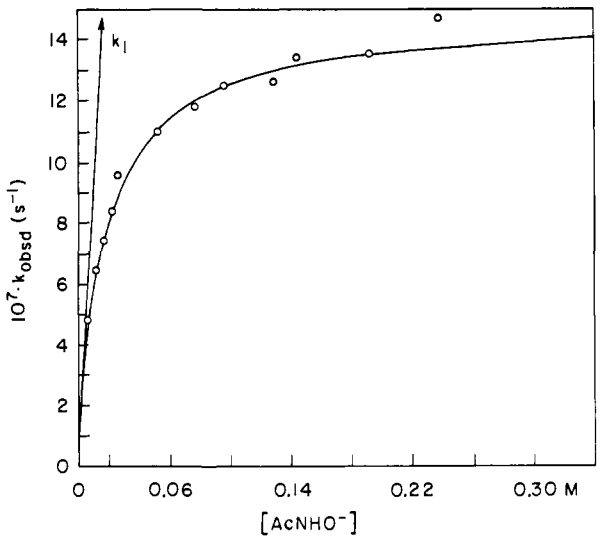


Figure 2. Dependence of k_{obsd} (s^{-1}) on acetohydroxamate concentration for the elimination reaction of *N*-(2-(*p*-nitrophenyl)ethyl)quinuclidinium ion (**1**) at 40 °C, μ = 1.0 M (KCl). Buffer ratio = R = $[AcNHO^-]/[AcNHOH]$ = 0.5. The circles are experimental points; the line was calculated by using eq 11 and the appropriate data from Table IV.

This result allows the conclusion that the observed buffer curvature signifies a change in rate-controlling step, hence, a multistep mechanism. The curvature was therefore analyzed according to the method outlined in the Experimental Section for the E1cB mechanism. The derived kinetic parameters are given in Table IV. A graphic example of the curvature is Figure 2 (for compound **1**). The circles are experimental points, and the line is calculated from eq 11 and the appropriate values from Table IV. In Figure 3 are shown the buffer curvatures obtained with the series of compounds, **1–5** and **7**.

Isotopic Hydrogen Exchange. The single tritium-exchange experiment with (2-(*p*-nitrophenyl)ethyl)trimethylammonium ions (**7**) was described in the Experimental Section. The deuterium exchange experiments are more direct. Figure 4 shows 270-MHz NMR spectra of a portion of the aliphatic region for compound **1** in D_2O with acetohydroxamate buffer ($[B^-]/[BD]$ = 0.15 M/0.45 M, 40 °C). The three spectra correspond to reaction times of 0%, ~25%, and ~50% elimination. By 50% elimination, the exchange at C-β is virtually complete: the H-β resonance has all but vanished and the H-α resonance has sharpened to a singlet. A sample of *p*-nitrostyrene was examined after ca. 17% elimination. As expected, it was partly deuterated (ca. 35%) at the benzylidene carbon.

Deuterium incorporation at C-β for compound **7** was not extensive and was difficult to detect for two reasons. The partitioning

(61) Swain, C. G.; Stivers, E. C.; Reuwer, J. F.; Schaad, L. J. *J. Am. Chem. Soc.* **1958**, *80*, 5885–5893.

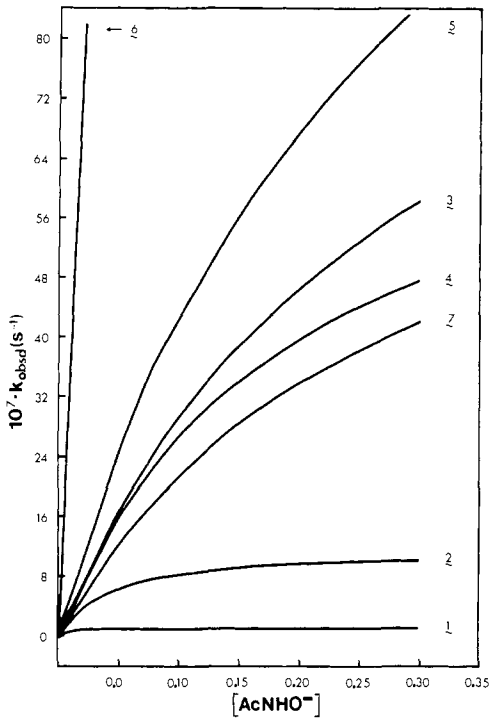


Figure 3. Dependence of k_{obsd} (s^{-1}) on acetohydroxamate concentration for the elimination reactions of compounds **1–5** and **7** at 25 °C; μ = 1.00 M (KCl), R = 0.5. The lines are calculated using eq 11 and data from Table IV. Experimental points are omitted here for simplicity (but see Figures 2, 6, and 7).

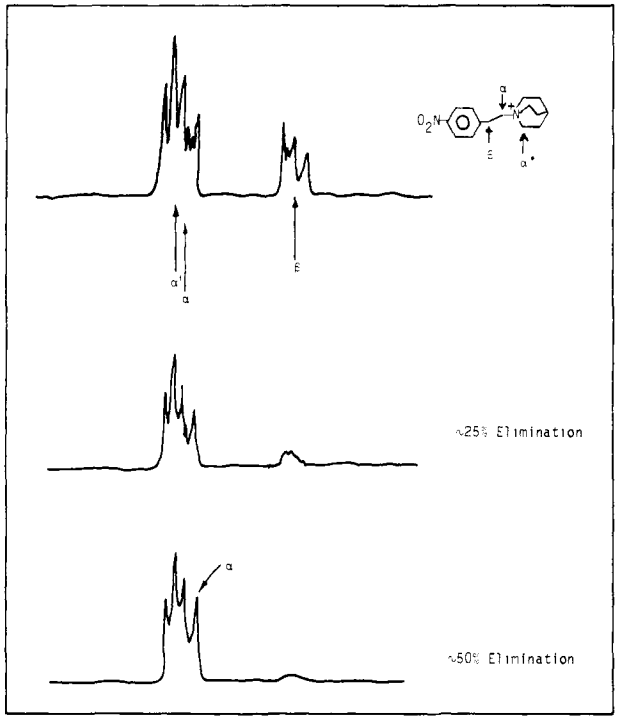


Figure 4. 270-MHz ^{1}H NMR spectra of part of the aliphatic region of compound **1** at times corresponding to (top) 0%, (middle) ca. 25%, and (bottom) ca. 50% elimination with an acetohydroxamate buffer (R = 0.33, [B^-] = 0.15 M) in D_2O at 40 °C, μ = 1.0 M (KCl).

ratio for return of the zwitterionic intermediate to reactant as opposed to leaving group departure is less favorable for **7** than for **1** since trimethylamine is a better leaving group than quinuclidine. Moreover there is a primary hydrogen isotope effect on the return step that further decreases its rate relative to elimination. The second problem was overcome by using compound **7** deuterated at C-β and observing *protium* incorporation from H_2O

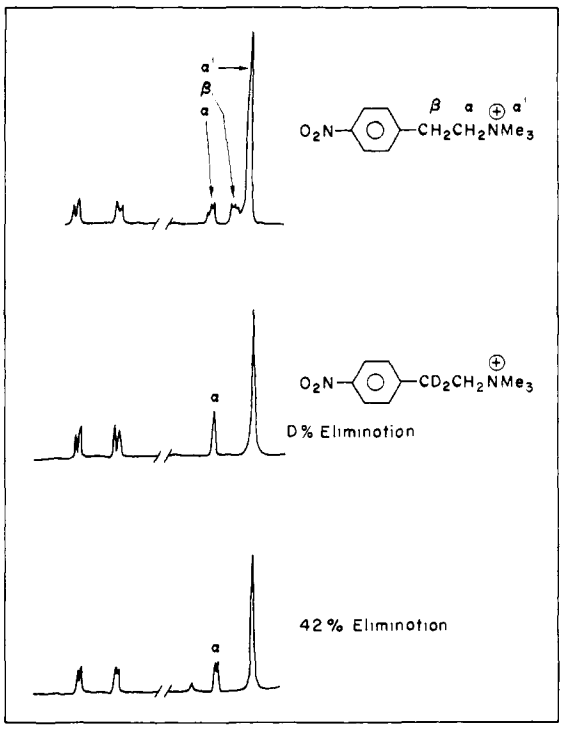


Figure 5. 270-MHz ^{1}H NMR spectrum of compound **7** in D_2O (top). The lower two spectra are of 7-β,β-d_2 after 0% and 42% elimination have occurred with acetohydroxamate buffer at 25 °C in H_2O; R = 0.5, μ = 1.0 M (NaCl). Unconverted substrate was isolated and redissolved in 60% D_2SO_4/D_2O for the lower two spectra.

with acetohydroxamate buffer ([B^-]/[BH] = 0.50 M/1.00 M, 25 °C). Figure 5 shows the NMR spectra of compound **7**, 7-β,β-d_2, and 7-β,β-d_2 after 42% elimination has occurred. Although one cannot see the growth of H-β directly, one does see that the α-protons, a singlet at time zero, have become split, indicating the presence of a *vicinal* proton on C-β.

