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When Is Intramolecular Proton Transfer between Carbon and Nitrogen or Oxygen Observable?

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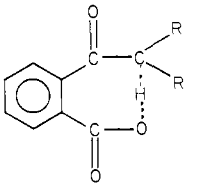
Abstract: Intramolecular proton transfer from oxygen or nitrogen to a carbanionic site within the same molecule ($^{z}HX–C^- \rightarrow {}^{z-1}X–CH$) has been reported to occur for systems in which the two reaction centers are separated by only one carbon. Apparently the inclusion of one (or two) water molecule(s) into the transition state allows the formation of large enough a cycle to make this a viable reaction, with effective molarities of up to 1 M. Whether the intramolecular pathway can compete favorably with pathways involving external acids and bases (including H^+, OH^-, and the solvent) depends not only on the effective molarity but also on the interplay of various factors whose effects were simulated on a computer for the following classes of compounds: carbonyl compounds, nitro- and 1,1-dinitroalkanes, 9-substituted fluorenes, and benzyl cyanides. The major conclusions are the following. (1) The detectability of the intramolecular pathway and the pH range within which it is detectable are very sensitive to the pK_a of the donor group (pK_a^{XH}) and to the Brønsted α value which relates carbon protonation rates to the pK_a^{XH} of oxygen or nitrogen proton donors. pK_a^{XH} values near the midpoint of the scale (near 7 in aqueous solution) and α values close to 0.5 are optimal. (2) Detectability depends only little on the pK_a of the carbanionic site (pK_a^{CH}) for carbonyl compounds, and not at all for the other compounds. Similarly, the Brønsted β value which relates carbon protonation rates to pK_a^{CH} has a relatively minor influence except for extreme (negative) β values (nitroalkane anomaly). (3) A large difference between the first and second pK_a ($pK_2^{XH} - pK_1^{XH}$ or $pK_2^{CH} - pK_1^{CH}$) of the respective functionalities enhances the relative importance of the intramolecular pathway, and so does a change to a solvent with a higher pK_w (e.g., Me_2SO–water mixtures). The theoretical predictions are compared with experimental results for nine compounds (**3**, **6**–**13**, Table X). For the six compounds where intramolecular proton transfer has been reported, the theory would have predicted it, while for the three negative cases the theory would have correctly predicted two of them. The one discrepancy between theory and experiment refers to 9-(dimethylaminomethyl)fluorene (**11**) for which we currently do not have a satisfactory explanation.

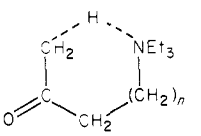
Introduction

The question posed in the title is a rather fundamental one. We propose to deal with it in a somewhat general way but with a focus on some specific recent observations made in our laboratory.

There has been a fair number of reports of intramolecular proton transfer between carbon and oxygen or nitrogen.[1] The majority of these reports refer to the deprotonation of ketones by an internal base such as a carboxylate,[2] amino,[3] phenoxide,[4] or phosphate group.[5] Similar reactions where the carbon acid is activated by one or two nitro groups,[6] or by an iminium nitrogen,[7] have also been reported. In most examples the separation between the activated carbon and the heteroatom of the internal base was three or four (sometimes five[7]) additional atoms, leading to six or seven (sometimes eight[7]) membered cyclic transition states (including the proton) as shown for two typical examples **1** and **2**. Such transition states appear to be optimal for the intramolecular proton transfer and lead to typical effective molarities[8] of ~0.1 to 1 M when the carbon skeleton is flexible as in **2**,[3b] of up to ~50 M when the rigidity of the molecule facilitates the formation of a cyclic transition state as in **1**.[2b,d]

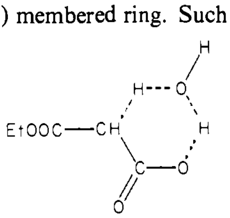


1 (R = CH_3[2d] or H[2b])



2[3b] (n = 1 or 2)

When the separation between the two functionalities becomes less than three atoms, the intramolecular pathway competes much less effectively with external proton transfer[2a,6,9] as is demonstrated by a comparison of $CH_3COC\mathit{H}_2CH_2CH_2COO^-$ with $CH_3COC\mathit{H}_2CH_2COO^-$[2a] or CH_3COCOO^-,[9] or of $CH_3C\mathit{H}(NO_2)CH_2CH_2COO^-$ with $O_2NCH_2CH_2COO^-$[6a] (H in italics is the one reacting). These examples show the change from six- to five-membered cyclic transition states. The geometrical constraints of a four-membered cyclic transition state would appear to be still more severe and perhaps prevent intramolecular transfer from being an observable reaction altogether. However, the problem can be alleviated by incorporation of one (or two) water molecules into the transition state which would make it a much more favorable six- (or eight-) membered ring. Such a case, **3**, has indeed been reported,[10] and it was assumed that the transition state includes one or several water molecules.[11]



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[1] For reviews, see: (a) Jones, J. R. "The Ionisation of Carbon Acids"; Academic Press: New York, 1973; p 44. (b) Capon, B. In "Proton Transfer Rections"; Caldin, E., Gold, V., Eds.; Wiley: New York, 1975; p 339.

[2] (a) Bell, R. P.; Fluendy, M. A. D. *Trans. Faraday Soc.* **1963**, *59*, 1623. (b) Bell, R. P.; Cox, B. G.; Henshall, J. B. *J. Chem. Soc., Perkin Trans. 2* **1972**, 1232. (c) Bell, R. P.; Earls, D. W.; Henshall, J. B. *Ibid.* **1976**, 39. (d) Harper, E. T.; Bender, M. L. *J. Am. Chem. Soc.* **1965**, *87*, 5625.

[3] (a) Coward, J. K.; Bruice, T. C. *J. Am. Chem. Soc.* **1969**, *91*, 5339. (b) Bell, R. P.; Timimi, B. A. *J. Chem. Soc., Perkin Trans. 2*, **1973**, 1519.

[4] (a) Bell, R. P.; Earls, D. W.; Timimi, B. A. *J. Chem. Soc., Perkin Trans. 2*, **1974**, 811. (b) Bell, R. P.; Earls, D. W. *Ibid.* **1976**, 45.

[5] Motiu-De Grood, R.; Hunt, W.; Wilde, J.; Hupe, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 2182.

[6] (a) Wilson, H.; Lewis, E. S. *J. Am. Chem. Soc.* **1972**, *94*, 2283. (b) Dronov, V. N.; Tselinskii, I. V. *Org. React.* **1970**, *7*, 115, 264.

[7] (a) Hine, J.; Cholod, M. S.; Jensen, J. H. *J. Am. Chem. Soc.* **1971**, *93*, 2321. (b) Hine, J.; Cholod, M. S.; King, R. A. *Ibid.* **1974**, *96*, 835.

[8] Effective molarity is equal to the rate constant for the intramolecular reaction divided by the rate constant for an intermolecular proton transfer involving an external base (acid) of the same pK_a as that of the internal base (acid); see, e.g., Page, M. I. *Chem. Soc. Rev.* **1973**, *2*, 295, or Kirby, A. J. *Adv. Phys. Org. Chem.* **1980**, *17*, 183.

[9] Albery, W. J.; Bell, R. P.; Powell, A. L. *Trans. Faraday Soc.* **1965**, *61*, 1194.

[10] Kirby, A. L.; Lloyd, G. J. *J. Chem. Soc., Perkin Trans. 2* **1976**, 1762.

[11] Incorporation of a water molecule into large cyclic transition states, e.g., into **2** to make it an eight-membered ring, is a possibility which has been discussed.[12]

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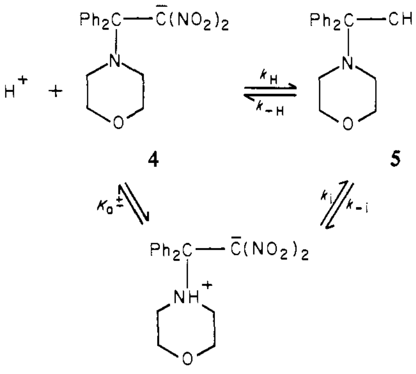
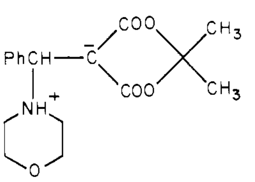
Our interest in the problem of detectability of intramolecular proton transfers in systems where there is only one additional atom separating the two functionalities (like in **3**) was kindled by observations we made while studying addition complexes of activated olefins with amines and hydroxide ion. For example, we found that the reaction of **4** with hydronium ion to form **5** occurs about



4 **5** **6**

10^4-fold faster via equilibrium protonation of nitrogen to form **6** followed by intramolecular proton transfer ($k_i/K_a^{\pm}$) than by the direct pathway (k_H).[13,14] Other examples where intramolecular proton transfer was found to be a significant pathway include **7**,[15]



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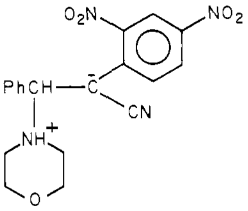

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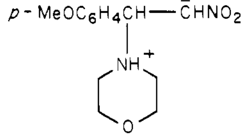

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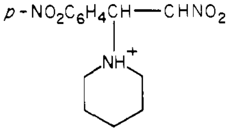

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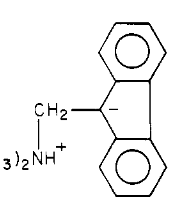
8,[16] **9**,[17] and **10**.[17] On the other hand, More O'Ferrall and Kelly[18] report that no contribution by the intramolecular reaction could be detected with **11**; the same holds true for **12**[19] and **13**.[20]



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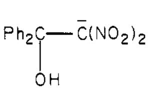

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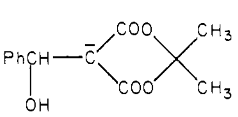

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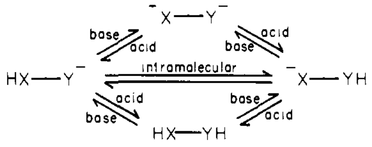
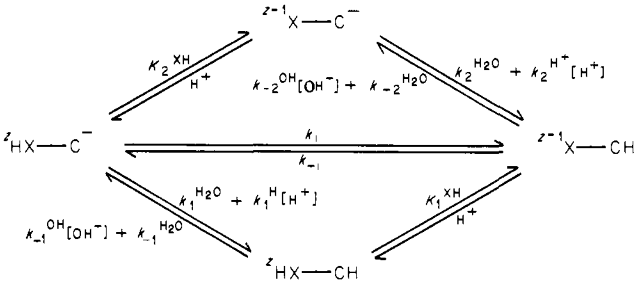
It is not immediately obvious why intramolecular proton transfer should be significant for **7**–**10** but insignificant for **11**–**13**. The main purpose of this paper is to examine this question in a general way and to develop some rules which would allow us to make semiquantitative predictions as to when an intramolecular pathway may be significant. Apart from geometrical constraints on the cyclic transition state (which determines the effective molarity), the factors which need to be considered primarily are the pK_a values of the donor and acceptor atoms, the pH (which determines the ionization state of the heteroatom), and the rate–pK_a relationship for proton transfer at carbon (Brønsted slopes, curvature).

