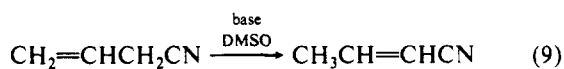


thiazolium zwitterion²⁶ discussed above are pertinent. For DMSO solution, Bordwell³⁹ has reported a study of the base-catalyzed isomerization of 3-butenitrile to 2-butenitrile



which proceeds by deprotonation and reprotonation. From the estimated $\text{p}K_a$ of 22.5 for 3-butenitrile, the $\text{p}K_a$'s of the catalyzing bases, and the rate constants for the isomerization, we can estimate rate constants for protonation of the carbanion (at the 2-position) by the conjugate acids of the bases. For protonation of the carbanion by cyclohexylammonium ion ($\text{p}K_a = 11.1$) and by thiophenol ($\text{p}K_a = 10.3$), $k \approx 2 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$. Protonations by phenols and carboxylic acids are only somewhat slower: $k \approx 3 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$ and $\text{p}K_a = 10.0$ for 2,3,4,5-tetrachlorophenol and $k \approx 2 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$ and $\text{p}K_a = 11.0$ for benzoic acid. It is also

pertinent to note in Table IV that the protonation of difluoroacetate ion by 2,4-dinitrophenol is considerably faster than those by the 2,6-disubstituted phenols.

The major fault with the postulation of desolvated, highly oriented, and specifically interacting complexes prior to proton transfer is that it provides enough flexibility to accommodate nearly any results. Nevertheless, we cannot see a simpler alternative. It is clear from the results presented here that proton transfers between electronegative atoms are considerably more complicated than previously thought and that the complications must arise from processes other than the actual proton transfer.

Acknowledgment. We acknowledge several helpful discussions with Dr. R. J. Kurland. Dr. Dinesh Sukumaran has helped clarify several points of NMR theory and has contributed substantial technical assistance with the NMR spectrometer. This research was supported by NSF Grant CHE-8603895. The Varian Model VXR-400S spectrometer used in this work was purchased under Department of Education Grant 2-2-01011.

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E2-E1cB Borderline: Elimination Reactions of 2-(2,4,6-Trinitrophenyl)ethyl Halides in Aqueous Solution

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Abstract: The base-promoted elimination reactions of 2-(2,4,6-trinitrophenyl)ethyl halides in aqueous solution have been investigated. The relative rate constant ratios for elimination of fluoride, chloride, bromide, and iodide are 1:1.6:4.7:3.9, 1:1.9:4.3:8.5, and 1:2.2:10.2:14.7 for the hydroxide ion, trifluoroethoxide ion, and hexafluoroisopropoxide ion promoted reactions, respectively. This small spread in relative halogen leaving group abilities extends a previously reported trend of decreasing sensitivity to the identity of the leaving halogens as the β -aryl substituent is made more electron withdrawing in the series 2-phenylethyl, 2-(*p*-nitrophenyl)ethyl, 2-(2,4-dinitrophenyl)ethyl, and 2-(2,4,6-trinitrophenyl)ethyl halides. The fluoride to chloride rate constant ratio, however, shows little or no change for the 2-(2,4-dinitrophenyl)ethyl (2.0) and 2-(2,4,6-trinitrophenyl)ethyl (1.6) derivatives. The reactions are general-base promoted, with Brønsted β values increasing in the order 0.37:0.41:0.49:0.54 for the iodide, bromide, chloride, and fluoride substrates. The Brønsted β values reported here are consistent with a previously reported trend of decreasing β values for strongly activated 2-arylethyl derivatives as the β -aryl substituent is made more electron withdrawing, e.g., $\beta = 0.61$, 0.46, and 0.41, for 2-(*p*-nitrophenyl)ethyl bromide, 2-(2,4-dinitrophenyl)ethyl bromide, and 2-(2,4,6-trinitrophenyl)ethyl bromide, respectively. A similar decrease is observed for the 2-(2,4-dinitrophenyl)ethyl ($\beta = 0.43$) and 2-(2,4,6-trinitrophenyl)ethyl ($\beta = 0.37$) iodides, but little or no change is observed for the corresponding chlorides and fluorides ($\beta \sim 0.50$). Rate constants for the hydroxide ion promoted reaction are about 100-fold smaller than expected on the basis of reactions of other 2-arylethyl derivatives, including the *p*-nitrophenyl and the 2,4-dinitrophenyl compounds, and suggest steric hindrance to resonance by the two *o*-nitro groups. Taken together, these results are consistent with an E2 ($A_{\text{EH}}D_{\text{H}}D_{\text{N}}$) mechanism for the iodide and bromide substrates and a reaction coordinate that has a large component of hydron transfer. The mechanisms of reaction of the fluoride and chloride substrates are, however, not established by these results, but a change to an E1cB_{irr} ($A_{\text{EH}}D_{\text{H}} + D_{\text{N}}$) mechanism appears possible.

Base-promoted elimination reactions of 2-arylethyl derivatives have been extensively studied and have played an important role in better understanding the relationship between the structure of the E2 transition state and changes in reactant and catalyst structure and reaction conditions.¹⁻⁶ Changes in the structure of the E2 transition state are important because these changes can give rise to changes in reaction mechanism, structure-reactivity

behavior, regioselectivity, and stereochemistry.¹⁻⁶

As the β -aryl substituent becomes more electron withdrawing in this series, there is evidence for a decrease in the extent of leaving group bond cleavage in the E2 transition state¹⁻⁶ as measured by decreases in heavy-atom leaving group^{2,7,8} and α -secondary-hydrogen⁹ isotope effects and other measures of leaving-group bond cleavage, including values of ρ_{lg} ¹⁰ and β_{lg} ¹¹ and the relative leaving group abilities of halide ions.¹² As a result

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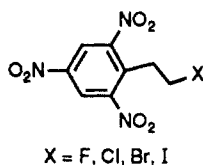
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of these changes in transition-state structure for substrates with relatively "poor" trimethylamine or quinuclidine leaving groups, a change to the E1cB mechanism is observed when the β -aryl group is *p*-nitrophenyl.¹³