Inverse Solvent Isotope Effects. During the deuterium incorporation experiments with **1**, we noticed that the rate of *p*-nitrostyrene production was faster than anticipated on the basis of kinetic experiments already done with H_2O. The result was rationalized by assuming the $(E1cB)_R$ mechanism, and it was decided to study the accelerating effect of D_2O in greater detail. The results were described in a previous communication.[25] Similar experiments were done with **7**, with the (less dramatic) results shown in Figure 6. From the curvature of these plots, with the method outlined in the Experimental Section, various E1cB kinetic parameters can be calculated. These are given for **1**, **6**, and **7** in Table V. Some of the values in Table V are slightly different from the corresponding values in Table IV. The most likely explanation for the differences is that a special, highly concentrated master buffer (H_2O/D_2O) was used to minimize [buffer] differences between isotopic media for the isotope effect study. Different master buffers were used in the rest of the kinetic work with H_2O. For comparing compounds **1–7** with one another, the results in Table IV and Figure 3 are appropriate. For the solvent isotope effects, see Table V.

The pK_a of acetohydroxamic acid in H_2O (25 °C, μ = 1.00 M, KCl) is 9.4 as obtained from pH measurements at several buffer ratios ([buffer] = 0.01–0.10 M). Identical buffer concentrations in D_2O gave pH readings averaging 0.21 ± 0.01 unit higher. Thus pD = pH + 0.61, and the solvent isotope effect is $K_a(H_2O)/K_a(D_2O)$ = 4.07 ± 0.10.

Salt, Medium, and Buffer-Association Effects. When working with high concentrations of buffer components, it is prudent to assess the effects of varying [M^+B^-] and [BH] even when ionic strength and buffer ratio are kept constant.[59b] The present work and earlier work in this laboratory[24] used an ionic strength of 1.0 M (KCl). Alunni noticed that the specific rate of compound **1** is 43% higher in 0.80 M KOH than that in 0.08 M KOH.[24]

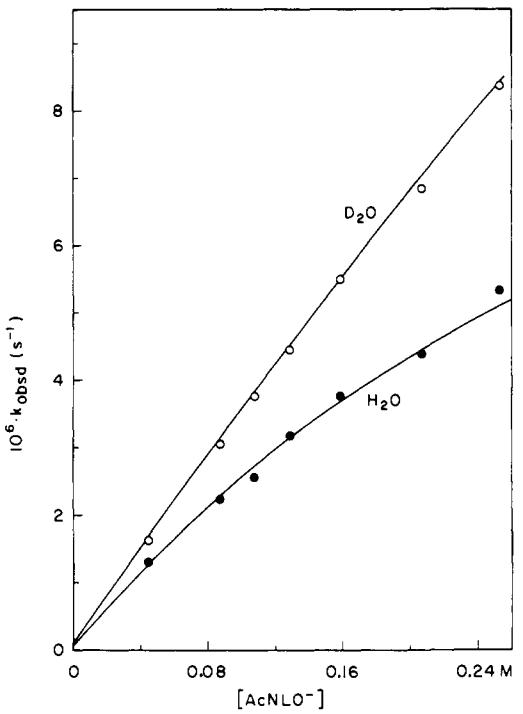


Figure 6. Plots of k_{obsd} (s^{-1}) vs. [AcNLO$^-$] for initial rates of *p*-nitrostyrene formation from **7** in H_2O and D_2O at 25 °C; μ = 1.0 M (KCl), R = 0.5. The open and filled circles are experimental points for D_2O and H_2O, respectively. The lines were calculated by using eq 11 and data from Table V.

Table V. Solvent Isotope Effects on ElcB Kinetic Parameters for Acetohydroxamate-Induced Eliminations at 25 °C and Ionic Strength 1.0 M (KCl)[a]

	H_2O	D_2O	k_{BH}/k_{BD}[b]	k_{H_2O}/k_{D_2O}[b]
	Compound 1			
k_{B^-}, M^{-1} s^{-1}	1.58×10^{-5}	1.86×10^{-5}		
k_{BL}/k_2, M^{-1}	67	10.1	6.6	
k_∞,[c] s^{-1}	4.75×10^{-7}	37.3×10^{-7}		
k_2/k_{L_2O}	13.5	70.4		5.2
k_{BL}/k_{L_2O}, M^{-1}	900	710		
	Compound 6			
k_{B^-}, M^{-1} s^{-1}	43.4×10^{-5}	48.1×10^{-5}		
	Compound 7			
k_{B^-}, M^{-1} s^{-1}	3.05×10^{-5}	3.60×10^{-5}		
k_{BL}/k_2, M^{-1}	1.03	0.18	5.7	
k_∞,[d] s^{-1}	14.8×10^{-6}	102×10^{-6}		
k_2/k_{L_2O}	270	1230		4.6
k_{BL}/k_{L_2O}, M^{-1}	280	225		

[a] Solvent isotope effects on hydroxide-induced reactions were not measured directly. From intercepts of the buffer plots, we estimate $k_{OD^-}/k_{OH^-} \approx 1.5$ for each compound. From the data, $k_{B^-}(D_2O)/k_{B^-}(H_2O)$ is calculated as 1.18, 1.11, and 1.18 for 1, 6, and 7. [b] Assuming no solvent isotope effect on k_2. [c] [B$^-$]/[BL] = 2.0. [d] [B$^-$]/[BL] = 0.5.

Similarly, we have observed that changing from 0.10 M KOH to 1.0 M KOH increases k_{OH^-} for compounds **1** and **7** by 74% and 52%, respectively. A smaller effect is observed for elimination from neutral substrates: the specific rate for dehydrochlorination of *p*-nitrophenethyl chloride is 19% faster in 1.0 M KOH than that in 0.10 M KOH with no added salt. The increases are attributable to the specific salt effect of OH^- on k_1, or (for *p*-nitrophenethyl chloride) on the E2 rate constant.

There appears also to be a small positive specific salt effect of K^+AcNHO^- on k_1. The reaction of **6** in acetohydroxamate buffers (R = 5.0, μ = 1.0 M, KCl) was expected to show a linear dependence of k_{obsd} (s^{-1}) on [AcNHO$^-$]. However, the plot shows slight upward curvature at high [buffer]. The rate for [AcNHO$^-$] = 0.45 M is 11% greater than predicted by linear extrapolation from lower [AcNHO$^-$].

The neutral buffer component, AcNHOH, also appears to exert an accelerating effect on these reactions. To establish this effect, we examined compound **6** with a buffer containing [AcNHO$^-$]/[AcNHOH] = 0.45 M/0.090 M with and without added acetamide and acetonitrile (used to mimic AcNHOH while adding no catalytic effect). After small corrections for hydroxide catalysis, it was seen that 0.48 M acetamide, 0.81 M acetamide, and 0.81 M acetonitrile exerted accelerating effects of 6%, 11%, and 20%, respectively, on k_{B^-}.

With buffer series where $R < 1.0$, a third effect dominated the positive salt and medium effects at higher [buffer]. This effect, a negative one, we attribute to complexation[59] between AcNHO$^-$ and AcNHOH to produce kinetically inactive complexes. The apparent association constant, K_{assoc}, contains contributions from the salt and medium effects discussed immediately above. However, with the buffer concentrations employed, the medium effects are relatively small, and with $R < 1.0$, so are the salt effects. Therefore, K_{assoc} represents mainly buffer association. The data for compounds **1–5** and **7** (R = 0.5) were corrected at high [buffer] by using K_{assoc}. This correction can only be approximate at best since its applicability depends on the extent to which k_1 is rate controlling for these substrates and (when k_2 is partly rate controlling) on the extent to which k_2/k_{-1} is subject to the medium effects. Fortunately the uncertainty is not very significant. We reemphasize here that none of the medium effects is large compared with the buffer curvature caused by a change in rate-controlling step.