Scheme I



Scheme II



Intra- vs. Intermolecular Proton Transfer

As illustrated in Scheme I, intramolecular transfer is only observable if it competes favorably with the pathways involving external acids and bases which include buffers, the solvent, H^+, and OH^-. In fact, the classical evidence for intramolecular proton transfer is the observation of an overall rate which is significantly higher than that expected or explainable based upon the external pathways only. For the situation where both X and Y are electronegative atoms, the problem can be dealt with in a general way because, for a given set of pK_a values and pH, the rates of all external steps can be estimated with a high degree of precision based on the work of Eigen[21] and his associates.[22] Schuster et al.[22b] and Bensaude et al.[23] have carried out such analyses for some specific examples.

The situation is different when one center is a carbon atom because rates involving proton transfer at carbon are usually much slower and depend in a different way on pK_a values than proton transfers between electronegative atoms.[21,24] We shall base our discussion on Scheme II where the charge $z = 0$ for X = oxygen, $z = 1$ for X = nitrogen. We shall assume that the ionization equilibria for XH (K_1^{XH}, K_2^{XH}) are always rapidly established compared to all the other processes in Scheme II. We also assume that in a typical situation the reaction solution would be buffered, assuring pseudo-first-order conditions, but in comparing the relative contributions of inter- vs. intramolecular pathways we shall assume that the data have been extrapolated to zero buffer concentration, so that buffer terms in the rate law can be neglected (these are already omitted from Scheme II). Under these conditions the pseudo-first-order rate constant, k_{obsd}, for equilibrium approach is given by

$$k_{obsd} = k_f + k_r \quad (1)$$

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(12) See, e.g., Gandour, R. D. *Tetrahedron Lett.* **1974**, 295.

(13) Bernasconi, C. F.; Carré, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 2698.

(14) Bernasconi, C. F.; Kanavarioti, A. *J. Org. Chem.* **1979**, *44*, 4829.

(15) Bernasconi, C. F.; Fornarini, S. *J. Am. Chem. Soc.* **1980**, *102*, 5329.

(16) Bernasconi, C. F.; Fox, J. P.; Murray, C. J., to be published.

(17) Bernasconi, C. F.; Tia, P., to be published.

(18) Kelly, R. P.; More O'Farrall, R. A. *J. Chem. Soc., Perkin Trans. 2* **1979**, 681.

(19) Bernasconi, C. F.; Carré, D. J.; Kanavarioti, A. *J. Am. Chem. Soc.* **1981**, *103*, 4850.

(20) Bernasconi, C. F.; Leonarduzzi, G. D. *J. Am. Chem. Soc.*, in press.

(21) Eigen, M. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 1.

(22) For recent reviews, see: (a) Crooks, J. E. In "Comprehensive Kinetics"; Bamford, C. H., Tipper, C. F. H., Eds.; Elsevier: New York, 1977; Vol. 8, p 197. (b) Schuster, P.; Wolschann, P.; Tortschanoff, K. In "Chemical Relaxation in Molecular Biology"; Pecht, I., Rigler, R., Eds.; Springer Verlag: New York, 1977; p 107.

(23) Bensaude, O.; Dreyfus, M.; Dodin, G.; Dubois, J. E. *J. Am. Chem. Soc.* **1977**, *99*, 4438.

(24) For recent reviews, see: (a) Hibbert, F. In ref 22a, p 97. (b) Bell, R. P. "The Proton in Chemistry"; Cornell University Press: Ithaca, N. Y., 1973; p 194. (c) ref 1a, pp 28, 124.

Table I. Summary of the Features of the Five Models

CH acid	$pK_2^{XH} - pK_1^{XH} = pK_2^{CH} - pK_1^{CH}$	log k	α	β	$k_1^{H_2O}, k_2^{H_2O}$ reduction	k_1^{H}, k_2^{H} reduction	k_i, EM	k_i (pK^{XH}) reduction
model I: carbonyl compounds	4	eq 8			30	5	(a) 3.3×10^{-3} (b) 0.1	10 (14–15.9) 3 (12–13.9)
model II: 1,1-dinitroalkanes	3	eq 14	0.30	0.30	300	4	(a) 1 (b) 0.1	30 (14–14.9) 10 (13–13.9) 3 (12–12.9)
model III: nitroalkanes	3	eq 15, 16	0.45	A: 0.10 B: −0.40 C: −0.90	100	2	0.1	10 (13.5–14.9) 3 (12–13.4)
model IV: 9-substituted fluorenes	5	eq 15, 16	0.33	0.51	300	4	0.1	30 (14–14.9) 10 (13–13.9) 3 (12–12.9)
model V: benzyl cyanides	3	eq 15, 16	0.39	0.45	100	10	0.02	30 (15–15.9) 10 (13.5–14.9) 3 (12–13.4)

where k_f and k_r refer to the forward and reverse directions, respectively, and are defined as

$$k_f = (k_1^{H_2O} + k_1^{H}[H^+])\frac{[H^+]}{K_2^{XH} + [H^+]} + (k_2^{H_2O} + k_2^{H}[H^+])\frac{K_2^{XH}}{K_2^{XH} + [H^+]} + k_i\frac{[H^+]}{K_2^{XH} + [H^+]} \quad (2)$$

$$k_r = (k_{-1}^{H_2O} + k_{-1}^{OH}[OH^-])\frac{[H^+]}{K_1^{XH} + [H^+]} + (k_{-2}^{H_2O} + k_{-2}^{OH}[OH^-])\frac{K_1^{XH}}{K_1^{XH} + [H^+]} + k_{-i}\frac{K_1^{XH}}{K_1^{XH} + [H^+]} \quad (3)$$

Since, according to the principle of microscopic reversibility, the relative contribution of each pathway is the same in both directions, we only need to consider either k_f or k_r. We shall choose k_f and express it as

$$k_f = \text{“}k_{H_2O}\text{”} + \text{“}k_H\text{”} + \text{“}k_i\text{”} \quad (4)$$

with

$$\text{“}k_{H_2O}\text{”} = k_1^{H_2O}\frac{[H^+]}{K_2^{XH} + [H^+]} + k_2^{H_2O}\frac{K_2^{XH}}{K_2^{XH} + [H^+]} \quad (5)$$

$$\text{“}k_H\text{”} = k_1^{H}[H^+]\frac{[H^+]}{K_2^{XH} + [H^+]} + k_2^{H}[H^+]\frac{K_2^{XH}}{K_2^{XH} + [H^+]} \quad (6)$$

$$\text{“}k_i\text{”} = k_i\frac{[H^+]}{K_2^{XH} + [H^+]} \quad (7)$$

where "k_{H_2O}" includes the two terms involving protonation by water, "k_H" includes the two terms involving protonation by H^+, and "k_i" is the term for intramolecular protonation.

In order to estimate the relative contribution of each term in eq 4 for a given experimental situation, we need a model which permits us to estimate the various rate coefficients as a function of the pK_a values of XH and CH. Since the rate–pK relationship depends strongly on the type of CH acid,[24] different models will be needed. Five such models will be developed, mimicking the expected behavior of five different classes of CH acids: carbonyl compounds, 1,1-dinitroalkanes, nitroalkanes, 9-substituted fluorenes, and benzyl cyanides. The principal features of these models are summarized in Table I and are now explained in detail.

Model I: Carbonyl Compounds

There exists a large body of data on the deprotonation of carbonyl compounds by carboxylate and aryl oxide ions. Bell[24b] has summarized more than 100 data points on a single curved Eigen[21] (log k vs. ΔpK) plot. Cohen and Marcus[25] have shown that such an Eigen plot gives an excellent fit with the simplified[26] Marcus equation (eq 8) with $\lambda = 46$ kcal/mol. We have used a theoretical Marcus curve constructed on the basis of eq 8 with $\lambda = 46$ kcal/mol to estimate the various rate constants of Scheme II after taking the following additional factors into consideration.

$$\Delta G^* = \left(1 + \frac{\Delta G^\circ}{\lambda}\right)^2 \frac{\lambda}{4} \quad (8a)$$

$$\log k = 11 - \Delta G^*/1.36;\ \Delta pK = -\Delta G^\circ/1.36 \quad (8b)$$

(1) Rate constants for the deprotonation of CH acids by OH^- and by water (or protonation of the carbanion by water and by H^+, respectively) usually deviate negatively from Brønsted plots based on carboxylate or phenoxide ions.[27] The extent of this deviation depends on how the data are treated. Brønsted plots for individual ketones which cover only a small pK range have been usually treated as being linear. In these cases the points for OH^- deprotonation (H_2O protonation) deviate by a factor around 10^3, those for H_2O deprotonation (H^+ protonation) by a factor around 30.[27] When the data are arranged on a curved Eigen plot, this translates into an approximate average 30-fold deviation for water protonation and an approximate average 5-fold deviation for H^+ protonation. We shall use these latter figures in estimating $k_1^{H_2O}$, $k_2^{H_2O}$, k_1^{H}, and k_2^{H}. Thus, in estimating k_1^{H} we find the uncorrected value from the plot according to eq 8 at $\Delta pK = pK_1^{CH} - pK^{H_3O^+} = pK_1^{CH} + 1.74$ and divide by 5; for k_2^{H} we proceed in a similar way except that $\Delta pK = pK_2^{CH} + 1.74$; pK_1^{CH} and pK_2^{CH} refer to the C–H acidity constants of ^{z}HX–CH and $^{z-1}$X–CH, respectively (see Scheme II). $k_1^{H_2O}$ and $k_2^{H_2O}$ are obtained by an analogous procedure ($\Delta pK = pK_1^{CH} - pK^{H_2O}$ and then divide by 30). This procedure for $k_1^{H_2O}$ and $k_2^{H_2O}$ results in bimolecular rate constants which are converted into unimolecular rate constants (in conformity with eq 2) by multiplication with the water concentration (55.5 M).