A change to an E1cB_{irr} mechanism has also been proposed in several systems in which the leaving group is a weakly basic halide ion. For example, a change to an E1cB mechanism has been proposed for alkoxide ion promoted elimination reactions of 1,1,1-trifluoro-2,2-bis(4-nitrophenyl)ethane¹⁴ and several polyhalogenated 2-phenylethanes (via a hydrogen-bonded carbanion intermediate)¹⁵ and for the methoxide ion promoted elimination reactions in methanol of 1,1,1-trichloro-2,2-diarylethanes¹⁶ (DDT derivatives) and 1,1-dichloro-2,2-bis(4-nitrophenyl)ethane;⁸ the latter assignment was supported by an intramolecular chlorine leaving group isotope effect of 1.00,⁸ but it has recently been reported that this same reaction shows an α -carbon isotope effect of 1.024.¹⁷ In these systems, an E1cB mechanism is favored by strongly electron-withdrawing β -substituents and by α -halogen substitution that makes the halide ion a poorer leaving group.¹⁸ On the other hand, in the absence of α -halogen substitution, a change to the E1cB mechanism is not observed even when the β -aryl substituent is the strongly electron-withdrawing 2-(2,4-dinitrophenyl) group. For example, 2-(2,4-dinitrophenyl)ethyl bromide and iodide follow the E2 mechanism.¹⁹ Although an E2 mechanism was also assigned to the elimination reactions of 2-(2,4-dinitrophenyl)ethyl fluoride and chloride,¹⁹ the small chlorine to fluorine rate constant ratio equal to 2 and Brønsted β values that are the same for both the fluoride and chloride can also be interpreted in terms of a change to the E1cB_{irr} mechanism for the reactions of these derivatives.¹

We were interested in knowing if by making the β -aryl substituent still more electron withdrawing in the 2-arylethyl series, so as to further activate the elimination reaction, a change to an E1cB mechanism could be established for these derivatives with halide ion leaving groups. We therefore report a study of the base-promoted elimination reactions of 2-(2,4,6-trinitrophenyl)-ethyl halides.



We also wanted to investigate the trend previously reported of increasing and then decreasing degrees of hydron transfer (as measured by Brønsted β values) as the β -aryl substituent in this series is made progressively more electron withdrawing.¹⁹ This inversion in the trend of β values is consistent with a "clockwise" rotation of the E2 reaction coordinate from one that is mostly diagonal to one that has a major component of hydron transfer as the E2 transition state becomes very carbanion like as described on More O'Ferrall-Jencks energy diagrams.^{1,11,19}

Experimental Section

All melting points were measured on a Meltemp or Thomas Hoover melting point apparatus and are uncorrected. ¹H NMR spectra were recorded on a Varian EM 360, Varian EM 390, or General Electric 270-MHz spectrophotometer; the latter instrument was made available to us by the Department of Chemistry at the University of California at Santa Cruz. Kinetic experiments and UV-vis spectra were run on a Perkin-Elmer Lambda 6 or Cary 17D UV-vis spectrophotometer.

Table I. Comparison of ¹H NMR Data for 2-Arylethyl Halides^a

substrate	α -methylene group ^b	β -methylene group
2,4,6-(NO ₂) ₃ C ₆ H ₂ (CH ₂) ₂ F	4.50, 5.05 ^c	3.46, 3.73 ^c
2,4,6-(NO ₂) ₃ C ₆ H ₂ (CH ₂) ₂ Cl	3.87 ^d	3.64 ^d
2,4,6-(NO ₂) ₃ C ₆ H ₂ (CH ₂) ₂ Br	3.69 ^e	3.69 ^e
2,4,6-(NO ₂) ₃ C ₆ H ₂ (CH ₂) ₂ I	3.46 ^e	3.62 ^e
2,4-(NO ₂) ₂ C ₆ H ₃ (CH ₂) ₂ F	4.39, 5.16 ^f	3.20, 3.65 ^f
2,4-(NO ₂) ₂ C ₆ H ₃ (CH ₂) ₂ Cl	3.90 ^d	3.50 ^d
2,4-(NO ₂) ₂ C ₆ H ₃ (CH ₂) ₂ Br	3.69 ^e	3.69 ^e
2,4-(NO ₂) ₂ C ₆ H ₃ (CH ₂) ₂ I	3.45 ^e	3.45 ^e
4-NO ₂ C ₆ H ₄ (CH ₂) ₂ Br	3.62 ^d	3.28 ^d
4-NO ₂ C ₆ H ₄ (CH ₂) ₂ I	3.27 ^e	3.27 ^e
C ₆ H ₅ (CH ₂) ₂ Cl	3.61 ^d	3.00 ^d
C ₆ H ₅ (CH ₂) ₂ Br	3.47 ^e	3.08 ^e
C ₆ H ₅ (CH ₂) ₂ I	3.19 ^e	3.08 ^e

^a Chemical shifts are reported in CDCl₃ relative to TMS for all compounds except 2-(2,4,6-trinitrophenyl)ethyl fluoride, whose spectrum was recorded in acetone-*d*₆. Data for the aromatic protons of the 2-(2,4,6-trinitrophenyl)ethyl halides are given in the Experimental Section. ¹H NMR data for the other compounds listed here (including data for the aromatic protons) can be found in the following references: for the 2-(2,4-dinitrophenyl)ethyl halides, ref 19; for 2-(*p*-nitrophenyl)ethyl iodide, ref 13; for 2-(*p*-nitrophenyl)ethyl bromide and the 2-phenylethyl halides, The Sadtler Standard Spectra, Sadtler Research Laboratories, Philadelphia. ^b The α -methylene group refers to the carbon that is bonded to the halogen. ^c Two proton doublets of triplets for both the β - and α -methylene groups, J = 24 and 6 Hz and 48 and 6 Hz, respectively. ^d Two-proton triplets. ^e Four-proton multiplet (not resolved). ^f Two-proton doublets of triplets for both the β - and α -methylene groups, J = 26 and 6 Hz and 46 and 6 Hz, respectively. ^g Two-proton multiplets.

Materials. Inorganic salts were reagent grade and were used without further purification. The acetonitrile used to prepare the substrate stock solutions was spectroscopic grade (Aldrich Gold Label). All other reagents were either distilled or recrystallized prior to use.

2-(2,4,6-Trinitrophenyl)ethyl Alcohol. This compound was prepared according to the method of Gilbert.²⁰ The product was recrystallized from 2-propanol: mp 112–113 °C (lit.²⁰ mp 111–112 °C); ¹H NMR (acetone-*d*₆) δ 3.35 (t, 2 H), 3.85 (t, 2 H), 4.10 (m, 1 H), 8.95 (s, 2 H).

2-(2,4,6-Trinitrophenyl)ethyl Fluoride. This compound was made from the reaction of 2-(2,4,6-trinitrophenyl)ethyl alcohol with (diethylamino)sulfur trifluoride.²¹ To 1.0 mL of (diethylamino)sulfur trifluoride in 10 mL of CH₂Cl₂ under N₂ was added, at a rate of 10 mL/min, 2.0 g of 2-(2,4,6-trinitrophenyl)ethyl alcohol in 70 mL of CH₂Cl₂. The solution was kept at 10 °C for 6 h and then left overnight at room temperature. After workup, the product was collected as the middle band on preparative TLC plates after the plates were developed with a 55:45 CHCl₃/cyclohexane solvent mixture. The product was then recrystallized three times from absolute ethanol; mp 124.5–125 °C. The structure of the fluoride follows from the method of synthesis, the ¹H NMR data, and the comparison of this data with ¹H NMR data of other 2-arylethyl halides that have been previously reported in the literature (these data are summarized in Table I): ¹H NMR (acetone-*d*₆) δ 3.46 and 3.73 (dt, 2 H, J = 24, 6 Hz), 4.50 and 5.05 (dt, 2 H, J = 48, 6 Hz), 9.00 (s, 2 H).