We have examined the effect of adding small organic molecules to the reaction medium more deliberately using 10–40 vol % ethanol and 10–30 vol % acetonitrile. These compositions correspond to 3–17 mol % ethanol and 4–13 mol % acetonitrile. Our goal was to establish the effects of organic addends on the kinetic parameters of the ElcB mechanism. In order to use eq 11, we needed to know the effective lyate concentrations in the buffered partly organic media. An empirical relation between pH_{obsd} and ["OH^-"] was not established. However, by measuring k_{OH^-} directly for compound **6**, and extrapolating the buffer plots for **6** to zero [buffer] (all such plots were linear provided [buffer] was not extended too high), lyate concentrations could be computed as [OH^-] = k_{obsd} (s^{-1}, [B$^-$] = 0) divided by k_{OH^-} (M^{-1} s^{-1}). The buffer-plot intercept for compound **1** could thereby be calculated for each medium. Although the intercepts were very small, and not accurately obtained directly from the buffer plots, they were apparently in excellent agreement with the calculated values.

We expected that buffer association would be a problem in the partly organic media. However, because [buffer] was kept low, association was not significant, as shown by the linearity of the buffer plots for compound **6**. Only for 40 vol % ethanol was negative curvature seen for **6**. An apparent K_{assoc} = 2.7 M^{-1} was calculated for acetohydroxamate buffers in this medium. The data for compound **1** were adjusted as described in the Experimental Section. Also in these partly organic media the measured pH values showed slight but regular increases with increasing [buffer]. As these changes were small, it was assumed that Δ log [OH^-] is linear with ΔpH. The lyate concentration for each buffer was recalculated on this basis. The changes were small.

Plots of k_{obsd} (s^{-1}) vs. [AcNHO$^-$] for **1** curve downward for the mixed solvents. The curvature is not as great as it is for water and becomes progressively less pronounced as the medium becomes less aqueous. Moreover, the rates of elimination are greater the more organic material is present. Figure 7 shows the results with added ethanol with a buffer ratio R = 1.0. The ElcB kinetic parameters for all solvent mixtures were calculated as described earlier. These are presented in Table VI for compounds **1** and **6**. Included are results obtained by Gandler and Jencks for aqueous Me_2SO.[26] The lines in Figure 7 were calculated from the derived kinetic parameters. Reproduction of the experimental curvature is excellent.

The Element Effect.[26,37a,c,43b] The four *p*-nitrophenethyl halides were subjected to dehydrohalogenation in dilute aqueous potassium

Table VI. Effect of Organic Addends on the ElcB Kinetic Parameters for the Acetohydroxamate-Induced Eliminations from Compounds 1 and 6 at 25 °C, Ionic Strength 1.0 M (KCl)[a]

compound	vol % addend	[lyate],[b] M	$10^3 k_{OH^-}$,[c] M^{-1} s^{-1}	$10^5 k_{AcNHO^-}$, M^{-1} s^{-1}	k_{AcNHOH}/k_2, M^{-1}	k_2/k_{H_2O}
			Ethanol			
1	0	[d]	0.77	1.48	85	10
	10	2.23×10^{-5}	1.43	1.82	35	17
	20	3.02×10^{-5}	2.76	2.88	17	20
	30	2.9×10^{-5}	5.53	3.63	5.6	40
	40	4.5×10^{-5}	10.7	4.68	1.6	59
6	0	[d]	21.8	37.0		
	10	2.23×10^{-5}	35.9	45.1		
	20	3.02×10^{-5}	53.1	53.3		
	30	2.9×10^{-5}	86.1	60.7		
	40[e]	4.5×10^{-5}	141	64.5		
			Acetonitrile			
1	10	1.34×10^{-5}	1.33	1.80	23.6	42
	30	4.1×10^{-5}	2.83	3.50	3.1	100
6	10	1.34×10^{-5}	29.9	50.3		
	30	4.1×10^{-5}	53.5	62.6		
			Me_2SO[f]			
1	20			6.0	17	
	40			29	3.6	
	60			291	<1	

[a] Buffer ratio $R = 1.0$ was used for all of the partly organic media. $[AcNHO^-] = 0$–0.10 M for 10, 20, and 30 vol % EtOH; 0–0.20 M for 40 vol % EtOH and 10 and 30 vol % acetonitrile. [b] Calculated from k_{OH^-} for 6 and the intercept of the (linear) plot for that compound of k_{obsd} (s^{-1}) vs. [buffer] in each medium. [c] Measured with 0.10 M KOH, ionic strength 1.0 M (KCl). [d] Various buffer ratios were used, R = 0.5 being the most common. [e] This was the only medium in which 6 displayed buffer curvature. From that curvature, an apparent K_{assoc} = 2.7 M^{-1} was calculated. [f] Reference 26, ionic strength 0.3 M (KCl), $[BH]/[B^-] = 2.2$.

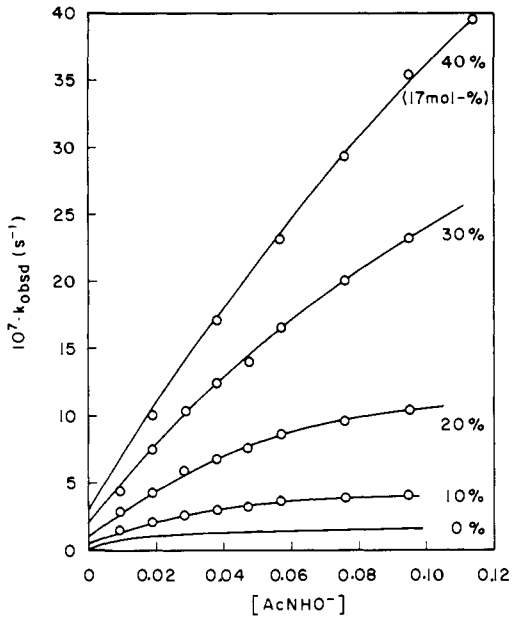


Figure 7. Plots of k_{obsd} (s^{-1}) vs. [$AcNHO^-$] for the elimination reaction of **1** in water with varying amounts of added ethanol at 25 °C; μ = 1.0 M (KCl), R = 1.0. The circles are experimental points; the lines were calculated from eq 11 by using data from Table VI.

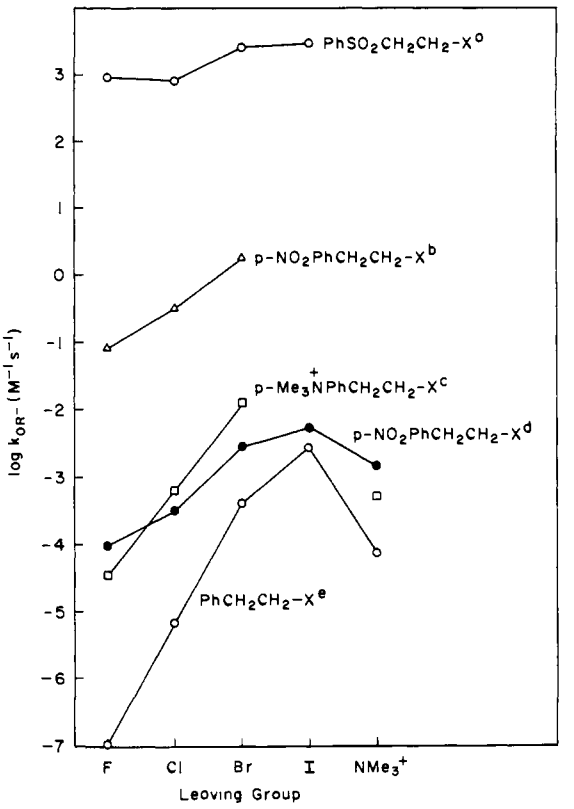


Figure 8. Graphical display of leaving group effects on the rates of several lyate-induced alkene-forming eliminations. The leaving groups are the halides and trimethylamine. References: (a) $EtO^-/EtOH$, 25 °C: Marshall, D. R.; Thomas, P. J.; Stirling, C. J. M. *J. Chem. Soc., Perkin Trans. 2* **1977**, 1914–1919. (b) OH^-/40% Me_2SO, 40 °C: ref 26. (c) OH^-/H_2O, 60 °C: ref 43b. (d) OH^-/H_2O, 25 °C: this work. (e) $EtO^-/EtOH$, 30 °C: ref 37c and 37e. The open square belongs to series (c).

hydroxide solution in order to test the effect of halide leaving group ability on these eliminations. Second-order rate constants are given in Table VII along with that for 1,2-dibromo-1-(*p*-nitrophenyl)ethane. The order of leaving group ability is I > Br > Cl > F, with the largest percent increase occurring between chloride and bromide and the smallest between bromide and iodide. These results, together with other element effect data, are shown in a graphical form in Figure 8.