(2) In estimating k_i we assume that log k_i follows a similarly shaped log k vs. ΔpK curve as above except for very high pK_1^{XH} and pK_2^{XH} values as discussed below. There are, however, two questions which need to be dealt with. One is how ΔpK should be defined. The other is what effective molarity (EM) should be assumed; i.e., does k_i deviate positively or negatively from the curve.

As to the first question, a definition of ΔpK (the difference between acceptor and donor pK_a) is needed because, unlike in an

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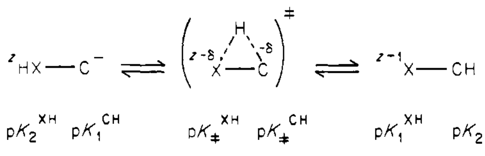
(25) Cohen, A. O.; Marcus, R. A. *J. Phys. Chem.* **1968**, *72*, 4249.
(26) Work terms were neglected.
(27) Kresge, A. J. *Chem. Soc. Rev.* **1973**, *2*, 475.

*inter*molecular proton transfer, ΔpK *changes* as the reaction proceeds. For example, if the proton is transferred from the ^zHX group to the C^- group, the pK_a of the ^zXH group decreases from pK_2^{XH} toward pK_1^{XH} while the pK_a of the C^- group increases from pK_1^{CH} toward pK_2^{CH}, with intermediate values at the transition state. These changes may be considered trivial in systems where the ^zXH and C^- groups are separated by several atoms; in systems where the separation is by only one atom, the substituent effect of one group on the other is large; i.e., pK_1^{CH} and pK_2^{CH}, or pK_1^{XH} and pK_2^{XH}, may differ by several pK units as described in eq 9.



(9)

The situation is schematically described by eq 9. Since we do not know the exact structure of the transition state, we shall assume that the pK values have changed halfway at the transition state, i.e.

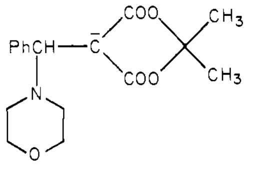
$$pK_‡^{XH} = \tfrac{1}{2}(pK_1^{XH} + pK_2^{XH}) \quad (10)$$

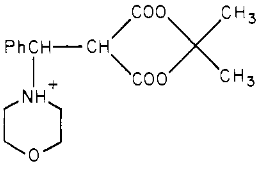
$$pK_‡^{CH} = \tfrac{1}{2}(pK_1^{CH} + pK_2^{CH}) \quad (11)$$

This leads to

$$\Delta pK = pK_1^{CH} - pK_1^{XH} = pK_2^{CH} - pK_2^{XH} \quad (12)$$

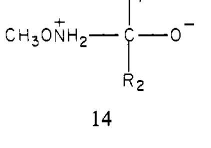
Regarding the second question, that of effective molarities, we first need a definition of this term for the types of systems under study. Because of the large difference between pK_1^{CH} and pK_2^{CH} or pK_1^{XH} and pK_2^{XH}, this definition poses the same problem as the definition of ΔpK for the intramolecular proton transfer. For consistency we shall again assume that the relevant pK's for the intramolecular reaction are $pK_‡^{XH}$ and $pK_‡^{CH}$ given in eq 10 and 11. With this assumption EM is defined as k_i/k_e, where k_e is the rate constant for protonation on carbon by an external acid, with the pK_a of the carbon and the pK_a of the external acid being such that their difference is equal to ΔpK given by eq 12. By way of an example, for **7** this would mean that k_e should either refer to the protonation of **7a** (pK_2^{CH}) by an acid whose pK_a is equal to that of **7** (pK_2^{XH}), or to the protonation of **7** (pK_1^{CH}) by an acid whose pK_a is equal to that of **7b** (pK_1^{XH}).

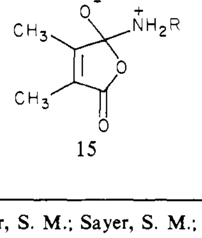

7a


7b

Little experimental information is available on EM's in systems where the ^zXH and C^- groups are separated by only one additional atom. The data on **3**[10] only allow a very rough estimate by extrapolation and suggest an EM between ~0.1 and ~1 M. Our data on **7**[15] suggest EM ~ 0.1 M although if one corrects for steric hindrance in the intermolecular protonation the EM could be as low as 10^{-3} M.[15]

Another approach is to use systems where the intramolecular proton transfer is between two electronegative atoms (e.g., **14**,[28] **15**[29]) as models for estimating EM's. These models suggest values in the order of 10^{-2} to 10^{-3} M.


14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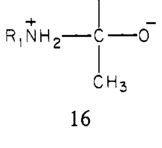

16

Owing to these conflicting conclusions, we shall adopt two different models: model Ia uses an EM of 3.3×10^{-3} M, model Ib one of 0.1 M; i.e., k_i is reduced 300- and 10-fold, respectively, from the value calculated based on the Marcus curve (eq 8).

Another reduction of k_i needs to be applied for high pK^{XH} values because rates of deprotonation by strongly basic oxyanions (and hence the rates of protonation by weakly acidic OH groups) tend to deviate negatively from Brønsted plots in a similar way as the OH^- (H_2O) points.[30] We shall assume a 30-fold reduction if the average of pK_1^{XH} and pK_2^{XH} is >16, a 10-fold reduction for average pK^{XH} values of 14 to 15.9, and a 3-fold reduction for average pK^{XH} values of 12 to 13.9.

(3) The various pK values of CH and ^zXH are interdependent as seen in eq 12. We need to estimate the differences $pK_2^{XH} - pK_1^{XH} = pK_2^{CH} - pK_1^{CH} = pK_2 - pK_1$. Fox and Jencks[31] report $pK_2^{NH} - pK_1^{NH} = pK_2^{OH} - pK_1^{OH} = 4.7$ to 4.8 for **16**. Since in a compound like **7** or **13** the negative charge is substantially delocalized, its electrostatic effect on the pK of the NH^+ group is expected to be smaller than in **16**, reducing the difference between pK_2^{XH} and pK_1^{XH}. On the other hand, stabilization of the zwitterion **7** by intramolecular hydrogen bonding to a carbonyl oxygen would tend to increase pK_2^{XH} and with it $pK_2^{XH} - pK_1^{XH}$; there is some evidence for such intramolecular hydrogen bonding.[15] For simplicity we shall assume $pK_2^{XH} - pK_1^{XH} = 4.0$ for all carbonyl compounds where ^zXH and C^- are separated by one additional carbon; the conclusions to be drawn are not very sensitive to some variation in this difference.

Model II: 1,1-Dinitroalkanes

Our model for 1,1-dinitroalkanes will be based on data by Bell and Tranter[32] and by Dronov et al.[6b,33] The former found that the deprotonation of 1,1-dinitroethane by a series of buffer bases is characterized by a linear Brønsted plot of slope $\beta = 0.70$ with the points for H_2O and OH^- deviating negatively by factors of about 4 and 300, respectively. Thus for the protonation of $CH_3\bar{C}(NO_2)_2$, $\alpha = 0.30$ with a 4- and 300-fold negative deviation for protonation by H_3O^+ and water, respectively. We obtained similar results in 50% Me_2SO–50% water, the solvent in which **6** and **12** were investigated, although we chose to represent the data as a curved plot including the H_3O^+ and water points on the plot.[14]

Dronov et al.[6b,33] report a large number of data on the protonation by H_3O^+ of anions $R\bar{C}(NO_2)_2$ with different aliphatic and aromatic R groups, spanning a pK_a range from 1.36 to 7.95. The majority of the data can be fitted to a linear Brønsted plot of slope $\beta = 0.26$ although some compounds show a substantial deviation from the plot.

The α value of 0.30 for the dependence on buffer acid pK_a (pK_a^{BH}) and the β value of 0.26 for the dependence on carbon pK_a (pK_a^{CH}) are close enough to allow us to describe the bulk of the data fairly well by an equation of the form

$$\log k = \alpha \Delta pK + \text{constant} \quad (13)$$

with $\Delta pK = pK_a^{CH} - pK_a^{BH}$ and $\alpha = 0.30$. In estimating the various rate constants of Scheme II we can use the special case of eq 13 where constant = 0 (eq 14) because we are only interested

$$\log k_{rel} = \alpha \Delta pK \quad (14)$$

in *relative* rates. Thus, $k_1^{H_2O}$, $k_2^{H_2O}$, k_1^H, and k_2^H are obtained from eq 14 in the usual way; e.g., $\log k_1^{H_2O} = \alpha(pK_1^{CH} - pK^{H_2O})$ and then dividing by 300, etc., while for k_1^H and k_2^H one has to divide by 4.

---

[28] Rosenberg, S.; Silver, S. M.; Sayer, S. M.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 7986.

[29] Kluger, R.; Chin, J.; Choy, W.-W. *J. Am. Chem. Soc.* **1979**, *101*, 6976.

[30] Hupe, D. J.; Wu, D. *J. Am. Chem. Soc.* **1977**, *99*, 7653.

[31] Fox, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 1436.

[32] Bell, R. P.; Tranter, R. L. *Proc. R. Soc. London, Ser. A* **1974**, *337*, 517.

[33] Dronov, V. N.; Tselinskii, I. V.; Shokhor, I. N. *Org. React.* **1969**, *6*, 408.