2-(2,4,6-Trinitrophenyl)ethyl Chloride. A 4-g portion of 2-(2,4,6-trinitrophenyl)ethyl alcohol was left to react with thionyl chloride for 2 days. The reaction mixture, after workup, was purified first by flash chromatography with CH₂Cl₂ as the eluting solvent and then on preparative TLC plates developed with a 55:45 CHCl₃/cyclohexane solvent mixture. The resulting material was then recrystallized from absolute ethanol; mp 75.5–76 °C. This compound was also made, in higher yield, by adding 2 g of 2-(2,4,6-trinitrophenyl)ethyl alcohol to 1.73 g of PCl₅ dissolved in 10 mL of CHCl₃. The solution was kept at reflux for 1 h. After workup, an oil was obtained. The oil was crystallized by saturating an ethanol solution with the oil and storing this solution in a refrigerator for 2 days. The product was then recrystallized several times from methanol: mp 75.5–76 °C; ¹H NMR (CDCl₃) δ 3.64 (t, 2 H), 3.87 (t, 2 H), 8.82 (s, 2 H). Anal. Calcd for C₈H₆N₃O₆Cl: C, 34.86; H, 2.20; N, 15.25; Cl, 12.86. Found: C, 34.97; H, 2.22; N, 14.89; Cl, 12.79.

2-(2,4,6-Trinitrophenyl)ethyl Tosylate. To 4.0 g of 2-(2,4,6-trinitrophenyl)ethyl alcohol in 50 mL of benzene was added 3.5 g of *p*-toluenesulfonyl chloride. The reaction was kept at 80 °C and monitored

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by TLC with an 80:20 pentane/ CH_2Cl_2 solvent mixture. The product mixture was purified by flash chromatography with the same TLC solvent. Very light yellow granules formed upon recrystallization from 2-propanol: mp 132–133 °C; ^1H NMR (acetone- d_6) δ 2.40 (s, 3 H), 3.55 (t, 2 H), 4.42 (t, 2 H), 7.51 (dd, 4 H), 8.95 (s, 2 H).

2-(2,4,6-Trinitrophenyl)ethyl Bromide. To 25 g of 1-(*p*-toluenesulfonyl)-2-(2,4,6-trinitrophenyl)ethane in acetone was added 1.50 g of LiBr following the procedure of Wiberg and Lowry.²² The reaction was heated overnight. The solvent was then removed and the reaction mixture dissolved in water and extracted with CHCl_3 . After removal of the CHCl_3 , the product was recrystallized from 95% ethanol: mp 78–79 °C; ^1H NMR (CDCl_3) δ 3.69 (m, 4 H), 8.83 (s, 2 H). Anal. Calcd for $\text{C}_8\text{H}_6\text{N}_3\text{O}_6\text{Br}$: C, 30.02; H, 1.89; N, 13.13; Br, 24.96. Found: C, 30.06; H, 1.86; N, 13.44; Br, 25.12.

2-(2,4,6-Trinitrophenyl)ethyl Iodide. This substrate was synthesized by reacting 92.6 mg of 1-(*p*-toluenesulfonyl)-2-(2,4,6-trinitrophenyl)ethane in 1.0 mL of acetone with 72.4 mg of lithium iodide.²² The crystals produced in this reaction were then purified on preparative TLC plates developed with a 55:45 CHCl_3 /cyclohexane solvent mixture and then by recrystallization from absolute ethanol: mp 97.5–98.5 °C; ^1H NMR (CDCl_3) δ 3.46 (t, 2 H), 3.62 (t, 2 H), 8.83 (s, 2 H). Anal. Calcd for $\text{C}_8\text{H}_6\text{N}_3\text{O}_6\text{I}$: C, 26.18; H, 1.65; N, 11.45; I, 34.57. Found: C, 26.31; H, 1.64; N, 11.41; I, 35.98.

2,4,6-Trinitrostyrene. This compound was synthesized according to the method of Wiley and Behr²³ and recrystallized from 95% ethanol: mp 63–63.5 °C (lit.²³ mp 64–65 °C); ^1H NMR (acetone- d_6) δ 5.50 (d, 1 H, $J = 18$ Hz), 5.68 (d, 1 H, $J = 13.5$ Hz), 7.09 (dd, 1 H, $J = 13.5$ Hz and 18.0 Hz), 9.00 (s, 2 H); UV_{max} (H_2O) 222 nm (ϵ 1.9×10^4).

Kinetics. Kinetics were carried out by following spectrophotometrically the appearance of 2,4,6-trinitrostyrene at wavelengths between 290 and 305 nm. Reactions were carried out at 25.0 °C in aqueous solution with a large excess of buffer or hydroxide ion at an ionic strength of 1.0 M maintained with potassium chloride. Reactions were initiated by injecting 5–10 μL of an ca. 10^{-2} M stock solution of substrate in acetonitrile into a cuvette containing 3.00 mL of the buffer or hydroxide ion solution. Cuvettes were temperature equilibrated for at least 15 min prior to a kinetic run. All reactions, except for the two noted in the following text, were followed to completion. The slower reactions of 2-(2,4,6-trinitrophenyl)ethyl fluoride and 2-(2,4,6-trinitrophenyl)ethyl chloride in hexafluoro-2-propanol buffer solutions were followed by the method of initial rates with $k_{\text{obsd}} = (\Delta A / \Delta t) / [S]_0(\epsilon_p - \epsilon_s)$ in which ΔA is the initial change in absorbance, $[S]_0$ is the initial substrate concentration, and ϵ_p and ϵ_s are the molar absorptivities of the product, 2,4,6-trinitrostyrene, and substrate, respectively. For the fluoride substrate, initial rate measurements were made at 290 nm where $\epsilon_p = 4843$ and $\epsilon_s = 1863$; for the chloride substrate, initial rate measurements were made at 283 and 281.5 nm where ϵ_p and ϵ_s are 5864 and 2520, and 5988 and 2589, respectively. Several runs were also made at higher hexafluoroisopropoxide ion concentrations (0.10 and 0.20 M) where the reactions could be followed to completion. The second-order rate constants derived from these runs were in excellent agreement ($\pm 5\%$) with the second-order rate constants calculated from the initial rate measurements at low hexafluoroisopropoxide ion concentrations.