Discussion

Mechanism. The observation of isotopic hydrogen exchange and large, [buffer]-dependent inverse solvent isotope effects for compounds **1** and **7** (identified in Table IV), together with the buffer curvature seen for **1**–**5** and **7**, establish the mechanism as a true E1cB elimination.[25] Initial rates via the E2 mechanism would not show this combination of effects even if isotopic hydrogen exchange were concurrent with elimination.[8c,25,62] An

Table VII. Rate Constants for the Elimination Reactions of HX from p-Nitrophenethyl Halides Induced by 0.100 M KOH, 25 °C[a]

halide	$\sigma^*_{CH_2X}$[b]	$10^3 k_{OH^-}$, $M^{-1}\ s^{-1}$
fluoride	1.10	0.0963
chloride	1.05	0.318
bromide	1.00	2.82
iodide	0.85	5.62
1,2-dibromo-1-(p-nitrophenyl)ethane[c]		38.5[c]

[a] Ionic strength 0.10 M; 0.3 vol % ethanol was present. [b] Taft, R. W. In "Steric Effects in Organic Chemistry"; Newman, M. S., Ed.; Wiley: New York, 1956, Chapter 13. Hine, J. "Structural Effects on Equilibria in Organic Chemistry"; Wiley-Interscience: New York, 1975; p 91. [c] This reaction may be ElcB. See text and ref 23.

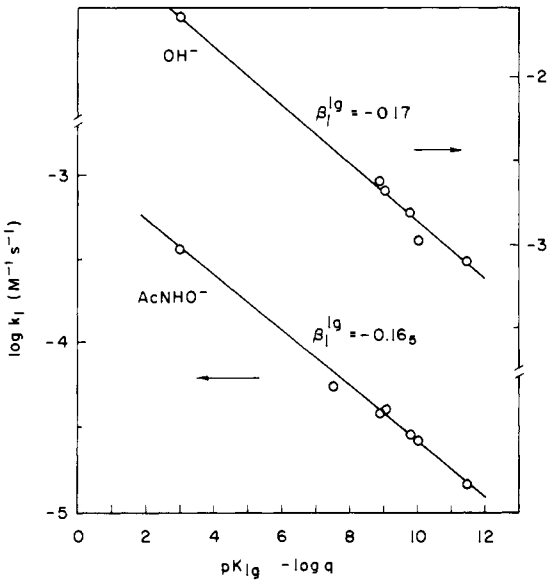


Figure 9. Plot of log k_{B^-} ($M^{-1}\ s^{-1}$) vs. pK_{lg} for the hydroxide- and acetohydroxamate-induced eliminations of compounds **1–7** in H_2O at 25 °C; μ = 1.0 M (KCl).

$(ElcB)_{ip}$ mechanism would not show buffer curvature. Nor would exchange and inverse solvent isotope effects be seen unless there were rapid exchange of deuterium into the BH–zwitterion complex. A freely solvated (liberated) intermediate is required.

None of the effects described above was observed with compound **6**, the substrate with the best leaving group. Nevertheless, plots of log k_{B^-} (see Table IV) vs. pK_{lg} are linear both for B^- = OH^- and $AcNHO^-$ and include the points for **6** (Figure 9). The slope of the line is $\beta_l^{lg} = -0.17$ for each base. The small slope is rational for a transition state in which proton removal but not leaving group departure is occurring.[24] Moreover, the invariance of the slope with the identity of the base ($\partial\beta_l^{lg}/\partial pK_{BH} = \partial\beta/\partial pK_{lg} \equiv p_{xy} = 0$) means that the actions of the base and the leaving group are not coupled in step one, the small effect of the leaving group on k_{B^-} being most simply explained as a polar substituent effect on the rate of proton removal. The observation of $p_{xy} = 0$ has been proposed as a criterion of mechanism in the difficult experimental distinction between E2 and $(ElcB)_I$.[26] The failure of the leaving group in **6** to accelerate step one beyond its expected polar influence indicates that **6** too uses the stepwise path. Our inability to see exchange, buffer curvature, or inverse solvent isotope effects for **6** is due to the unfavorable partitioning of the zwitterion: we estimate $k_{AcNHOH}/k_2 < 0.01$ for this case (Table IV, $k_{AcNHOH} = k_{-1}$ for AcNHOH).

As discussed in the introduction, past work on base-induced eliminations in $ArCH_2CH_2$–lg systems has provided strong evidence for the E2 mechanism. The study of Gandler and Jencks[26] shows that this is indeed the norm and that only *p*-nitro among substituents so far examined is sufficiently electron withdrawing to cause the switch to ElcB. Even here the leaving group must not be too good. The *p*-nitrophenethyl halides undergo elimination in the usual "element effect" kinetic order: F < Cl < Br < I (Table VII, Figure 8, ref 26). This result cannot be due to use of the $(ElcB)_R$ mechanism because general base catalysis has been established for lg = F, Cl, Br.[26] The $(ElcB)_{ip}$ mechanism is a conceivable alternative, but the observed Brønsted coefficients, β = 0.76, 0.67, and 0.55, respectively, are small for a mechanism in which proton transfer occurs prior to the rate-controlling transition state. In addition, the trend in β is equivalent to a positive interaction coefficient, $p_{xy} > 0$, a result characteristic of other E2 reactions.[26] It seems clear that of the halides, I, Br, and Cl use the E2 mechanism while the fluoride mechanism might be E2 or $(ElcB)_I$. We return to this point below under Choice of Mechanism.

There is in the literature a prior example of mechanistic change in a base-induced elimination brought about by a β-aryl substituent effect. This change too is caused by the *p*-nitro substituent. McLennan[21b] has reported that 1,1-bis(*p*-nitrophenyl)-2,2-dichloroethane (*p*-nitroDDD) undergoes elimination (NaOMe/MeOH, 30 °C) roughly three times faster than might be expected by extrapolation from the elimination rates of other ring-substituted DDD's.[63] The rate constant fits a linear free energy relationship generated by the elimination rates of 1,1-diaryl-2,2,2-trichloroethanes (DDT's), reactions assigned the $(ElcB)_I$ mechanism.[20] The surmise that *p*-nitroDDD reacts by the $(ElcB)_I$ mechanism while the other DDD's use the E2 mechanism is reinforced by the observation that only the *p*-nitro compound fails to show a primary chlorine isotope effect upon elimination.[21c]

The data described so far do not completely rule out the possibility that the mechanistic switch in the DDD series is less radical than asserted by McLennan. It is possible that in dry methanol *p*-nitroDDD uses the $(ElcB)_I$ mechanism while the other DDD's, with much poorer carbanion stabilizing substituents, require the $(ElcB)_{ip}$ mechanism: that is, the methanol molecule formed by proton abstraction is still associated with the resulting carbanion during the subsequent, rate-controlling loss of chloride ion. To resolve this point, it would be valuable to have a reliable estimate of the extent of C-β–H bond breaking at the rate-controlling transition state. For the ion-pair mechanism the bond has already been cleaved, but for the $(ElcB)_I$ path C-β–H cleavage is less than complete. No Brønsted β value is available. The Brønsted α value for ring-substituted DDD's (exclusive of *p*-nitroDDD) is low—only 0.36.[21b] McLennan argues that this value does not accurately reflect the extent of proton transfer because α will measure charge relocation to the aromatic rings, a process hindered by the "substantially pyramidal" geometry at C-β in the transition state for proton loss.[20,21b,64] Primary hydrogen isotope effects for DDD and *p*-chloroDDD are k_H/k_D = 7.7 and 12.1, respectively (25 °C).[21b] Such large effects are generally taken to indicate almost symmetrical transition states with respect to proton transfer. However, both reactions show substantial proton tunneling; thus the semiclassical isotope effects are smaller. We note here the existence of model calculations which conclude that even highly unsymmetrical transition states may generate sizable semiclassical primary hydrogen isotope effects.[66] McLennan concludes that the proton is more than half transferred in the DDD transition

(62) Breslow, R. S. *Tetrahedron Lett.* 1964, 399–403.

(63) The factor of 3 derives from comparison of dedeuteriochlorination rates. This comparison is preferred because tunneling contributions to the elimination rates are of variable importance for the isotopically light members of the DDD series.

(64) There are several cases in the literature that indicate that in the formation of delocalized carbanions, covalency change and charge delocalization are not in step. Good examples include the deprotonation of 1-arylnitroalkanes[65] and nucleophilic addition to electrophilic alkenes.[13e]

(65) (a) Bordwell, F. G.; Boyle, W. J., Jr.; Hautala, J. A.; Yee, K. C. *J. Am. Chem. Soc.* 1969, *91*, 4002–4003. (b) Fukuyama, M.; Flanagan, P. W. K.; Williams, F. T.; Trainier, L.; Miller, S. A.; Schecter, H. *Ibid.* 1970, *92*, 4689–4699.