In estimating k_i we assume the log k_i also follows eq 14 with ΔpK defined by eq 12 as for the carbonyl compounds. For the effective molarity we shall assume 1 M (model IIa) and 0.1 M (model IIb); the former value seems more consistent with our data for **6**.[13] As with the carbonyl compounds we will also assume a negative deviation for high pK^{XH} values. Based on the 300-fold reduction for the water reaction, we will assume a 300-, 100-, 30-, 10-, and 3-fold reduction for an average between pK_1^{XH} and pK_2^{XH} of >16, 15–15.9, 14–14.9, 13–13.9, and 12–12.9, respectively. Finally we shall assume $pK_2^{XH} - pK_1^{XH} = pK_2^{CH} - pK_1^{CH} = 3$, a somewhat smaller value than for carbonyl compounds because the stronger delocalization of the negative charge is expected to reduce the substituent effects on the pK_a values.[34]

Model III: Nitroalkanes

Brønsted plots for the deprotonation of nitroalkanes are generally linear with slopes β between 0.5 and 0.65,[24a] but mostly around 0.55. For example, $\beta = 0.57$ for the deprotonation of $PhCH_2NO_2$ with an approximately 4-fold negative deviation for water and 10-fold deviation for OH^-;[35] a range of β values from 0.52 to 0.57 was found for the deprotonation of 1-arylnitroethanes by amines;[36] in the deprotonation of ethyl nitroacetate $\beta = 0.65$, with water on the Brønsted line but OH^- deviating negatively by about 1000-fold.[37] For our purposes we shall use average values: $\beta = 0.55$, implying $\alpha = 0.45$ in the protonation direction, 2-fold deviation for protonation by H_3O^+, and a 100-fold deviation for protonation by water.

The dependence of deprotonation rates on the carbon pK_a leads to a wide range of α values,[24a] for example, from 0.94 to 1.40 for $ArCH(CH_3)NO_2$,[36] from 1.29 to 1.54 for $ArCH_2NO_2$,[36] and up to 1.89 for secondary aliphatic nitroalkanes.[38] These results imply β values in the protonation direction of 0.06 to −0.89.[39]

The fact that α for the dependence of the protonation rates on buffer acidity (pK_a^{BH}) is much different from β for the dependence on pK_a^{CH} precludes the use of eq 13 or 14. Instead log k_{rel} needs to be expressed by

$$\log k_{rel} = \beta pK_a^{CH} - \alpha pK_a^{BH} \quad (15)$$

Note that eq 14 is a special case of eq 15 for $\alpha = \beta$. Since there is such a wide spread in the β values, we shall adopt three submodels: model IIIA with $\beta = 0.1$, model IIIB with $\beta = -0.4$, and model IIIC with $\beta = -0.9$, all with $\alpha = 0.45$. In order to estimate $k_1^{H_2O}$, $k_2^{H_2O}$, k_1^{H}, and k_2^{H}, we proceed through the usual steps; e.g., for $k_2^{H_2O}$ in model IIIB we first use eq 15 ($\log k_{rel} = -0.40pK_2^{CH} - 0.45pK_a^{H_2O}$) and then divide the obtained rate constant by 100.

For k_i we assume again that the transition state pK_a values are halfway between those of the reactant and product, i.e., eq 15 becomes

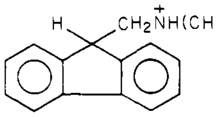
$$\log k_{rel} = 0.5\beta(pK_1^{CH} + pK_2^{CH}) - 0.5\alpha(pK_1^{XH} + pK_2^{XH}) \quad (16)$$

Our data for **9** and **10** suggest an EM of ~0.1 M which will be used for our models. It should be noted that the inequality of α and β (eq 15 and 16) introduces a restriction into the choice of the external reaction (k_e in k_i/k_e ratio) used for defining EM. According to our definition adopted earlier, this external reaction should be between a carbon whose $pK_a = pK_{\ddagger}^{CH}$ (eq 11) and an acid with a $pK_a = pK_{\ddagger}^{XH}$ (eq 10). Since for the carbonyl and the 1,1-dinitro compounds proton transfer rate constants only depend on ΔpK and not on absolute values for pK^{CH} and pK^{XH} (pK^{BH}), the external reaction only needs to have the right $\Delta pK = pK_2 - pK_1$, a requirement which can be met not only with the combinations ($pK_{\ddagger}^{XH}$, $pK_{\ddagger}^{CH}$) but also with (pK_1^{XH}, pK_1^{CH}), (pK_2^{XH}, pK_1^{XH}), or any combination for which $\Delta pK = pK_2 - pK_1$. With the nitroalkanes the rate constants depend on the actual pK^{CH} and pK^{XH} values (eq 15 and 16), and here there is only one correct choice, ($pK_{\ddagger}^{XH}$, $pK_{\ddagger}^{CH}$), for the external reaction.

Regarding the reductions in k_i for high pK^{XH} values, based on the average 100-fold deviation of the water reaction, we will assume a 10- and 3-fold reduction in k_i for an average pK^{XH} of 13.5–14.9 and 12.0–13.4, respectively. A value of 3 for $pK_2^{CH} - pK_1^{CH} = pK_2^{XH} - pK_1^{XH}$ will again be assumed as for the 1,1-dinitroalkanes.

Model IV: 9-Substituted Fluorenes

Our model for **11** is based on the following reasoning. Kelly and More O'Ferrall[18] measured the rates of CH deprotonation of the conjugate acid of 9-(dimethylaminomethyl)fluorene (**17**)



17

by *N*-methylmorpholine, *N*-methyldiethanolamine, trimethylamine, triethylamine, and OH^- in aqueous solution. These data are not very suitable for obtaining a reliable β value because the Brønsted plot is somewhat scattered owing to the inclusion of the two bulky bases triethylamine and *N*-methyldiethanolamine. However, a good linear free energy relationship (LFER) is obtained with the rate constants for the elimination of HCl from 9-(chloromethyl)fluorene[40] catalyzed by four of the same bases used for **17**, indicating that the steric effects are the same for both systems. By means of this LFER and using $\beta = 0.5$ reported for the reaction of 9-(chloromethyl)fluorene catalyzed by a large number of amines,[40] we calculated $\beta \approx 0.67$ for the deprotonation of **17**, or $\alpha \approx 0.33$ for the protonation of the carbanion.[41]

By drawing a Brønsted line of slope $\beta = 0.67$ through the trimethylamine point,[18] one can now estimate the negative deviation for the rate of deprotonation of **17** by OH^- to be ~300-fold. In the absence of any experimental data referring to the deviation by the water reaction, a fourfold deviation will be assumed just as for the 1,1-dinitroalkanes.

An estimate of $\alpha \approx 0.49$ for the deprotonation rates as a function of pK_a^{CH} is obtained as $\rho^* = 2.25$ for the rates of deprotonation of 9-substituted fluorenes by MeO^- in methanol,[42,43] divided by $\rho^* = -4.60$ for the pK_a^{CH} of 9-substituted fluorenes.[44]

In estimating the rate constants of Scheme II we use eq 15 ($\alpha = 0.33$, $\beta = 0.51$) for $k_1^{H_2O}$, $k_2^{H_2O}$, k_1^{H}, and k_2^{H}, and eq 16 for k_i. The water reactions are reduced 300-fold, the H^+-reactions 4-fold. For k_i, in the absence of experimental data, we assume an effective molarity of 0.1 M, and additional reductions of 300-, 100-, 30-, 10-, and 3-fold will be applied for an average pK^{XH} of >16, 15–15.9, 14–14.9, 13–13.9, and 12–12.9, respectively. For $pK_2^{XH} - pK_1^{XH} = pK_2^{CH} - pK_1^{CH}$, a value of 5 will be assumed; this value is larger than that for the other models, based on evidence that substituent effects on pK_a's are larger in the fluorene series.[34,44]

Model V: Substituted Benzyl Cyanides

The Brønsted plot for the detritiation of *p*-nitrobenzyl cyanide by various buffers is linear with $\beta = 0.61$, with the water and OH^- points both deviating negatively by 40-fold.[45] The deprotonation of 2,4-dinitrobenzyl cyanide in 50% Me_2SO–50% water is characterized by a Brønsted $\beta = 0.62$, with the water point deviating

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(34) See, e.g., Algrim, D.; Bares, J. E.; Branca, J. C.; Bordwell, F. G. *J. Org. Chem.* **1978**, *43*, 5024.

(35) Keeffe, J. R.; Munderloh, N. H. *J. Chem. Soc., Chem. Commun.* **1974**, 17.

(36) Bordwell, F. G.; Boyle, W. J., Jr. *J. Am. Chem. Soc.* **1972**, *94*, 3907.

(37) Barnes, D. J.; Bell, R. P. *Proc. R. Soc. London, Ser. A* **1970**, *318*, 421.

(38) Bordwell, F. G.; Bartmess, J. E.; Hautala, J. A. *J. Org. Chem.* **1978**, *43*, 3107.

(39) The α values > 1 and β values < 0 are known as the nitroalkane anomaly.[36,38]

(40) Spencer, T. A.; Kendall, M. C. R.; Reingold, I. D. *J. Am. Chem. Soc.* **1972**, *94*, 1250.

(41) Even though Spencer et al.[40] interpret their data in terms of an E1cB mechanism with rate-limiting deprotonation, the actual mechanism seems more likely to be a concerted E2 elimination.[42] However, this has no bearing on the use of the LFER for our purposes.

(42) More O'Ferrall, R. A.; Warren, P. J. *J. Chem. Soc., Chem. Commun.* **1975**, 483.

(43) Extrapolated to 25 °C[42] from data by Streitwieser, A.; Marchand, A. P.; Pudjaatmaka, A. H. *J. Am. Chem. Soc.* **1967**, *89*, 693.

(44) Bowden, K.; Cockerill, A. F.; Gilbert, J. R. *J. Chem. Soc. B* **1970**, 179.

(45) Hibbert, F.; Long, F. A. *J. Am. Chem. Soc.* **1972**, *94*, 2647.