In the absence of base, at the concentrations of substrates used in the kinetic runs, the absorbance of the solution of these substrates increased slowly and then leveled off (this was most pronounced for the bromide and iodide substrates). It is unlikely that these absorbance changes correspond to chemical reactions because the shape of the spectra did not change (the absorbance of the solution grew proportionally at all wavelengths) and because the absorbance changes were much smaller or disappeared in water and in 5% or 10%, by volume, acetonitrile in water in the absence of added KCl, solutions in which the substrates are more soluble. These absorbance changes were generally much smaller than the observed changes in absorbance associated with the elimination reactions at the wavelengths at which the reactions were monitored. In all cases, except those noted below, the elimination reactions followed good pseudo-first-order behavior with plots of $\log(A_\infty - A_t)$ against time linear for at least 2 or more reaction half-lives. The solubility problems were serious enough, however, to interfere with the reactions of the bromide and iodide substrates in hydroxide ion and trifluoroethoxide ion solutions. To get around this problem, these substrates and 2.00–2.50 mL of 1.0 M KCl were premixed before the reactions were initiated with base; after the initial absorbance change noted previously, 0.50–1.0 mL of the buffer or hydroxide ion solution was added to initiate reaction. For the reactions promoted by the trifluoroethoxide ion, the concentration of trifluoroethoxide ion after mixing was corrected for hydrolysis with the expression $[B] = [B]_0 / (1 + 10^{(\text{pK} - \text{pH})})$, where $[B]$ and $[B]_0$ are the concentration of

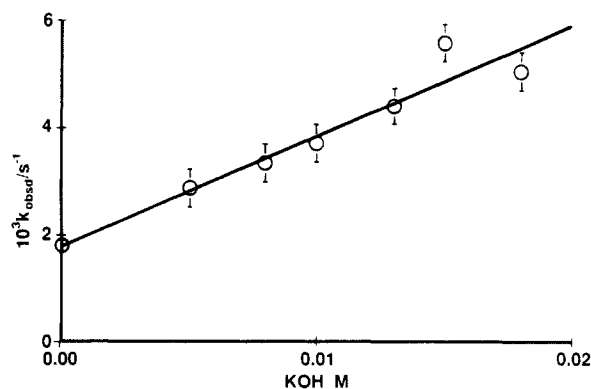


Figure 1. Dependence of k_{obsd} on trifluoroethoxide ion concentration for the elimination reaction of 2-(2,4,6-trinitrophenyl)ethyl chloride in aqueous solution at 25 °C, $I = 1.0$ M (KCl). Fraction-free base = 0.167, pH = 11.58.

trifluoroethoxide ion and the total buffer concentration, respectively, and pK is the apparent pK_a of trifluoroethanol (12.28). To correct for changes in the pH of the buffer solutions that are a result of buffer hydrolysis and that give rise to changes in the contribution to k_{obsd} from the hydroxide ion promoted reaction, second-order rate constants for the trifluoroethoxide ion promoted reactions were calculated from plots of $k_{\text{obsd}} - k_{\text{OH}}[\text{OH}^-]$ against the concentration of trifluoroethoxide ion, where k_{OH} is the second-order rate constant for the hydroxide ion promoted reaction and $[\text{OH}^-]$ is the calculated hydroxide ion concentration.

Measurements of pH were made on a Beckman Altrex 71 pH meter with either an Orion gel or an Orion Ross combination electrode. For the hexafluoro-2-propanol buffer solutions, a marked decrease in pH was observed when the stock solution (0.50 M buffer, pH = 9.5) was diluted to buffer concentrations between 0.005 and 0.018 M (pH = 9.18–9.20). Similar dependencies of the pH of these buffer solutions on buffer concentration have been reported previously.¹⁹ To suppress buffer hydrolysis and maintain a constant pH, buffer solutions of trifluoroethanol were prepared by diluting a stock buffer solution (fraction-free base = 0.167 M, total buffer concentration = 1.0 M) with a solution at the same pH and ionic strength but without buffer.

Product Analysis. The product of the base-promoted reactions of 2-(2,4,6-trinitrophenyl)ethyl halides was shown to produce 2,4,6-trinitrostyrene by comparing the UV-vis spectrum of the product of each reaction with the UV-vis spectrum of an authentic sample of 2,4,6-trinitrostyrene under the same reaction conditions. In hydroxide and trifluoroethoxide ion solutions, 2,4,6-trinitrostyrene undergoes a further reaction that gives rise to an absorption in the visible region with a maximum absorbance at 445 nm and a shoulder at ca. 480 nm. This reaction, although of interest in its own right, did not interfere with the kinetics of the elimination reaction and will not be discussed further here.

Results

The elimination reactions of 2-(2,4,6-trinitrophenyl)ethyl halides in aqueous solution follow the rate law of eq 1. The rate constants

$$k_{\text{obsd}} = k_{\text{OH}}[\text{OH}^-] + k_{\text{B}}[B] \quad (1)$$

for the hydroxide ion and buffer promoted reactions are k_{OH} and k_{B} , respectively. At the concentrations of the bases used (generally ≤ 0.02 M), there was no evidence for downward curvature in plots of k_{obsd} against base concentration that would be expected if significant amounts of a Meisenheimer complex were formed in a rapid preequilibrium step. No evidence of curvature in these plots, or of color formation, was observed in reactions promoted by higher concentrations of the weaker hexafluoroisopropoxide ion (0.10 and 0.20 M in base).

Rate constants for catalysis by the hydroxide ion were obtained in dilute solutions of potassium hydroxide in water. Rate constants for the buffer-promoted reactions were obtained from the slopes of k_{obsd} against buffer base concentration at constant pH and generally at five or more buffer concentrations. For the trifluoroethoxide ion promoted reactions, the hydroxide ion reactions contribute significantly to the value of k_{obsd} (Figure 1). For these reactions, the intercepts of plots of k_{obsd} against trifluoroethoxide ion concentration agree satisfactorily with the intercepts calculated from the second-order rate constants for the hydroxide-promoted reactions and the pH of the buffer solutions. Table II summarizes

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Table II. Rate Constants and Brønsted β Values for the Base-Promoted Elimination Reactions of 2-(2,4,6-Trinitrophenyl)ethyl Halides^a

substrate	$10^2 k$, M ⁻¹ s ⁻¹			β
	HO ⁻	CF ₃ CH ₂ O ⁻	(CF ₃) ₂ CHO ⁻	
2,4,6-(NO ₂) ₃ C ₆ H ₂ (CH ₂) ₂ F	3.86	2.00	0.0919	0.54 ^d
2,4,6-(NO ₂) ₃ C ₆ H ₂ (CH ₂) ₂ Cl	6.13	3.84	0.203	0.49 ^d
2,4,6-(NO ₂) ₃ C ₆ H ₂ (CH ₂) ₂ Br	18.0	8.59	0.936	0.41 ^d
2,4,6-(NO ₂) ₃ C ₆ H ₂ (CH ₂) ₂ I	15.1	17.1	1.35	0.37 ^d

^a In aqueous solution at 25 °C and $I = 1.0$ M maintained with potassium chloride. ^b In buffer solutions of fraction-free base = 0.167. ^c In buffer solutions of fraction-free base = 0.50. ^d Calculated from plots of $\log k$, with OH⁻, CF₃CH₂O⁻, and (CF₃)₂CHO⁻ as base catalysts, against $\log k$ for 2-(*p*-nitrophenyl)ethyl bromide for which we take $\beta = 0.61$. A β of 0.61 is the average of β values of 0.55 and 0.67 that have previously been reported for this substrate in 60 vol % dimethyl sulfoxide in water with oxyanions¹¹ and in ethanol with phenoxide ions,²⁴ respectively.

the second-order rate constants for the substrates investigated in this study.