(66) Motell, E. L.; Boone, A. W.; Fink, W. H. *Tetrahedron* 1978, *34*, 1619–1620.

states.[21b] The situation is further clouded by a question that has arisen over the assignment of the $(E1cB)_I$ mechanism to the DDT's. Fry has reported positive primary carbon isotope effects at both C-α and C-β for three members of the DDT series (*p*-methyl, unsubstituted, and *p*-chloro, NaOMe/MeOH, 30 °C).[67] These results are more easily accommodated by the E2 mechanism that the $(E1cB)_I$ mechanism.

It is reasonable and even likely that the DDD's, other than *p*-nitroDDD, eliminate by the E2 mechanism. But the matter cannot be said to be unambiguously settled.

The final entry in Table VII is the rate constant for hydroxide-induced dehydrobromination of 1,2-dibromo-1-(*p*-nitrophenyl)ethane. Koch and Dahlberg argue that unsubstituted 1,2-dihalo-1-phenylethanes eliminate (in ethanol) by an E1cB mechanism,[23] in which case the *p*-nitro compounds certainly do. However we have no direct evidence on the point.

Factors That Affect the Partitioning Ratio. There are several features of structure and medium that influence the partitioning of an E1cB intermediate between reprotonation ($\sum k_{-1}$) and loss of leaving group (k_2). Among them is the effect of the aryl substituent on the stability of the intermediate. A more stabilizing substituent will presumably reduce both $\sum k_{-1}$ and k_2. Our experiments do not bear on this effect. Any factor, steric or electronic, that destabilizes the olefinic product could retard elimination at the expense of reprotonation. Again, our data shed no light on this point. In fact, these two points are not well established; examples of E1cB reactions that would allow the necessary systematic studies are scarce and have not been exploited toward these ends.

The effects of other variables are found in Tables IV and VI and are graphically shown in Figures 2, 3, 6, and 7. Among tertiary-amine leaving groups, it is clear that the better leaving groups accelerate step two relative to reprotonation and work against reversibility of the E1cB path. This result makes it more difficult to detect exchange, inverse solvent isotope effects, and buffer curvature.

Reprotonation efficiency can be increased, raising $\sum k_{-1}/k_2$, by using stronger buffer acids at higher concentration. The use of *N*-hydroxysuccinimidate (NHS) buffers (pK_a = 5.85) with compound **5** gave much sharper buffer curvature than did the use of acetohydroxamate buffers (pK_a = 9.4). The former data were relatively imprecise but allow an estimate of the partitioning ratio, k_{NHS}/k_2 = 20–25, compared with k_{AcNHOH}/k_2 = 1.6. (With compound **6** and NHS buffers, no curvature was seen.) Without added buffer acid, i.e., with water as the strongest acid present, even compound **1**, with the poorest leaving group in our series, reacts by the $(E1cB)_I$ mechanism (k_2/k_{H_2O} = 10.9).

The effect of temperature on various kinetic parameters for the reaction of compound **1** was determined. Activation parameters for step one, estimated from two temperatures, are given in the footnotes to Table IV. A higher temperature has the effect of increasing k_2 relative either to k_{AcNHOH} or k_{H_2O}, a result leading to less reversibility at higher temperatures. Similar results were obtained with compound **7**.

At 25 °C, reprotonation of **1±** by AcNHOH is favored over elimination by 2.6 kcal/mol while elimination is easier than protonation by water by 1.4 kcal/mol. The activation enthalpy differences, however, favor reprotonation in both cases and by substantial amounts: 13 kcal/mol for AcNHOH and 11.3 kcal/mol for water. Elimination is competitive only because $\Delta S^{\ddagger}_2 - \Delta S^{\ddagger}_{-1}$ is large: 35 cal/(mol deg) for a 1 M AcNHOH solution and 43 cal/(mol deg) for water alone. The large values for $\Delta S^{\ddagger}_2 - \Delta S^{\ddagger}_{-1}$ are rational considering that elimination is unimolecular while protonation is bimolecular and also that elimination converts a zwitterion into two neutral particles while protonation produces two ions. The transition state leading to the latter is likely to constrict more solvent molecules than the transition state in the elimination direction.[68]

As the reaction medium is made less polar by the addition of organic solvents, the partitioning of the zwitterion becomes biased toward elimination. These data are found in Table VI and are especially clear from Figure 7. All the $(E1cB)_R$ experimental criteria are more difficult to detect the less polar the solvent. The simplest rationalization of this result is that in the elimination transition state charge is dispersed relative to the reprotonation transition state, which is therefore more affected by changes in solvent polarity. Thus, k_2 rises relative to k_{-1} as the solvent is made less polar.

Disagreement with Earlier Studies. In the introduction the results of several heavy-atom isotope effect experiments,[31,34,35] and a tritium exchange experiment,[33] all on compound **7** were described. These results seem to require the E2 mechanism for this substrate; yet our results clearly indicate the E1cB mechanism: irreversible in H_2O/OH^- and more or less reversible when buffer acids of sufficient strength and concentration are present.

Of the factors discussed above that affect the partitioning of the zwitterion, the effects of temperature and buffer acid are pertinent to the failure of Hodnett and Flynn to observe tritium incorporation into **7**. These authors used a dilute dihydrogen phosphate buffer ($[H_2PO_4^-]$ = 0.02 M) and worked at 100 °C. The low [buffer acid] and the high temperature conspire to reduce $\sum k_{-1}/k_2$ so that elimination under these conditions is likely to be $(E1cB)_I$ rather than the partly reversible E1cB mechanism we see at 25 °C and with considerably higher [buffer acid]. The large, primary tritium isotope effect on k_{-1} (see Experimental Section) would also work against tritium incorporation.

The heavy-atom isotope effects are more difficult to explain. These experiments too were done at 100 °C in buffered solution. But the rate ratios, particularly those measured by Hodnett and co-workers,[31,34] seem too large to be accommodated by the $(E1cB)_I$ mechanism. We note that the α-carbon isotope effects from different laboratories are not in good agreement,[34,35,44] suggesting that these experiments are experimentally difficult to reproduce. So it is possible that the large observed effects are not accurate. Two other explanations should be considered as well. It is possible, as Thibblin suggests, that weakening of the C-α–lg bond may occur in order to stabilize the transition state of step one in the $(E1cB)_I$ mechanism,[69] this in spite of the lack of a chlorine isotope effect for the $(E1cB)_I$ elimination of $(p\text{-}NO_2C_6H_4)_2CHCHCl_2$.[21c] It is also conceivable that the E2 pathway, repressed at room temperature by its high activation energy, becomes dominant at 100 °C.

Lifetime of the Intermediate Zwitterion. Although we have data for the rates of deprotonation of substrates (k_1) and for the partitioning ratio of the zwitterion (k_{-1}/k_2), we do not have absolute rates for the two processes by which the intermediate zwitterion is destroyed. Nevertheless, it is worthwhile to make a rough estimate of these figures in order to get an idea of how close to the diffusion limit (for protonation) or to the vibrational frequency limit (for elimination) these two rates are.

We have used two kinds of evaluation. The first requires an estimate of the pK_a for $p\text{-}NO_2C_6H_4CH_2CH_2NR_3^+$. Bordwell gives pK_a = 20.5 for *p*-nitrotoluene in Me_2SO.[70] A value can be calculated for *p*-nitrotoluene in 50 mol % Me_2SO/water (80% Me_2SO, v/v) from the equilibrium measurements of Chatrousse et al.[71] and the ion product of water in variously aqueous Me_2SO.[72] It is ca. 20.6. Additional relevant information includes the following: *p*-nitrophenylacetonitrile is about 0.2–1.3 pK_a units more acidic in water[73] than in Me_2SO;[74] *p*-nitrophenol is more acidic in water by 3.8 pK_a units.[75] Despite the extensive charge delo-