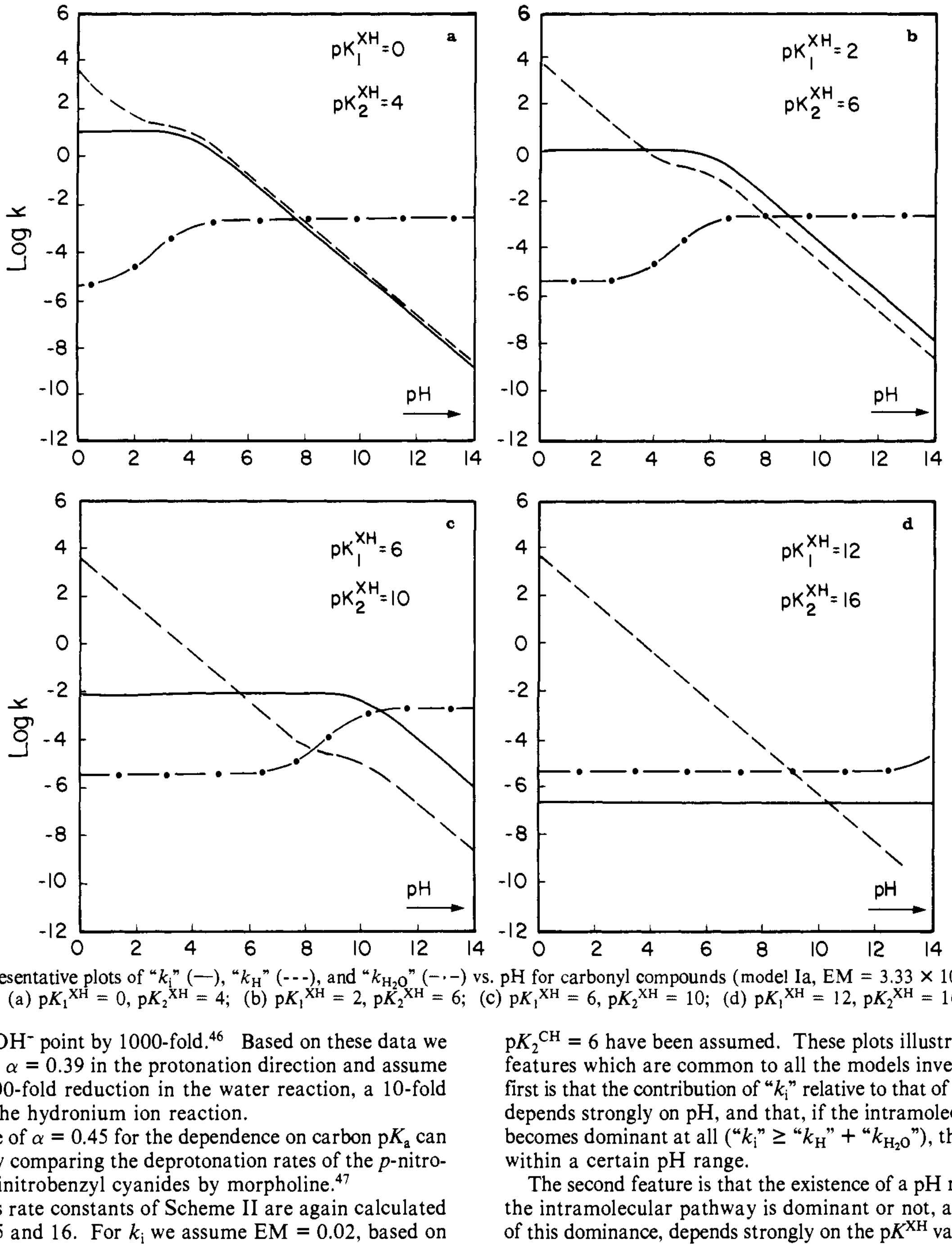

Figure 1. Representative plots of "k_i" (—), "k_H" (---), and "k_{H_2O}" (-·-) vs. pH for carbonyl compounds (model Ia, EM = 3.33 × 10^{-3} M, pK_1^{CH} = 2, pK_2^{CH} = 6). (a) pK_1^{XH} = 0, pK_2^{XH} = 4; (b) pK_1^{XH} = 2, pK_2^{XH} = 6; (c) pK_1^{XH} = 6, pK_2^{XH} = 10; (d) pK_1^{XH} = 12, pK_2^{XH} = 16.

~5-fold, the OH⁻ point by 1000-fold.[46] Based on these data we shall adopt an α = 0.39 in the protonation direction and assume an average 100-fold reduction in the water reaction, a 10-fold reduction in the hydronium ion reaction.

An estimate of α = 0.45 for the dependence on carbon pK_a can be obtained by comparing the deprotonation rates of the *p*-nitro- and the 2,4-dinitrobenzyl cyanides by morpholine.[47]

The various rate constants of Scheme II are again calculated by using eq 15 and 16. For k_i we assume EM = 0.02, based on the reaction of **8**.[16] Additional reductions of 30-, 10-, and 3-fold are assumed for average pK^{XH} values of 15–15.9, 13.5–14.9, and 12.0–13.4, respectively. For $pK_2^{XH} - pK_1^{XH} = pK_2^{CH} - pK_1^{CH}$, a value of 3 will be assumed.

Results and Discussion

General Features. Using the various models described in the Introduction and summarized in Table I, we have generated, by means of a computer, a large number of logarithmic plots of "k_i", "k_{H_2O}", and "k_H" (eq 5–7) as a function of pH. Figure 1 shows four representative examples; they refer to model Ia (carbonyl compounds, EM = 3.33 × 10^{-3} M) for which pK_1^{CH} = 2 and pK_2^{CH} = 6 have been assumed. These plots illustrate two major features which are common to all the models investigated. The first is that the contribution of "k_i" relative to that of "k_H" + "k_{H_2O}" depends strongly on pH, and that, if the intramolecular pathway becomes dominant at all ("k_i" ≥ "k_H" + "k_{H_2O}"), this occurs only within a certain pH range.

The second feature is that the existence of a pH range in which the intramolecular pathway is dominant or not, and the degree of this dominance, depends strongly on the pK^{XH} values.[49] When pK^{XH} is very low (Figure 1a: pK_1^{XH} = 0, pK_2^{XH} = 4), we have "k_i" < (≪) "k_H" + "k_{H_2O}" over the entire pH range; i.e., the intramolecular pathway never plays a significant role. When pK^{XH} is increased by 2 units (Figure 1b: pK_2^{XH} = 2, pK_2^{XH} = 6), "k_i" ≥ "k_H" + "k_{H_2O}" in the range of pH 3.6 to 8.7, with a maximum at pH 6.25. At this maximum "k_i" is six times larger than "k_H" + "k_{H_2O}". When pK^{XH} is increased by an additional 4 units (Figure 1c: pK_1^{XH} = 6, pK_2^{XH} = 10), the pH range in which "k_i" ≥ "k_H" + "k_{H_2O}" shifts upward (5.7–10.6) with a maximum at pH 8.25 at which "k_i" is 117 times larger than "k_H" + "k_{H_2O}". For very high pK^{XH} (Figure 1d: pK_1^{XH} = 12, pK_2^{XH} = 16) the situation resembles that for very low pK^{XH}; i.e., "k_i" < (≪) "k_H" + "k_{H_2O}" over the entire pH range.

These results indicate that the intramolecular pathway is relatively most favored when pK^{XH} is not too far from the midpoint of the pK^{XH} scale (7 in aqueous solution), and relatively disfavored

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(46) Bernasconi, C. F.; Hibdon, S. A., to be published.

(47) k^{Mor} ≈ 2.0 M^{-1} s^{-1} for *p*-nitrobenzyl cyanide (pK_a^{CH} = 13.4), based on a rate constant of 0.1 M^{-1} s^{-1} for detritiation[45] and by assuming a tritium kinetic isotope effect of 20.[48] k^{Mor} = 1.71 × 10^3 M^{-1} s^{-1} for 2,4-dinitrobenzyl cyanide (pK_a^{CH} = 8.07) in 50% Me_2SO–50% water.[46] This latter reaction is probably intrinsically slightly faster because of the Me_2SO cosolvent,[14b] but this rate enhancement is likely to be (partially) compensated by the slightly lower basicity of piperidine[46] and the somewhat lower temperature (20 °C instead of 25 °C) in the mixed solvent.

(48) More O'Ferrall, R. A. In ref 1b, p 201.

(49) pK^{XH} stands for both pK_1^{XH} and pK_2^{XH}; pK^{CH} stands for both pK_1^{CH} and pK_2^{CH}.

Table II. Model I: Carbonyl Compounds[a]