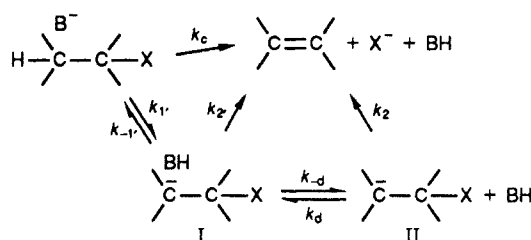
It is known that strongly basic alkoxide and hydroxide ions show negative deviations from Brønsted plots relative to oxyanions of lower pK_a (these deviations have been attributed to a solvation effect). We have therefore determined Brønsted β values by plotting $\log k$ for the 2-(2,4,6-trinitrophenyl)ethyl halides, using hydroxide ion and the anions of trifluoroethanol and hexafluoro-2-propanol as base catalysts, against $\log k$ for 2-(*p*-nitrophenyl)ethyl bromide, our standard substrate, for which we have taken $\beta = 0.61$.¹⁹ A β of 0.61 is the average of β values of 0.55 and 0.67 that have previously been reported for this substrate in 60 vol % dimethyl sulfoxide in water with oxyanions¹¹ and in ethanol with phenoxide ions,²⁴ respectively. The apparent Brønsted β values calculated in this way for the 2-(2,4,6-trinitrophenyl)ethyl halides are listed in Table II.

Discussion

Rates of Elimination. When the rate constants for the elimination reactions of the 2-(2,4,6-trinitrophenyl)ethyl halides are compared with the rate constants for the elimination reactions of other 2-arylethyl halides, the data show that the trinitro compounds react anomalously slow—about 100 times slower than expected. For example, whereas the relative reactivities of the hydroxide-promoted reactions of 2-(2,4-dinitrophenyl)ethyl bromide,¹⁹ 2-(*p*-nitrophenyl)ethyl bromide,¹³ and 2-phenylethyl bromide²⁵ in aqueous solution are in the order 7398:109:1, 2-(2,4,6-trinitrophenyl)ethyl bromide reacts at the same rate as 2-(2,4-dinitrophenyl)ethyl bromide.¹⁹ Similarly, 2-(2,4,6-trinitrophenyl)ethyl fluoride, chloride, and iodide react at rates comparable to the rates at which the corresponding 2-(2,4-dinitrophenyl)ethyl derivatives¹⁹ react—1.8 and 1.4 times faster for the fluoride and chloride, respectively, and 0.53 times slower for the iodide.

We attribute these abnormally slow rates of elimination to steric hindrance to resonance in the transition state by the two *o*-nitro groups. Space-filling models show that the developing double bond must be twisted out of the plane of the benzene ring to avoid steric hindrance with the *o*-nitro groups. This appears to be the case even when both *o*-nitro groups are twisted out of the plane of the benzene ring in order to try to accommodate the developing double bond. Related, in part, to steric hindrance to resonance is a resonance leveling or saturation effect²⁶ that is probably also a contributing factor. Steric hindrance to resonance by a second β -phenyl group has also been reported for base-promoted imine-forming elimination reactions of YC₆H₅CH(Ph)N(Cl)CH₃²⁷ and thiocarbonyl-forming elimination reactions of YC₆H₅CH(Ph)SSO₂Ph.²⁸

Steric hindrance to hydron transfer (involving hindrance between the base catalyst and α or β substituents) is believed to be

Scheme I

a contributing factor responsible for the changes in rates, regiochemistry, and stereochemistry that have been observed in elimination reactions.^{2,5,29–32} Although steric hindrance to hydron transfer (by an *o*-nitro group) is a possible factor contributing to the anomalously slow rates of elimination reported here, it does not appear to be a significant factor. If it were, then as the substrate's reaction site is made progressively more hindered, the trifluoroethoxide to hexafluoroisopropoxide rate constant ratio should become larger. On the contrary, for the reactions of 2-arylethyl bromides, this ratio decreases from 26 to 15 to 9 for the elimination reactions of 2-(*p*-nitrophenyl)ethyl bromide,¹³ 2-(2,4-dinitrophenyl)ethyl bromide,¹⁹ and 2-(2,4,6-trinitrophenyl)ethyl bromide derivatives, respectively. For the fluorides, chlorides, and iodides, the ratio varies only slightly when the 2-(2,4-dinitrophenyl)ethyl halides are compared with the corresponding 2-(2,4,6-trinitrophenyl)ethyl derivatives (comparable data in the same solvent for the 2-(*p*-nitrophenyl)ethyl derivatives are not available), 11.2 compared to 12.7, 17.7 compared to 18.9, and 17.5 compared to 21.8 for the iodide, chloride, and fluoride substrates, respectively.

It is well-known that nitroalkanes show anomalously slow rates of hydron transfer compared to other carbon acids.³³ These slow rates have been attributed to the solvent and structural reorganization that accompanies the delocalization of the negative charge.³³ We considered that an analogous effect could be responsible for the slow rates of elimination of the 2-(2,4,6-trinitrophenyl)ethyl halides because the negative charge in the transition state should be delocalized over the nitro groups. The available evidence, although it does not rule out this possibility, provides no support for it. For example, neither 2-(*p*-nitrophenyl)ethyl nor 2-(2,4-dinitrophenyl)ethyl bromides react slower than expected on the basis of their normal polar and resonance effects. This is shown by their adherence to a Hammett plot¹⁹ ($\rho = 1.67$) based on rates of elimination of other meta- and para-substituted 2-arylethyl bromides in which the substituents are incapable of direct resonance interaction with the reaction site and in which the substituent constant used for the nitro groups is based on equilibrium ionization constants (phenols and anilines).

Reaction Mechanisms. Under the reaction conditions reported here, Scheme I depicts the commonly accepted mechanisms for base-promoted β -elimination reactions, either via carbanion intermediates (free or ion-paired) in a stepwise mechanism (E1cB or A_{xh}D_H + D_N)³⁴ or via a one-step concerted mechanism (E2 or A_{xh}D_HD_N).³⁴ The observation of general-base catalysis with Brønsted β values ranging from 0.37 to 0.54 (Table II) rules out mechanisms in which breakdown of either an ion-paired or hydrogen-bonded carbanion (k_2) or free carbanion (k_2) is rate-limiting because these mechanisms would either not show general-base catalysis (k_2 rate-limiting) or give rise to Brønsted β

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values near 1 (k_2 , rate-limiting). General-base catalysis with β values in the range reported here are instead consistent with either the E2 (via k_2) or E1cB_{irr} mechanisms (k_1 , rate-limiting) in which the rate-limiting step involves hydron transfer.