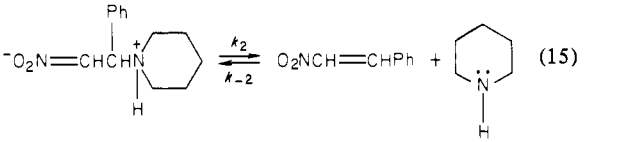
(67) Fry, A. "Abstracts of Papers", Second Chemical Congress of the North American Continent, Las Vegas, NV, Aug 1980; ORGN 82.
(68) Wynne-Jones, W. F. K.; Eyring, H. *J. Chem. Phys.* **1935**, *3*, 492–502.
(69) Thibblin, A. *Chem. Scr.* **1980**, *15*, 121–127.
(70) (a) Bordwell, F. G.; Algrim, D.; Vanier, N. R. *J. Org. Chem.* **1977**, *42*, 1817–1819. (b) Bordwell, F. G. *Pure Appl. Chem.* **1977**, *49*, 963–968.
(71) Chatrousse, A. P.; Terrier, F.; Fouad, F. M.; Farrell, P. G. *J. Chem. Soc., Perkin Trans. 2* **1979**, 1243–1247.
(72) Hallé, J.-C.; Gaboriaud, R.; Schaal, R. *Bull. Soc. Chim. Fr.* **1969**, 1851–1857.
(73) Stearns, R. S.; Wheland, G. W. *J. Am. Chem. Soc.* **1947**, *69*, 2025–2029.
(74) Estimated from data of: Algrim, D.; Bares, J. E.; Branca, J. C.; Bordwell, F. G. *J. Org. Chem.* **1978**, *43*, 5024–5026.

calization in these *p*-nitro conjugate bases, hydrogen bonding opportunities exist for these anions that act to increase the acidity in water compared with Me_2SO. On the other hand, the *p*-nitrobenzyl anion has poorer H-bonding ability than the anions just mentioned, and it is known that acids with highly delocalized carbanionic conjugate bases can be more acidic in Me_2SO than in water.[76] On balance we take the pK_a of *p*-nitrotoluene to be about the same in water as in Me_2SO—let $pK_a = 20.5 \pm 1.5$.[77] The effect of the attached $-CH_2NR_3^+$ unit will be to lower pK_a. Thomas and Stirling give $\sigma^* = +1.9$ for $-CH_2NMe_3^+$.[78] Cann and Stirling have measured $\rho^* = +2.1$ for the rates of deprotonation of $O_2NCH_2CH_2Z$ species in water.[79] We anticipate that separation of the nitro group from the reaction site by an intervening $-C_6H_4-$ group will enhance the polar effect of $-CH_2Z$. Let $\rho^* \cong +3.0$ for the rates of deprotonation of p-$NO_2C_6H_4CH_2CH_2Z$. The ρ values for equilibrium deprotonation of nitro-activated carbon acids in hydrogen bonding solvents are *smaller* than for the rates of deprotonation.[65] It is not clear whether this will also be true for p-$NO_2C_6H_4CH_2CH_2Z$, but we shall guess $\rho^*_{eq} \cong +2.5$. With this value we estimate the pK_a of p-$NO_2C_6H_4CH_2CH_2NMe_3^+$ (**7**) in water to be in the vicinity of 15.5. The equilibrium constant for deprotonation of **7** by hydroxide ions then is 3×10^{-2} M^{-1}. Our experimental value for k_{OH}-(**7**) is 1.50×10^{-3} M^{-1} s^{-1}; thus we reach an estimate for the rate of protonation of the zwitterionic conjugate base (**7**±) of $k_{H_2O} \cong 5 \times 10^{-2}$ s^{-1} and $k_{AcNHOH} \cong 25$ M^{-1} s^{-1}. The rate of trimethylamine loss is $k_2(\mathbf{7}) \cong 15$ s^{-1}.

Similar estimates for our other compounds require an additional step. We show below that the effect of the leaving group on the acidity of **1** through **7** is $\Delta pK_a \cong 0.25\ \Delta pK_{lg}$. Thus we can estimate pK_a for **1** at 16 ± 2 and pK_a for **6** at 14 ± 2. For compound **1** (with quinuclidine, our worst leaving group), we may thereby estimate $k_{H_2O}(\mathbf{1}) \cong 6 \times 10^{-2}$ s^{-1} and $k_2(\mathbf{1}) \cong 0.7$ s^{-1}. Compound **6** contains our best leaving group, *N*-MeDabco$^+$. For deprotonation by acetohydroxamate, we estimate $K_{eq} = k_{AcNHO^-}/k_{AcNHOH} \cong 2.5 \times 10^{-5}$. With this figure and data from Table IV, we get $k_{AcNHOH}(\mathbf{6}) \cong 15$ M^{-1} s^{-1} and $k_2(\mathbf{6}) > 1500$ s^{-1}.

A second estimate of k_2 is simpler and goes as follows: When **1** is rapidly mixed with 10 M KOH no burst of color can be seen. Since p-$NO_2C_6H_4CH_2^-$ is known to be colored,[80] we take this to mean that the zwitterion is a genuine steady-state intermediate and that $(k_{H_2O} + k_2)/(k_{OH}\text{-}[OH^-]) \geq 50$. From this number and Table IV, we find $k_2(\mathbf{1}) \geq 1$ s^{-1}, in satisfactory agreement with the estimate above. Neither this estimate nor the previous one is claimed to be numerically accurate. Nevertheless they demonstrate that protonation by water and departure of the tertiary-amine leaving groups are *very* much slower than limiting rates.

Comparison of our estimates with data from the literature inspires a measure of confidence in our conclusion. Margerum gives $k_{H_2O} = 2 \times 10^{-2}$ s^{-1} for the protonation of p-$NO_2C_6H_4CH_2^-$ (H_2O, 22 °C).[82] Wettermark reports $k_{H_2O} = 1.0$ s^{-1} for protonation of o-$NO_2C_6H_4CH_2^-$ (H_2O, 22 °C).[84] Langmuir et al. studied the protonation of 2,6-$(NO_2)_2C_6H_3CH_2^-$ by general acids (H_2O, 30 °C) and gives $k_{H_2O} = 9$ s^{-1} and $k_{H_3O^+} \cong 10^5$ M^{-1} s^{-1}.[85] Chatrousse et al. estimate $k_{H_2O} \cong 0.8$ s^{-1} for the rate of protonation of p-$NO_2C_6H_4CH_2^-$ in 50 mol % Me_2SO (20 °C).[71] All these results are similar to our estimates and are far below the diffusion limit, even when $K_{eq} \cong 10^{20}$! By contrast, the protonation of unsubstituted benzyl anion by water (in THF, 24 °C) has $k_{H_2O} = 5.3 \times 10^7$ M^{-1} s^{-1}.[81] As for the rates of leaving group departure, direct comparison is unavailable. Possibly relevant is reaction 15 for which Bernasconi, Carrē, and Fox give $k_2 \cong 30$ s^{-1} (19 mol % Me_2SO, 20 °C).[86]



(15)

A more direct way of assessing *relative* rates of leaving group departure is given in the next section. The absolute values estimated in this section are fully consistent with those relative values.

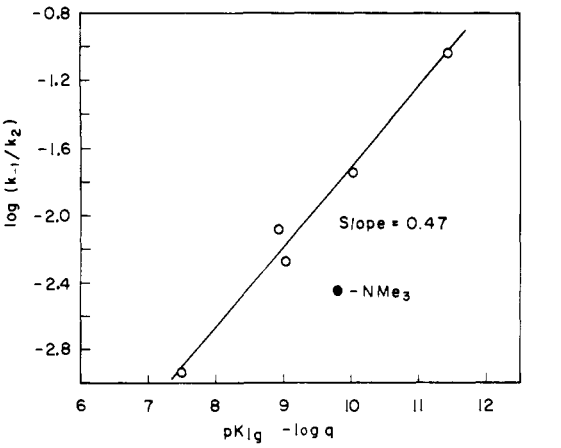


Figure 10. Plot of log (k_{H_2O}/k_2) vs. pK_{lg} for the elimination reactions of compounds **1–5** and **7** in H_2O at 25 °C; μ = 1.0 M (KCl), slope = $\beta_p = (\beta_{-1}^{lg} - \beta_2^{lg})$; $\beta_2^{lg} = -0.4$ (see text).

Extent of Leaving Group Departure in Step Two. The partitioning ratio of the intermediate zwitterion, log (k_{H_2O}/k_2) is plotted against pK_{lg} in Figure 10 and follows a slope of $\beta_p = 0.47$. The dependence of log k_∞ on pK_{lg}, for rate-determining leaving group expulsion when formation of the zwitterion is at equilibrium, is $\beta_{lg} = \beta_1^{lg} - \beta_p = -0.17 - 0.47 = -0.64$, for k_1k_2/k_{-1}.