	$pK_1^{XH} = 0$ $pK_2^{XH} = 4$	$pK_1^{XH} = 2$ $pK_2^{XH} = 6$	$pK_1^{XH} = 4$ $pK_2^{XH} = 8$	$pK_1^{XH} = 6$ $pK_2^{XH} = 10$	$pK_1^{XH} = 8$ $pK_2^{XH} = 12$	$pK_1^{XH} = 10$ $pK_2^{XH} = 14$	$pK_1^{XH} = 12$ $pK_2^{XH} = 16$
A. $pK_1^{CH} = 0$, $pK_2^{CH} = 4$							
pH range[b]	none	3.8-8.9	4.9-9.9	6.0-10.8	7.3-11.6	9.1-11.8	none
pH range[c]	1.3-9.3	2.3-10.5	3.4-11.4	4.5-12.3	5.8-13.1	7.6-13.3	9.5-13.6
pH_{max}[b,c]	5.50	6.50	7.50	8.50	9.50	10.50	11.50
Δ_{max}[b]	−0.40	0.57	1.43	1.94	1.83	0.61	−1.12
Δ_{max}[c]	1.08	2.05	2.91	3.42	3.31	2.09	0.36
C.[d] $pK_1^{CH} = 4$, $pK_2^{CH} = 8$							
pH range[b]	none	3.5-8.4	4.5-9.5	5.4-10.4	6.5-11.2	8.4-11.6	none
pH range[c]	1.1-8.8	2.0-9.9	3.0-11.0	3.9-11.9	5.0-12.7	6.9-13.1	8.7-13.6
pH_{max}[b,c]	5.00	6.00	7.00	8.00	9.00	10.00	11.00
Δ_{max}[b]	−0.06	1.00	1.85	2.14	1.78	0.36	−1.33
Δ_{max}[c]	1.42	2.48	3.33	3.62	3.26	1.84	0.15
D.[d] $pK_1^{CH} = 5$, $pK_2^{CH} = 9$							
pH range[b]	none	3.5-8.3	4.4-9.4	5.3-10.3	6.4-11.2	8.4-11.6	none
pH range[c]	1.2-8.5	2.0-9.8	2.9-10.9	3.8-11.8	4.9--12.7	6.9-13.1	8.5-13.6
pH_{max}[b,c]	5.00	6.00	7.00	8.00	9.00	10.00	11.00
Δ_{max}[b]	0.02	1.11	1.92	2.14	1.72	0.29	−1.39
Δ_{max}[c]	1.50	2.59	3.40	3.26	3.20	1.77	0.09
E.[d] $pK_1^{CH} = 6$, $pK_2^{CH} = 10$							
pH range[b]	2.8-6.4	3.3-8.2	4.3-9.3	5.2-10.3	6.2-11.2	8.4-11.6	none
pH range[c]	1.3-7.9	1.8-9.7	2.8-10.8	3.7-11.8	4.7-12.7	6.9-13.1	8.3-13.6
pH_{max}[b,c]	4.75	5.75	6.75	7.75	8.75	9.75	10.75
Δ_{max}[c]	0.10	1.21	1.99	2.14	1.66	0.21	−1.44
Δ_{max}	1.58	2.69	3.47	3.62	3.14	1.69	0.04
G.[d] $pK_1^{CH} = 10$, $pK_2^{CH} = 14$							
pH range[b]	2.4-6.1	3.1-7.6	3.9-8.9	4.8-10.0	5.7-11.1	none	none
pH range[c]	0.9-7.6	1.6-9.1	2.4-10.4	3.3-11.5	4.2-12.6	5.8-13.1	none
pH_{max}[b,c]	4.50	5.50	6.50	7.50	8.50	9.50	10.50
Δ_{max}[b]	0.42	1.52	2.06	1.98	1.30	−0.12	−1.66
Δ_{max}[c]	1.90	3.00	3.54	3.46	2.78	1.36	−0.18
H.[d] $pK_1^{CH} = 12$, $pK_2^{CH} = 16$							
pH range[b]	2.3-5.9	3.0-7.3	3.8-8.7	4.6-9.8	5.5-11.0	none	none
pH range[c]	0.8-7.4	1.5-8.8	2.3-10.1	3.1-11.3	4.0-12.5	5.4-13.1	none
pH_{max}[b,c]	4.25	5.25	6.25	7.25	8.25	9.25	10.25
Δ_{max}[b]	0.57	1.61	2.03	1.81	1.09	−0.29	−1.77
Δ_{max}[c]	2.05	3.09	3.51	3.29	2.57	1.19	−0.29

[a] "pH range" indicates the region of intramolecular dominance, "pH_{max}" is the pH where intramolecular dominance is at a maximum, "Δ_{max}" is defined as log "k_i"/("k_H" + "k_{H_2O}") at pH_{max}. [b] EM = 3.3×10^{-3} M. [c] EM = 0.1 M. [d] Series B ($pK_1^{CH} = 2$, $pK_2^{CH} = 6$), F ($pK_1^{CH} = 8$, $pK_2^{CH} = 12$) and I ($pK_1^{CH} = 14$, $pK_2^{CH} = 18$) are included in Table S1.[50]

Table III. Model II: 1,1-Dinitroalkanes[a]

	$pK_1^{XH} = 0$ $pK_2^{XH} = 3$	$pK_1^{XH} = 2$ $pK_2^{XH} = 5$	$pK_1^{XH} = 4$ $pK_2^{XH} = 7$	$pK_1^{XH} = 5.5$ $pK_2^{XH} = 8.5$	$pK_1^{XH} = 7$ $pK_2^{XH} = 10$	$pK_1^{XH} = 9$ $pK_2^{XH} = 12$	$pK_1^{XH} = 11$ $pK_2^{XH} = 14$	$pK_1^{XH} = 13$ $pK_2^{XH} = 16$
pH range[b]	0.2-7.4	0.6-8.8	1.3-10.2	1.6-11.3	2.2-12.3	2.9-13.7	3.7-14.3	5.5-14.0
pH range[c]	1.2-6.4	1.6-7.8	2.3-9.2	2.6-10.3	3.2-11.3	3.9-12.7	4.7-13.3	none
pH_{max}[b,c]	3.75	4.75	5.75	6.50	7.25	8.25	9.25	10.25
Δ_{max}[b]	2.16	3.40	3.94	3.74	3.35	2.76	1.68	0.08
Δ_{max}[c]	1.16	2.40	2.94	2.74	2.35	1.76	0.68	−0.92

[a] See footnote *a* in Table II. [b] Effective molarity = 1 M. [c] Effective molarity = 0.1 M.

when pK^{XH} is very high or very low. This is one of the most important qualitative conclusions of the present study. It is general; as shown below it not only applies to carbonyl compounds irrespective of pK^{CH}, but to the other classes of compounds as well.

Plots like the ones shown in Figure 1 have been used to obtain the three pieces of relevant information discussed above: the pH range within which "k_i" ≥ "k_H" + "k_{H_2O}", pH_{max} which is the pH at which the ratio "k_i"/("k_H" + "k_{H_2O}") is at a maximum, and the value of this maximum (in logarithmic form Δ_{max} = log "k_i"/("k_H" + "k_{H_2O}")). Table II summarizes this information for carbonyl compounds as functions of pK^{XH} for six sets of pK^{CH} values while Table S1[50] is an expanded version of Table II. Tables III–VI contain similar information for the other compounds. It is to be noted that for these other compounds calculations were carried out only for one set of pK^{CH} values since the *relative* magnitudes of "k_i", "k_H", and "k_{H_2O}" are independent of pK^{CH}. This is so (a) because the pH dependence of "k_i", "k_H", and "k_{H_2O}" is a function of pK^{XH} rather than pK^{CH} and (b) because the *relative* values of k_1^H, k_2^H, $k_1^{H_2O}$, $k_2^{H_2O}$, and k_i are independent of pK^{CH}, as shown for $k_i/k_1^{H_2O}$ and k_i/k_2^H calculated as eq 17 and 18, respectively.

$$\log k_i/k_1^{H_2O} = 0.5\beta(pK_2^{CH} - pK_1^{CH}) + \alpha pK_a^{H_2O} - 0.5\alpha(pK_1^{XH} + pK_2^{XH}) \quad (17)$$

$$\log k_i/k_2^{H} = -0.5\beta(pK_2^{CH} - pK_1^{CH}) + \alpha pK_a^{H_3O^+} - 0.5\alpha(pK_1^{XH} + pK_2^{XH}) \quad (18)$$

Since $pK_2^{CH} - pK_1^{CH}$ is constant, $k_i/k_1^{H_2O}$ and k_i/k_2^H are indeed independent of pK^{CH}, and the same can be shown to be true for $k_i/k_2^{H_2O}$ and k_i/k_1^H.

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(50) See paragraph concerning supplementary material at the end of this paper.

Table IV. Model III: Nitroalkanes[a]

	$pK_1^{XH} = 0$ $pK_2^{XH} = 3$	$pK_1^{XH} = 2$ $pK_2^{XH} = 5$	$pK_1^{XH} = 4$ $pK_2^{XH} = 7$	$pK_1^{XH} = 5.5$ $pK_2^{XH} = 8.5$	$pK_1^{XH} = 7$ $pK_2^{XH} = 10$	$pK_1^{XH} = 9$ $pK_2^{XH} = 12$	$pK_1^{XH} = 11$ $pK_2^{XH} = 14$	$pK_1^{XH} = 13$ $pK_2^{XH} = 16$
A. $\alpha = 0.45, \beta = 0.10$								
pH range	2.3-8.4	3.1-9.5	3.9-10.4	4.7-11.3	5.3-12.2	6.2-13.3	7.5-13.6	none
pH$_{max}$	5.25	6.25	7.25	8.00	8.75	9.75	10.75	11.75
Δ_{max}	0.69	1.77	2.68	2.91	2.57	1.76	0.39	−1.03
B. $\alpha = 0.45, \beta = -0.40$								
pH range	3.0-9.2	3.9-10.3	4.7-11.3	5.4-12.3	6.2-13.0	6.9-14.0	none	none
pH$_{max}$	6.00	7.00	8.00	8.75	9.50	10.50	11.50	12.50
Δ_{max}	1.43	2.42	2.83	2.50	2.90	1.02	−0.36	−1.78
C. $\alpha = 0.45, \beta = -0.90$								
pH range	3.9-9.8	4.6-11.0	5.5-12.1	6.3-12.9	6.9-13.7	7.8-14.0	none	none
pH$_{max}$	6.75	7.75	8.75	9.50	10.25	11.25	12.25	13.25
Δ_{max}	2.12	2.75	2.42	1.82	1.16	0.27	−1.11	−2.53

[a] See footnote *a* in Table II.

Table V. Model IV: 9-Substituted Fluorenes[a]

	$pK_1^{XH} = -1$ $pK_2^{XH} = 4$	$pK_1^{XH} = 1$ $pK_2^{XH} = 6$	$pK_1^{XH} = 3$ $pK_2^{XH} = 8$	$pK_1^{XH} = 4.5$ $pK_2^{XH} = 9.5$	$pK_1^{XH} = 6$ $pK_2^{XH} = 11$	$pK_1^{XH} = 8$ $pK_2^{XH} = 13$	$pK_1^{XH} = 10$ $pK_2^{XH} = 15$	$pK_1^{XH} = 12$ $pK_2^{XH} = 17$
pH range	0.5-7.1	1.2-8.3	1.8-9.7	2.2-10.7	2.7-11.7	3.4-12.9	4.4-14.0	none
pH$_{max}$	3.75	4.75	5.75	6.50	7.25	8.25	9.25	10.25
Δ_{max}	1.25	2.55	3.53	3.67	3.36	2.74	1.60	−0.06

[a] See footnote *a* in Table II.