Leaving Group Effects. Table II shows that the relative rate constants for the hydroxide ion and buffer promoted elimination reactions of the 2-(2,4,6-trinitrophenyl)ethyl halides are inversely related to the order of carbon-halogen bond strengths. The relative leaving group abilities are 1:1.6:4.7:3.9 for the hydroxide ion promoted reactions, 1:1.9:4.3:8.5 for the trifluoroethoxide ion promoted reactions, and 1:2.2:10.2:14.7 for the hexafluoroisopropoxide ion promoted reactions of the fluoride, chloride, bromide, and iodide derivatives, respectively. These halogen leaving group effects are consistent with an E2 mechanism in which there is partial cleavage of the carbon-halogen bond in the transition state.³⁵ The opposite order of halogen leaving group abilities is normally expected for an E1cB_{irr} mechanism in which the rate-limiting step is a hydron transfer (however, see the following text); the order $F > Cl > Br > I$ would reflect the decreasing ability of the halogens to accommodate a negative charge on the β -carbon via a polar effect³⁶—the relatively small difference in σ^* values for the CH_2X group,³⁷ 1.10, 1.05, 1.00, and 0.85 for X equal to fluoro, chloro, bromo, and iodo, respectively, suggests, however, that the differences in rates of reaction of the fluoride, chloride, bromide, and iodide, according to this model, would be relatively small. The relative leaving group ability of chloride and fluoride, k_{Cl}/k_F , that is greater than 1 (ca. 2) does not, however, establish an E2 mechanism for the fluoride because this ratio can also be accounted for by a change in mechanism: from an E1cB_{irr} mechanism for the fluoride to a E2 mechanism for the chloride and other halide derivatives that is manifested by an increase in reaction rate.³⁸ Furthermore, the small k_{Cl}/k_F ratio (1.6–2.2) makes it difficult to rule out the possibility that the chloride may also react via an E1cB_{irr} mechanism.

A small-element effect of the kind observed here might also be the result of anionic hyperconjugation,³⁹ in which the negative charge on the β -carbon is stabilized by overlap between the β -electron pair and the C–X orbitals. Ab initio calculations with use of an STO-3G basis set for the energy difference between β -substituted ethyl anions in the eclipsed and perpendicular conformations show that there are large barriers to rotation around the carbon-carbon bond that have been attributed to anionic hyperconjugation.^{40,41} It has been suggested that anionic hyperconjugative stabilization energies (HSE) follow the order $I > Br > Cl > F$ and overshadow the polar effect of the halogens.^{39,42} If this is true, then it would make it difficult or impossible to distinguish between the E1cB and E2 mechanisms, because the E1cB_{irr} mechanism would then be expected to show most of the same characteristics of an E2 mechanism. Some evidence that bears on this problem has been summarized elsewhere.¹ For example, several reported cases of elimination reactions show fluoride derivatives to be more reactive than the chlorides (up to a factor of ca. 10-fold).^{43–46} These are results expected of the

Table III. Relative Halogen Leaving Group Abilities for the Base-Promoted Elimination Reactions of 2-Arylethyl Halides^a

substrate	$k_I:k_F^b$	$k_{Br}:k_F^c$	$k_{Br}:k_{Cl}^d$	$k_{Cl}:k_F^e$
2,4,6-(NO ₂) ₃ C ₆ H ₂ (CH ₂) ₂ X	4	5	2.9	1.6
2,4-(NO ₂) ₂ C ₆ H ₃ (CH ₂) ₂ X	14	9	4.4	2.0
4-NO ₂ C ₆ H ₄ (CH ₂) ₂ X ^f	58	29	8.8	3.3
C ₆ H ₅ (CH ₂) ₂ X ^g	26667	4020	60	67

^a In aqueous solution at 25 °C and $I = 1.0$ M maintained with potassium chloride. ^b Refers to the relative leaving group abilities of iodide and fluoride ions. ^c Refers to the relative leaving group abilities of bromide and fluoride ions. ^d Refers to the relative leaving group abilities of bromide and chloride ions. ^e Refers to the relative leaving group abilities of chloride and fluoride ions. ^f Reference 13. ^g For the ethoxide ion-promoted elimination reactions in ethanol (from ref 12). The relative leaving group abilities of the halide ions are expected to be smaller in aqueous solution.¹⁹

classical model in which the negative charge is stabilized via a polar effect, but not with the model in which anionic hyperconjugation is important, because calculations show that chlorine stabilizes a β negative charge by anionic hyperconjugation more strongly than does fluorine (the energy difference between the perpendicular (I) and eclipse (II) conformations is calculated to be either 10.1⁴⁰ or 9.2⁴¹ kcal/mol for fluorine and 16.7⁴⁰ kcal/mol for chlorine).



Dependency of Leaving Group Ability on the β -Aryl Substituent.

As shown in Table III, there is a progressive decrease in the sensitivity of the elimination reactions to changes in the leaving halogen as the β -aryl substituent in this series is made more electron withdrawing. For example, the iodide to fluoride rate constant ratio decreases from 58 to 14 to 4, the bromide to fluoride ratio from 29 to 9 to 5, and the bromide to chloride ratio from 8.8 to 4.4 to 2.9 for the hydroxide ion promoted elimination reactions of 2-(*p*-nitrophenyl)ethyl,¹³ 2-(2,4-dinitrophenyl)ethyl,¹⁹ and 2-(2,4,6-trinitrophenyl)ethyl iodides and fluorides, bromides and fluorides, and bromides and chlorides, respectively.⁴⁷ Furthermore, plots of the log of the rate constants for the hydroxide ion promoted reactions of 2-(2,4-dinitrophenyl)ethyl, 2-(*p*-nitrophenyl)ethyl, and 2-phenylethyl⁴⁷ halides against those for the 2-(2,4,6-trinitrophenyl)ethyl halides are linear with slopes 1.59, 2.48, and 5.23, respectively (plots not shown). These results can be described by a negative p_{yy} interaction coefficient,⁴⁸ $p_{yy} = \partial \beta_{1y} / \partial \sigma = -\partial \rho / \partial pK_{1y}$, that describes the interaction between the leaving group and a β activating group; a negative p_{yy} coefficient is consistent with an E2 mechanism in which more strongly electron-withdrawing β -aryl substituents result in E2 transition states that have less leaving group bond cleavage. These changes in the relative leaving group ability of the halogens can be described on More O'Ferrall-Jencks energy diagrams^{49,50} as a shift toward the top edge of the diagram in Figure 2 that is a result of substituent changes that stabilize the carbanion intermediate in the upper left-hand corner of the diagram (arrow 2 in Figure 2).