The effect of pK_{lg} on step two alone (β_2^{lg}) can be estimated from $\beta_p = \beta_{-1}^{lg} - \beta_2^{lg}$ where β_{-1}^{lg} and β_2^{lg} are Brønsted-type coefficients describing the effect of pK_{lg} on reprotonation and leaving group departure, respectively. A value for β_{-1}^{lg} must be found. This is obtained in the following way. We take the effect of the leaving group on reprotonation (and deprotonation) to depend proportionately on the extent of proton transfer at the transition state of step one.[88] The proportion is given by eq 16, where β_1 and

$$-\beta_{-1}^{lg}/\beta_1^{lg} = \alpha_{-1}/\beta_1 \qquad (16)$$

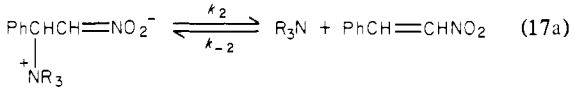
(75) Kolthoff, I. M.; Chantooni, M. K., Jr.; Bhowmik, S. *J. Am. Chem. Soc.* **1968**, *90*, 23–28.
(76) Ritchie, C. D. In "Solute–Solvent Interactions"; Coetzee, J. F., Ritchie, C. D., Eds.; Marcel Dekker: New York, 1969; Chapter 4.
(77) Buncel and Menon (Buncel, E.; Menon, B. C. *J. Am. Chem. Soc.* **1980**, *102*, 3499–3507) make the same argument.
(78) Thomas, P. J.; Stirling, C. J. M. *J. Chem. Soc., Perkin Trans. 2* **1977**, 1909–1913.
(79) Cann, P. F.; Stirling, C. J. M. *J. Chem. Soc., Perkin Trans. 2* **1974**, 817–819.
(80) The position of the absorption maximum for p-$NO_2C_6H_4CH_2^-$ is not clear from the literature. Buncel and Menon[77] argue that λ_{max} ranges from 430 nm (THF) to 450 nm (Me_2SO) with $\epsilon_{max} \sim 15000$. The argument is buttressed by the observation of Bockrath and Dorfman that unsubstituted free benzyl anion has $\lambda_{max} = 360$ nm in THF.[81] The *p*-nitro group is expected to shift the maximum to longer wavelengths. On the other hand, Margerum gives $\lambda_{max} = 355$ nm (tailing beyond 400 nm) for the species generated by photodissociation of p-$NO_2C_6H_4CH_2CO_2^-$ in water.[82] It is worth noting that nitro-stabilized carbanions exhibit large red spectral shifts when transferred from hydrogen bond donor solvents (H_2O, small alcohols) to non-H-bond donor solvents (CH_3CN, Me_2SO, HMPTA).[65b,71,83]
(81) Bockrath, B.; Dorfman, L. M. *J. Am. Chem. Soc.* **1974**, *96*, 5708–5615.
(82) Margerum, J. D. *J. Am. Chem. Soc.* **1965**, *87*, 3772–3773.
(83) (a) Crampton, M. R. *J. Chem. Soc. B* **1967**, 85–87. (b) Caldin, E. F.; Jarczenski, A.; Leffek, K. T. *Trans. Faraday Soc.* **1971**, *67*, 110–118. (c) Minch et al. (Minch, M. J.; Giaccio, M.; Wolff, R. *J. Am. Chem. Soc.* **1975**, *97*, 3766–3772) report micellar effects on these spectra as well. (d) Walters, E. A. *J. Phys. Chem.* **1977**, *81*, 1995–2000.
(84) Wettermark, G. *J. Phys. Chem.* **1962**, *66*, 2560–2562.
(85) Langmuir, M. E.; Dogliotti, L.; Black, E. D.; Wettermark, G. *J. Am. Chem. Soc.* **1969**, *91*, 2204–2207.
(86) Bernasconi, C. F.; Carrē, D. J.; Fox, J. P. In "Techniques and Applications of Fast Reactions in Solution"; Gettins, W. J., Wyn-Jones, E., Eds.; Reidel: Dordrecht, Holland, 1979; p 453.
(87) A similar plot, using k_{AcNHO^-}/k_2, yields the same information in principle. The plot has more scatter however. Its apparent slope lies between 0.4 and 0.6.
(88) This assumption is tantamount to the Leffler–Grunwald interpretation of ordinary Brønsted exponents.[89]

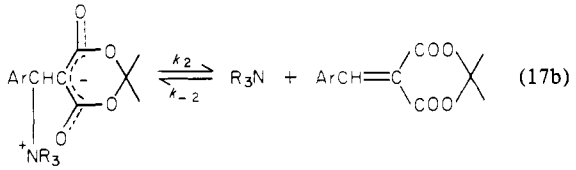
α_{-1} are the usual Brønsted catalysis exponents for step one and sum to 1.00. From the values of k_B- for deprotonation of **6** induced by acetohydroxamate and *N*-hydroxysuccinimidate (Table IV), we get a two-point $\beta_1 = 0.61$. Alunni and Jencks obtained $\beta_1 = 0.68$ for deprotonation of **3** by four-substituted quinuclidines.[24] Gandler and Jencks measured $\beta_1 = 0.66$–0.70 for compounds **1**, **3**, and **6** by using oxyanion bases in 60% (v/v) Me_2SO. Let $\beta_1 = 0.68$; then $\alpha_{-1} = 0.32$. We find β_1^{lg} to be −0.17 (Figure 9). From eq 16 we may calculate $\beta_{-1}^{lg} \cong 0.08$. Allowing for some uncertainty, these figures and the slope of Figure 10 provide a value of $\beta_2^{lg} = -0.4 = \partial \log k_2/\partial pK_{lg}$. Continuing the Leffler–Grunwald interpretation of these results allows the estimate that the equilibrium position of step one is not largely affected by pK_{lg}: $\delta \log (k_1/k_{-1})/\delta pK_{lg} \equiv \beta_{eq1}^{lg} = -0.24$.

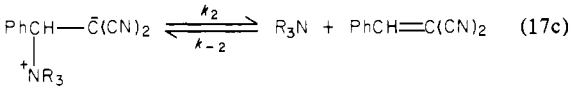
The value of $\beta_2^{lg} = -0.4$ refers to departure of the leaving group from the zwitterionic intermediate. Application of the Leffler–Hammond interpretation requires a value for β_{eq2}^{lg}. Alunni and Jencks have measured $\beta_{eq}^{lg} = -0.89$ for the overall reaction.[24] Thus we have $\beta_{eq2}^{lg} = (\beta_{eq}^{lg} - \beta_{eq1}^{lg}) = -0.65$. A value of $\beta_2^{lg} = -0.4$ therefore suggests that leaving group departure is more than half realized at the transition state of step two.

There have been few assessments of nucleofugic progress at the transition states of reactions in which leaving groups are ejected from transient carbanions in aqueous solution. Fedor and Glave give $\beta_2^{lg} = -0.67$ for loss of para-substituted phenoxide ions from the enolates of 4-(aryloxy)-2-butanones.[8b] An argument like ours (above) would suggest that the aryloxides are something like 70% formed at the transition state. Williams and co-workers have measured a very high $\beta_2^{lg} = -2.0$ for sulfene formation from aryl phenylmethanesulfonate carbanions when the leaving group is a relatively basic aryloxide (eq 4).[17b] The necessary equilibrium β value is not available,[90] but it is likely that aryloxide formation is very advanced at the transition state. Pratt and Bruice determined $\beta_2^{lg} = -1.29$ for loss of aryloxides from $CH_3CO^-CHCO_2Ar$ species.[14b] Similarly, Douglas and Yaggi measured $\beta_2^{lg} = -1.13$ for thiolate departure from $CH_3CO^1CHCOSR$.[15] Again the results suggest considerable leaving group departure at the transition state. Grout, McLennan, and Spackman used the absence of an intramolecular chlorine isotope effect on the dehydrochlorination of *p*-nitroDDD to argue that loss of the comparatively nucleofugic chloride ion from the *p*-nitroDDD anion (in methanol) has barely begun at the transition state.[21c]

More closely resembling our work are several studies involving alkene formation via loss of amines from carbanions. In a detailed study of the nucleophilic additions of piperidine and morpholine to electrophilic olefins (in water or 50% v/v Me_2SO; eq 17),


(17a)


(17b)


(17c)

Bernasconi and co-workers were able to measure β_2^{lg} (normalized by β_{eq2}^{lg}). Formation of β-nitrostyrene was accompanied by $\beta_2^{lg} = -0.65$;[86] several benzylidene Meldrum's acids gave β_2^{lg} ranging from −0.86 to −0.92;[13c] benzylidinemalononitrile gave $\beta_2^{lg} = -0.70$.[91] In addition, the loss of piperidine and morpholine to yield benzylidene Meldrum's acid in acetonitrile gives rise to $\beta_2^{lg} = -0.57$.[92] All these results suggest late transition states with respect to loss of positive charge on nitrogen.