Table VI. Model V: Benzyl Cyanides[a]

	$pK_1^{XH} = 0$ $pK_2^{XH} = 3$	$pK_1^{XH} = 2$ $pK_2^{XH} = 5$	$pK_1^{XH} = 4$ $pK_2^{XH} = 7$	$pK_1^{XH} = 5.5$ $pK_2^{XH} = 8.5$	$pK_1^{XH} = 7$ $pK_2^{XH} = 10$	$pK_1^{XH} = 9$ $pK_2^{XH} = 12$	$pK_1^{XH} = 11$ $pK_2^{XH} = 14$	$pK_1^{XH} = 13$ $pK_2^{XH} = 16$
pH range	1.0-6.7	1.8-8.1	2.5-9.2	3.1-10.0	3.7-11.0	4.5-12.2	5.8-12.6	none
pH$_{max}$	3.75	4.75	5.75	6.50	7.25	8.25	9.25	10.25
Δ_{max}	0.75	1.93	2.78	2.82	2.41	1.67	0.42	−0.88

[a] See footnote *a* in Table II.

The fact that the relative values of the rate constants, and hence pH range, pH$_{max}$, and Δ_{max} are independent of pK^{CH} is a consequence of log k being *linearly* dependent on pK^{CH} (eq 14–16). Conversely, the nonlinear dependence of log k on pK^{CH} for the carbonyl compounds (eq 8) is responsible for the fact that pH range, pH$_{max}$, and Δ_{max} do depend on pK^{CH} as discussed in more detail below.

We now discuss the various classes of compounds in detail.

Model I: Carbonyl Compounds. Inspection of Table II reveals six main features. (1) As pK^{XH} increases, pH range and pH$_{max}$ shift toward higher pH values. E.g., for series A, model Ib, the shift is from pH range 1.3–9.3 (pH_{max} = 5.50) for pK_1^{XH} = 0, pK_2^{XH} = 4 to pH range 9.5–13.6 (pH$_{max}$ = 11.50) for pK_1^{XH} = 12, pK_2^{XH} = 16, corresponding to an overall shift in pH$_{max}$ of six units.

(2) Δ_{max} is relatively small for very low and very high pK^{XH} values but large for intermediate pK^{XH} values. Figure 2 shows how Δ_{max} depends on pK^{XH} for the representative cases A, D, G, and I.

(3) pH range and pH$_{max}$ are shifted toward lower values as pK^{CH} increases. E.g., for pK_1^{XH} = 4, pK_2^{XH} = 8, model Ib, the shift is from pH range 3.4–11.4 (pH$_{max}$ = 7.5) when pK_1^{CH} = 0, pK_2^{CH} = 4, to pH range 2.3–10.1 (pH$_{max}$ = 6.25) when pK_1^{CH} = 12, pK_2^{CH} = 16. This corresponds to a total shift of 1.25 units which is in the opposite direction and much smaller than the shift of 6 units which occurs when pK^{XH} is changed by the same amount.

(4) Δ_{max} tends to increase with increasing pK^{CH} when pK^{XH} is low and to decrease with increasing pK^{CH} when pK^{XH} is high. This changes the shape of the Δ_{max} vs. pK^{XH} plots in the direction of moving the maximum of Δ_{max} ((Δ_{max})$_{max}$) toward lower pK^{XH} values (Figure 2, A → D → G → I).

(5) pH range, pH$_{max}$, and (Δ_{max})$_{max}$ seem all slightly shifted toward the alkaline region. This is best appreciated for the "symmetrical" situation where the average pK values are 7 (pK_1^{CH} = pK_1^{XH} = 5, pK_2^{CH} = pK_2^{XH} = 9, series D in Table II and Figure 2). One expects a symmetry in pH$_{max}$ and Δ_{max} with respect to the center of the pK^{XH} scale, with (Δ_{max})$_{max}$ close to pH 7.[51] However, the data show that this maximum occurs at an average pK^{XH} between 7.5 and 8. This shift into the alkaline region is a consequence of applying larger reductions to $k_1^{H_2O}$ and $k_2^{H_2O}$ than to k_1^{H} and k_2^{H}.

(6) As EM is increased, the pH range increases at both ends by an amount which is equivalent to the increase in EM, i.e., 1.48 log units for a 30-fold increase in EM.

It is helpful to develop a qualitative understanding for some of the above conclusions, in particular, for the fact that the pH range, pH$_{max}$, and Δ_{max} depend strongly on pK^{XH} but only weakly on pK^{CH}.

For the intramolecular pathway to be significant, two conflicting requirements have to be met: pK^{XH} should be high so that the reactant is present in the reactive form ^{z}HX–C^{-} over as wide a pH range as possible ("k_i" = k_i when [H$^+$] ≫ K_2^{XH}, eq 7), but a low pK^{XH} is desirable so that k_i becomes large. E.g., when pK^{XH} is very low, k_i will indeed be quite large but the ^{z}HX–C^{-} form can only be dominant at very low pH. At such low pH the "k_H" pathway should still dominate because the hydrogen ion concentration is large enough to make "k_H" > "k_i" since even with a low pK^{XH} one still has k_1^{H} ≫ k_i. As the pH is increased, the reduction in "k_H" is soon being matched by a similar reduction in the [^{z}HX–C^{-}] and with it a reduction in "k_i" so that "k_i" cannot gain over "k_H" by an increase in pH.

When pK^{XH} is intermediate, k_i is reduced, but this is overcompensated by the fact that the ^{z}HX–C^{-} form dominates up to pH ∼ pK_2^{XH} and hence "k_i" = k_i up to pH = pK_2^{XH} (Figure 1c). This overcompensation comes about because the decrease in "k_H" which can be achieved by increasing the pH is larger ($-\partial$ log "k_H"$/\partial pH = 1$) than the reduction in k_i brought about by the increased pK^{XH} ($-\partial \log k_i/\partial pK_2^{XH} < 1$).

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(51) Calculations show it is closer to 6.8. The reason for the nonperfect symmetry is that the plot of log k vs. ΔpK is curved.

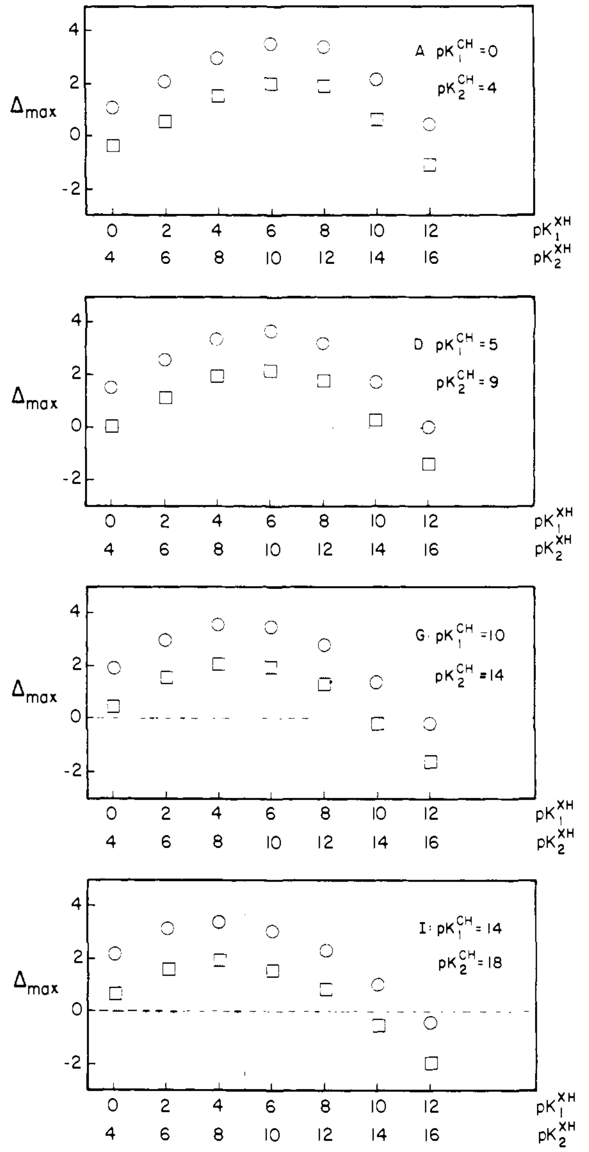

Figure 2. Δ_{max} vs. pK^{XH} for carbonyl compounds: (□) model Ia (EM = 3.33×10^{-3} M); (○) model Ib (EM = 0.1 M). Series A, D, G data from Table II; series I data from Table S1.

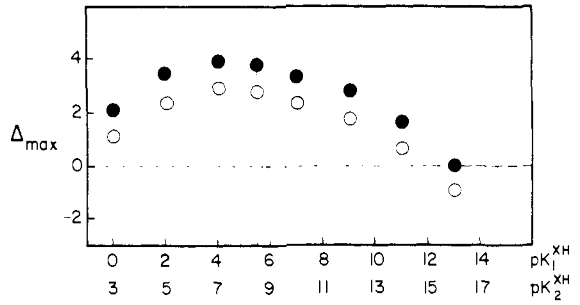

Figure 3. Δ_{max} vs. pK^{XH} for 1,1-dinitroalkanes: (●) model Ia (EM = 1 M); (○) model Ib (EM = 0.1 M).

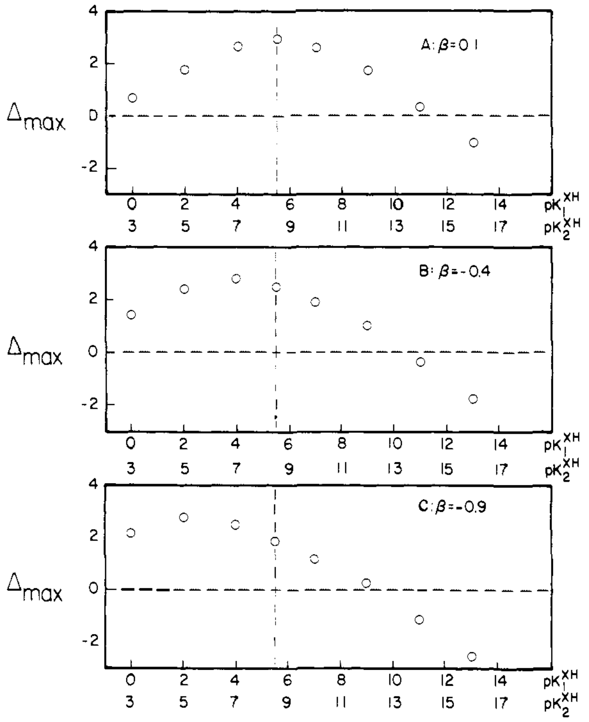

Figure 4. Δ_{max} vs. pK^{XH} for nitroalkanes.