For the hydroxide ion promoted elimination reactions of 2-(*p*-nitrophenyl)ethyl and 2-(2,4-dinitrophenyl)ethyl fluorides and chlorides, the chloride to fluoride rate constant ratio, $k_{Cl}:k_F$, decreases from 3.3 to 2.0. On the other hand, for the analogous reactions of the 2-(2,4-dinitrophenyl)ethyl and 2-(2,4,6-trinitrophenyl)ethyl derivatives, the $k_{Cl}:k_F$ ratio is essentially unchanged with values of 2.0 and 1.6, respectively. This small or negligible

(47) The relative rates of the ethoxide-promoted elimination reactions of 2-phenylethyl halides in ethanol solution are in the order 26667:4020:67:1 for the iodide, bromide, chloride, and fluoride derivatives, respectively.¹² The relative leaving group abilities of the halide ions are expected to be smaller in aqueous solution.¹⁹

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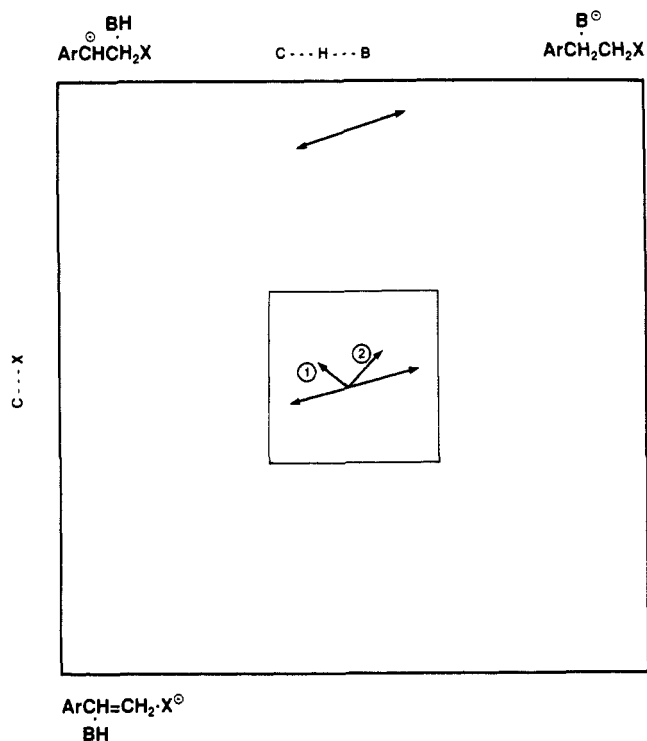


Figure 2. More O'Ferrall-Jencks energy diagram for the β -elimination reactions of 2-(2,4,6-trinitrophenyl)ethyl halides. Hydron transfer occurs along the x axis and leaving group bond cleavage along the y axis. A reaction coordinate with a major component of hydron transfer is drawn near the top edge of the diagram, consistent with the small halogen leaving group effects observed in these reactions. Also included, in a box near the center of the diagram, is this same reaction coordinate including arrows denoting changes in the E2 transition state that are a result of making the leaving group less nucleofugic (giving rise to an increase in hydron transfer, arrow 1) and making the β -aryl substituent more electron withdrawing (giving rise to less hydron transfer and leaving group bond cleavage, arrow 2).

dependence of the k_{Cl}/k_F ratio on the β -aryl substituent and the small k_{Cl}/k_F rate ratios of ca. 2 cited previously suggest that a change to the $E1cB_{irr}$ mechanism is possible for the elimination reactions of these compounds.

Dependency of Brønsted β Values on the Leaving Group. The data in Figure 3 and Table II show that the Brønsted β values for general-base catalysis increase in the order I (0.37), Br (0.41), Cl (0.49), and F (0.54). This observed increase in β values as the leaving group is made less nucleofugic is a characteristic of E2 reactions (and a variable E2 transition-state structure). These changes in β values can be described by a positive p_{xy} interaction coefficient,⁴⁸ $p_{xy} = \partial\beta/\partial pK_g = \partial\beta_g/\partial pK_{BH}$, that describes the interaction between the base catalyst and the leaving group. The observed increase in the relative leaving group abilities of the halogens as the catalyst is made less basic is another manifestation of this same effect: 1:1.6:4.7:3.9, 1:1.9:4.3:8.5, and 1:2.2:10.2:14.7 for the hydroxide ion ($pK_a = 15.7$), trifluoroethoxide ion ($pK_a = 12.3$), and hexafluoroisopropoxide ion ($pK_a = 9.20$) promoted reactions, respectively. On the More O'Ferrall-Jencks diagram in Figure 2, a poorer halogen leaving group will raise the energy of the bottom half of the diagram, resulting in a net shift toward the left side, in the direction of increased hydron transfer and larger Brønsted β values¹¹ (arrow 1 in Figure 2). On the other hand, for an $E1cB_{irr}$ mechanism, the rate-limiting step occurs along the top edge of the diagram where a change to a poorer leaving group is expected to result in no change ($p_{xy} = 0$) or a small decrease in β .¹¹ Examples of both positive and zero p_{xy} coefficients, characteristic of E2 and $E1cB_{irr}$ reactions, respectively, have been summarized previously.^{1,11} These results do not, however, establish an E2 mechanism for the fluoride because a decrease in β from 0.54 for the fluoride to 0.49 for the chloride can also be accounted for by a change in mechanism: from $E1cB_{irr}$ for the fluoride ($\beta = 0.54$) to E2 for the chloride ($\beta = 0.49$) and other halides

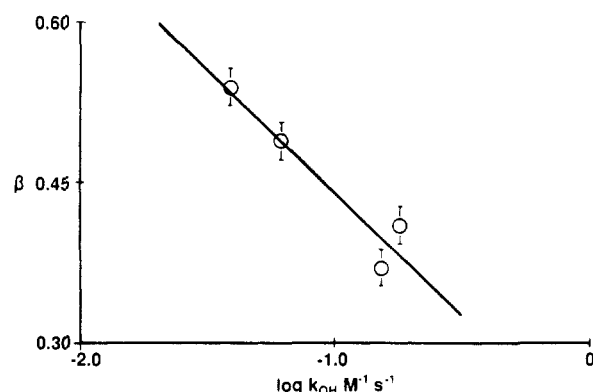


Figure 3. Dependence of Brønsted β values on $\log k$ for the hydroxide ion promoted elimination reactions of 2-(2,4,6-trinitrophenyl)ethyl halides in aqueous solution at 25 °C, $I = 1.0 \text{ M}$ (KCl).

derivatives ($\beta = 0.41$ and 0.37)—a change in mechanism that is manifested by a decrease in β values. Furthermore, although the β value for the chloride is smaller than for the fluoride, this difference is small, and in light of the data cited above, the mechanism of elimination of the chloride substrate should not be considered established by this result.