In contrast with the indications of extensive leaving group departure cited so far are the results of Barlow, Marshall, and Stirling.[93] These workers studied reaction 18 among others

$$PhSO_2CH_2CH_2N^+R_3 + B: \rightarrow PhSO_2CH{=}CH_2 + BH + R_3N \quad (18a)$$

$$NCCH_2CH_2N^+R_3 + B: \rightarrow NCCH{=}CH_2 + BH + R_3N \quad (18b)$$

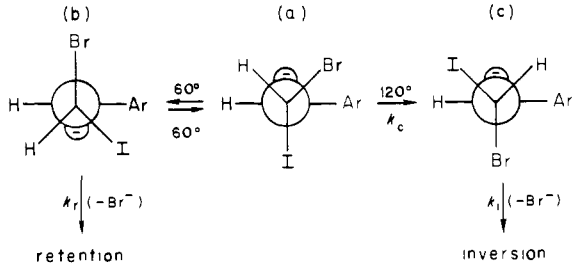
(ethanolic triethylamine buffers, 25 °C). Buffer saturation kinetics were observed to prompt the E1cB interpretation. Analysis of the buffer curvature yielded the partitioning ratio k_2/k_{-1}. These values were different for 18a and 18b, but for a given activator, cyano or sulfonyl, were virtually constant for a variety of tertiary amine leaving groups. The authors take the effect of pK_{lg} on k_{-1} to be small (exoergic protonations of α-sulfonyl- and α-cyanocarbanions are close to the diffusion rate in any case)[94] and conclude that β_2^{lg} is so small as to be consistent only with a small degree of C–N bond cleavage in the transition state. A possible explanation is that unlike most of the cases cited above, the substrates in reaction 18 have only one carbanion stabilizing group (ignoring the quaternary nitrogen). Thus the zwitterionic E1cB intermediates are so reactive toward elimination that they show no dependence upon pK_{lg}. That step two is very exoergic for reaction 18 (unlike reaction 17) is indicated by apparently complete conversion of substrates to alkene at equilibrium even in the presence of triethylamine buffers. If this is true of substrates, it is more true of the zwitterions.

While the carbanions studied by Stirling and his collaborators are very much more reactive than those considered above, there is nevertheless a difficulty with the interpretation of their behavior. In another study, Thomas and Stirling had synthesized $PhSO_2CH_2CH_2N^+Me_3^+$ labeled at C-β with tritium.[78] This was accomplished by treating the isotopically light ion (5 mmol) with tritiated water in 1,4-dioxane with ca. 2.5 M *triethyl*amine as a catalyst. The labeled ion was used to study the kinetics of detritiation in ethanol catalyzed by *unbuffered* triethylamine. The extent of detritiation was determined by isolating the ammonium ion at intervals and assessing the level of tritium. The synthetic and kinetic methods both tell us that $PhSO_2CH_2CH_2NMe_3^+$ can be reversibly deprotonated, in the absence of a buffer acid, without significant loss of trimethylamine, i.e., that (eventual) elimination under these conditions is $(E1cB)_R$. Yet the buffer curvature observed for the same salt (and similar ones) in ethanolic triethylamine buffers is ascribed to use of the $(E1cB)_1$ mechanism at low [buffer], changing to $(E1cB)_R$ at higher [buffer]. It cannot be simultaneously true that deprotonation is reversible with no buffer acid, becomes irreversible with small amounts of buffer acid, and changes back to reversible with larger amounts of buffer acid. Until this anomaly is cleared up, it remains uncertain what the partitioning ratio and β_2^{lg} for reaction 18 really are.

Choice of Mechanism: The Question of Enforced Concertedness for the *p*-Nitrophenethyl Halides. The use of the E2 mechanism by *p*-nitrophenethyl halides is apparently *not* enforced by an impossibly short lifetime of the E1cB intermediate toward reprotonation. That this lifetime is appreciable is strongly supported by our preceding discussion, by the large kinetic isotope effect on the protonation of *p*-nitrobenzyl anion: $k_{CH_3OH}/k_{CH_3OD} = 10$ (25 °C),[95] and by a large solvent discrimination isotope effect for

(89) Leffler, J. E.; Grunwald, E. "Rates and Equilibria of Organic Reactions"; Wiley: New York, 1963; pp 156–159, 238–241.
(90) It should be large. The sulfonyl group will probably cause aryloxy oxygen to be less negative in $PhCHSO_2OAr$ than in HOAr.
(91) Bernasconi, C. F.; Fox, J. P.; Fornarini, S. *J. Am. Chem. Soc.* **1980**, *102*, 2810–2816.
(92) Schreiber, B.; Martinek, H.; Wolschann, P.; Schuster, P. *J. Am. Chem. Soc.* **1979**, *101*, 4708–4713.
(93) Barlow, K. N.; Marshall, D. R.; Stirling, C. J. M. *J. Chem. Soc., Perkin Trans. 2* **1977**, 1920–1927.
(94) (a) Hine, J.; Philips, J. C.; Maxwell, J. I. *J. Org. Chem.* **1970**, *35*, 3943–3945. (b) Bell, R. P.; Cox, B. G. *J. Chem. Soc. B* **1971**, 652–656. (c) Hibbert, F. *J. Chem. Soc., Perkin Trans. 2* **1973**, 1289–1292. (d) Hibbert, F.; Long, F. A.; Walters, E. A. *J. Am. Chem. Soc.* **1971**, *93*, 2829–2835. (e) Hibbert, F.; Long, F. A. *J. Am. Chem. Soc.* **1972**, *94*, 2647–2651.
(95) Macciantelli, D.; Seconi, G.; Eaborn, C. *J. Chem. Soc., Perkin Trans. 2* **1978**, 834–838.

Scheme II



the addition of CH_3O^- to p-$NO_2PhCH{=}CF_2$.[96]

On the other hand the E2 path may be enforced by insufficient stability of the carbanion intermediate toward loss of halide. There are pertinent results in the literature, but as the following argument shows, only a rough estimate of this barrier can be made at the present time. Miller and Yonan found that reaction of iodide ions with *cis*-*p*-nitro-β-bromostyrene (in butyl carbitol at 196 °C) gives (prior to equilibration) substitution with retention of configuration faster than either isomerization or substitution with inversion.[97] The result may be rationalized by postulating the formation of an intermediate, p-$NO_2C_6H_4^-CHCHBrI$, which must assume a conformation in which a carbon–halogen bond is coplanar with the orbital containing the electron pair before expulsion of halide. On this basis the dominance of retention occurs because the suitable conformation is achieved through a small, 60° rotation during which only the eclipsing of a pair of hydrogens is necessary. Isomerization and inversion require more rotation and the eclipsing of larger groups. The competition is illustrated in Scheme II, beginning with the conformation (a) first formed by attack of iodide perpendicular to the double-bond plane. If we assume hyperconjugative stabilization of the anions[69,98] and that (a) is more stable than (b), then the preference for retention also requires that $k_r \gg k_c$. Molecular orbital calculations indicate that the barrier for k_c can be substantial,[98] but would be lowered by the electron-withdrawing p-nitrophenyl group.[98c] It is possible to say only that expulsion of bromide from a suitable conformation of p-$NO_2C_6H_4^-CHCH_2Br$ probably has a barrier considerably less than ca. 10 kcal/mol.

Similarly, Marchese, Naso, and Modena have shown that nucleophilic substitution of benzenethiolate for chloride or bromide in the isomeric p-nitro-β-halostyrenes (CH_3OH, 25 °C) occurs with complete retention of configuration.[99] In contrast, the kinetically controlled substitution of benzenethiolate for fluoride in *cis*- or *trans*-*p*-nitro-β-fluorostyrene gives the thermodynamically more stable trans product in both cases.[99]

In summary it can be said that of the p-nitrophenethyl halides, only the fluoride has been demonstrated to be capable of giving a carbanion that is not impossibly short-lived. It will be interesting to see whether the fluoride uses the E2 or the E1cB mechanism. If it is the former it will mean that elimination is concerted even though it is not required to be by the impossibility of intermediate formation, i.e., that concertedness is not enforced. It remains to be determined whether the unusual stability of p-nitrobenzyl anions can be accounted for by the large σ value of the p-nitro group or whether it reflects a special barrier for protonation of a delocalized nitrocarbanion.[26,65a,96]

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Registry No. **1**·Br^-, 73997-48-5; **2**·ClO_4^-, 83967-66-2; **3**·$2ClO_4^-$, 83967-68-4; **4**·Br^-, 73997-50-9; **5**·Br^-, 83967-69-5; **6**·$2I^-$, 83967-70-8; **7**·Cl^-, 83967-71-9; p-nitrophenethyl fluoride, 56153-06-1; p-nitrophenethyl chloride, 20264-95-3; p-nitrophenethyl bromide, 5339-26-4; p-