Dependency of Brønsted β Values on the β -Aryl Substituent.

The results reported here of a normal element effect and positive and negative p_{xy} and $p_{yy'}$ coefficients, respectively, support an E2 mechanism for the reactions of the 2-(2,4,6-trinitrophenyl)ethyl bromide and iodide (steric hindrance to resonance is a factor that favors the E2 mechanism), while the mechanism of reaction of the fluoride and chloride is not established by these results.

We have previously reported that as the β -aryl substituent becomes more electron withdrawing in the 2-arylethyl series, Brønsted β values for general-base catalysis first increase from 0.51 for the reactions of 2-phenylethyl bromide to 0.61 for the reactions of 2-(*p*-nitrophenyl)ethyl bromide but then decrease to 0.47 for the reactions of the 2-(2,4-dinitrophenyl)ethyl bromide.¹⁹ This dependence of β values on the β activating group can be described by the p_{xy} interaction coefficient,⁴⁸ $p_{xy} = \partial\beta/\partial\sigma = \partial p/\partial pK_{BH}$; positive and negative p_{xy} coefficients correspond to increasing and decreasing extents of hydron transfer, respectively, as a β activating group is made more electron-withdrawing.

The results reported here show that the Brønsted β value of 0.41 for the reactions of 2-(2,4,6-trinitrophenyl)ethyl bromide is smaller than the values of 0.61 and 0.47 for the reactions of 2-(*p*-nitrophenyl)ethyl bromide¹³ and 2-(2,4-dinitrophenyl)ethyl bromide,¹⁹ respectively. The β value of 0.37 for the reactions of 2-(2,4,6-trinitrophenyl)ethyl iodide is also smaller than the value of 0.43 that has been reported for the reactions of 2-(2,4-dinitrophenyl)ethyl iodide¹⁹ (comparable data for 2-(*p*-nitrophenyl)ethyl iodide are not available). These results provide additional evidence for a decrease in the extent of hydron transfer in an E2 transition state as the β activating group is made more electron withdrawing ($p_{xy} < 0$). Negative p_{xy} coefficients have been observed in a number of other systems as well.^{7,11,51} These negative p_{xy} coefficients are apparently not in accord with the valence-bond configurational mixing model,⁵² which predicts that hydron transfer should increase in the transition state of an E2 elimination⁵³ as the β substituent is made more electron withdrawing ($p_{xy} > 0$), because in this case the transition state should look more like the carbanion in which the C-H bond is completely broken ($\beta = 1$). The negative p_{xy} coefficients that have been observed in elimination reactions are, however, consistent with an E2 transition state and a reaction coordinate that has a large component of hydron transfer so that stabilization of the carbanion intermediate results in perturbations both perpendicular and parallel to the reaction coordinate as described on More O'Fer-

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rall-Jencks energy diagrams (arrow 2 in Figure 2).^{11,19} A reaction coordinate with a large component of hydron transfer can give rise to a Hammond effect that can result in a decrease in the extent of hydron transfer.^{11,19,54} A reaction coordinate with a large component of hydron transfer is expected here, because the small halogen leaving group effects mean that the E2 transition states in these reactions are very carbanion-like and are near the top edge of the energy diagram in Figure 2. In contrast to these results, the Brönsted β values of 0.50⁵⁵ and 0.54, and 0.50⁵⁵ and

0.49 for the elimination reactions of 2-(2,4-dinitrophenyl)ethyl¹⁹ and 2-(2,4,6-trinitrophenyl)ethyl fluoride, and 2-(2,4-dinitrophenyl)ethyl¹⁹ and 2-(2,4,6-trinitrophenyl)ethyl chlorides, respectively, are consistent with a zero p_{xy} interaction coefficient⁵⁶ that, along with the small $k_F:k_{Cl}$ ratio and the small dependence of this ratio on the β -aryl substituent cited above, may signify a change to the E1cB_{irr} mechanism for the reactions of these substrates.

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(56) On its own, a zero p_{xy} coefficient does not establish the E1cB_{irr} mechanism because it is not clear why this coefficient would be smaller for an E1cB_{irr} than an E2 mechanism.

Conformation of the Glycolipid Globoside Head Group in Various Solvents and in the Micelle-Bound State

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Abstract: The three-dimensional (3D) structure of the oligosaccharide part of the globotetraosylceramide (globoside), GalNAc β 1-3Gal α 1-4Gal β 1-4Glc β 1-1Cer, was modeled in Me₂SO and Me₂NCHO solutions with use of a distance mapping procedure, which involved NOE contacts between the amido, hydroxy, and C-linked protons. The oligosaccharide chain showed a pronounced flexibility of each of the glycosidic linkages, while preserving a global "L" shape. A similar conformation was found for globoside anchored in mixed dodecylphosphocholin micelles in D₂O solution, where it experiences a fast internal rotation on a time scale of 0.4 ns. It was concluded that the hard-sphere exo-anomeric (HSEA) model applied elsewhere did not predict correctly the 3D structure of globoside, while molecular mechanics calculations, used extensively in the present work, approach more closely the true oligosaccharide conformations.

The biological role of glycan moieties of glycolipids^{1a} and glycoproteins^{1b} is well-documented, and a great number of observations suggest that conformation of oligosaccharide chains is responsible for their specific interaction with a variety of receptors.^{1c-e} NMR studies of solution conformation of biomolecules of any class are mainly based on the proton-proton distance information gained from the quantitative evaluation of NOE data.^{2a} However, in contrast to proteins, oligopeptides, and nucleic acids, which usually display a sufficient number of NOE connectivities to be used (in combination with energy minimum calculations) in the modeling of well-founded three-dimensional structures,^{2b,c} oligosaccharides show very few structurally relevant NOE contacts so that the conformational analysis is slanted toward theoretical calculations. At the same time, systematic scanning of the conformational space of oligosaccharides by means of quantum mechanical^{3a} and molecular mechanics^{3b-f} calculations does not presently extend beyond disaccharides because of the excessive computational time required. The energy minimization of more complex systems is usually trapped in local minima, which can be very different from the global one. Restarting the minimization process with different, randomly chosen geometries often yields a number of energetically similar, yet different conformations whose relative importance with respect to one another cannot be assessed properly owing to the limited accuracy of

empirical energy calculations. These computational difficulties can be skipped if one uses a simplified or "smoothed" potential energy hypersurface as in the HSEA (hard-sphere exo-anomeric) model where only van der Waals (vdW) interactions and the exo-anomeric effect are taken into account.^{4a-c} Recently, however, this method has been subjected to criticism^{3b} (cf. a discussion reviewed in ref 3b); also the present study shows that the torsional freedom for glycosidic bonds is far more pronounced than predicted by the HSEA model.

In a preliminary communication we have shown that many more structurally important NOE contacts can be observed in rotating

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