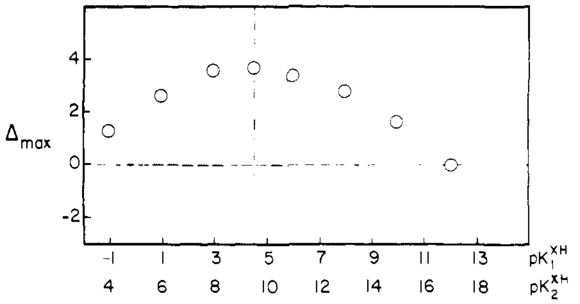

Figure 5. Δ_{max} vs. pK^{XH} for 9-substituted fluorenes.

When pK^{XH} is very high, the $^zHX–C^-$ form will be dominant over most of the pH range but k_i is too small to compete favorably with "k_{H_2O}".

Why do pH range, pH$_{max}$, and Δ_{max} depend only little on pK^{CH}? This is because a change in pK^{CH} changes all the rate constants by comparable amounts (in contrast to a change in pK^{XH} which only affects k_i). In fact, if log k depended linearly on pK^{CH}, the change in all the rate constants would be identical and there would be no dependence on pK^{CH} at all as was shown to be the case for models II–V. Because of the nonlinear dependence of log k on pK^{CH} (eq 8), the changes in the various rate constants are not exactly the same: $k_1^{H_2O}$ and $k_2^{H_2O}$ change somewhat more than k_i, and k_i changes somewhat more than k_1^{H} and k_2^{H}. But since the curvature is not very strong, the effect of changing pK^{CH} remains quite small.

Models II–V. The dependence of pH range, pH$_{max}$, and Δ_{max} on pK^{XH} is qualitatively similar to that for the carbonyl compounds. E.g., in all cases pH range and pH$_{max}$ are shifted toward higher values as pK^{XH} increases as seen in Tables III–VI. Figures 3–5 show how Δ_{max} depends on pK^{XH} for the 1,1-dinitroalkanes, for the nitroalkanes, and the 9-substituted fluorenes, respectively. Figure S1[50] shows similar data for the benzyl cyanides.

Δ_{max} is again going through a maximum, usually at pK^{XH} values close to the midpoint, but the plots of Δ_{max} vs. pK^{XH} for the various models differ in some important details. These differences arise from an interplay of various parameters, in particular, α, β, pK_2^{CH} – pK_1^{CH} = pK_2^{XH} – pK_1^{XH}, EM, and the amount of reduction assumed for the various rate constants.

In order to acquire a better understanding of how each parameter affects the various quantities of interest, computer plots were generated in which some of these parameters were systematically varied one at a time. Thus the consequences of changing α, β, and pK_2^{CH} – pK_1^{CH} = pK_2^{XH} – pK_1^{XH} were investigated, all for EM = 1 M; in order to avoid distortions of these effects which can arise from the different reductions applied to the rate constants in models II–V, no reductions were applied to any of the rate constants in these "hypothetical models". We also studied the influence of changing the solvent from water to 50% Me$_2$SO–50% water since this latter solvent was used in several experimental studies.

Table VII. "Hypothetical Models" Showing Effect of α and β[a]

	$pK_1^{XH} = 0$ $pK_2^{XH} = 3$	$pK_1^{XH} = 2$ $pK_2^{XH} = 5$	$pK_1^{XH} = 4$ $pK_2^{XH} = 7$	$pK_1^{XH} = 5.5$ $pK_2^{XH} = 8.5$	$pK_1^{XH} = 7$ $pK_2^{XH} = 10$	$pK_1^{XH} = 9$ $pK_2^{XH} = 12$	$pK_1^{XH} = 11$ $pK_2^{XH} = 14$
A. $\alpha = 0.2, \beta = 0.2$							
pH range	0.6-3.8	0.9-5.3	1.3-6.8	1.6-7.8	none	none	none
pH_{max}	2.00	3.00	4.00	4.75	5.50	6.50	7.50
Δ_{max}	1.07	0.97	0.60	0.31	0.01	−0.39	−0.79
B. $\alpha = 0.5, \beta = 0.2$							
pH range	1.6-8.0	2.5-8.9	3.4-9.9	4.3-10.7	5.0-11.4	6.0-12.4	6.9-12.8
pH_{max}	4.75	5.75	6.75	7.50	8.25	9.25	10.25
Δ_{max}	1.08	2.04	2.73	2.66	2.13	1.17	0.18
C. $\alpha = 0.8, \beta = 0.2$							
pH range	3.2-12.0	4.2-12.6	5.6-12.9	6.8-13.2	8.1-13.5	9.6-14.0	11.2-14.1
pH_{max}	7.25	8.25	9.25	10.00	10.75	11.75	12.75
Δ_{max}	0.11	0.51	0.91	1.20	1.48	1.63	0.95
D. $\alpha = 0.2, \beta = 0.5$							
pH range	0.2-3.3	0.5-4.8	0.9-6.4	1.2-7.6	1.5-8.7	1.9-9.3	none
pH_{max}	1.75	2.75	3.75	4.50	5.25	6.25	7.25
Δ_{max}	1.11	1.34	1.05	0.76	0.46	0.06	−0.34
E. $\alpha = 0.5, \beta = 0.5$							
pH range	1.0-7.5	2.0-8.5	3.0-9.5	3.8-10.2	4.5-11.0	5.5-12.0	6.5-13.0
pH_{max}	4.25	5.25	6.25	7.00	7.75	8.75	9.75
Δ_{max}	0.63	1.61	2.49	2.78	2.49	1.61	0.63
F. $\alpha = 0.8, \beta = 0.5$							
pH range	none	4.7-12.1	5.3-12.5	6.4-12.8	7.6-13.1	9.2-13.5	10.7-13.8
pH_{max}	6.75	7.75	8.75	9.50	10.25	11.25	12.25
Δ_{max}	−0.34	0.06	0.46	0.76	1.05	1.34	1.11
G. $\alpha = 0.2, \beta = 0.8$							
pH range	−0.1-2.8	0.0-4.4	0.5-5.9	0.8-7.2	1.1-8.4	1.4-9.8	2.0-10.8
pH_{max}	1.25	2.25	3.25	4.00	4.75	5.75	6.75
Δ_{max}	0.95	1.63	1.48	1.20	0.91	0.51	0.11
H. $\alpha = 0.5, \beta = 0.8$							
pH range	1.2-7.1	1.6-8.0	2.6-9.0	3.3-9.7	4.1-10.6	5.1-11.5	6.0-12.4
pH_{max}	3.75	4.75	5.75	6.50	7.25	8.25	9.25
Δ_{max}	0.18	1.17	2.13	2.66	2.73	2.04	1.08
I. $\alpha = 0.8, \beta = 0.8$							
pH range	none	none	none	6.2-12.4	7.2-12.7	8.7-13.9	10.2-13.4
pH_{max}	6.50	7.50	8.50	9.25	10.00	11.00	12.00
Δ_{max}	−0.79	−0.39	0.01	0.31	0.60	0.97	1.07

[a] See footnote a in Table II.

Table VIII. "Hypothetical Model" Showing Effect of $pK_2^{XH} - pK_1^{XH}$[a]

	$pK_1^{XH} = -1$ $pK_2^{XH} = 4$	$pK_1^{XH} = 1$ $pK_2^{XH} = 6$	$pK_1^{XH} = 3$ $pK_2^{XH} = 8$	$pK_1^{XH} = 4.5$ $pK_2^{XH} = 9.5$	$pK_1^{XH} = 6$ $pK_2^{XH} = 11$	$pK_1^{XH} = 8$ $pK_2^{XH} = 13$	$pK_1^{XH} = 10$ $pK_2^{XH} = 15$
DD. $\alpha = 0.2, \beta = 0.5$							
pH range	−0.2-3.8	0.1-5.5	0.4-7.0	0.9-8.1	1.1-9.2	1.4-10.7	1.9-11.7
pH_{max}	1.75	2.75	3.75	4.50	5.25	6.25	7.25
Δ_{max}	1.61	1.84	1.55	1.26	0.96	0.56	0.16
EE. $\alpha = 0.5, \beta = 0.5$							
pH range	0.7-7.9	1.6-9.0	2.5-10.0	3.3-10.7	4.0-11.5	5.0-12.4	6.1-13.3
pH_{max}	4.25	5.25	6.25	7.00	7.75	8.75	9.75
Δ_{max}	1.13	2.11	2.99	3.28	2.99	2.11	1.13
FF. $\alpha = 0.8, \beta = 0.5$							
pH range	2.3-12.1	3.3-12.6	4.8-12.9	5.9-13.1	7.0-13.6	8.5-13.9	10.20-14.2
pH_{max}	6.75	7.75	8.75	9.50	10.25	11.25	12.25
Δ_{max}	0.16	0.56	0.96	1.26	1.55	1.84	1.61
BB. $\alpha = 0.5, \beta = 0.2$							
pH range	1.3-8.7	2.3-9.7	3.3-10.7	4.0-11.5	4.9-12.2	5.9-13.2	6.9-13.9
pH_{max}	5.00	6.00	7.00	7.75	8.50	9.50	10.50
Δ_{max}	1.87	2.80	3.28	2.99	2.35	1.38	0.38
HH. $\alpha = 0.5, \beta = 0.8$							
pH range	0.1-7.1	0.8-8.1	1.8-9.1	2.5-10.0	3.3-10.7	4.3-11.7	5.3-12.7
pH_{max}	3.50	4.50	2.35	2.99	7.00	8.00	9.00
Δ_{max}	0.38	1.38	2.35	2.99	3.28	2.80	1.87

[a] See footnote a in Table II.

Table VII and Figure 6 show the effects resulting from changing α and β for the situation where $pK_2^{XH} - pK_1^{XH} = 3$. Table VIII summarizes similar data for $pK_2^{XH} - pK_1^{XH} = 5$ while Table IX lists data for $pK_2^{XH} - pK_1^{XH} = 3$ in 50% Me_2SO–50% water. The following conclusions can be drawn.

(1) An increase in α shifts pH range and pH_{max} to higher values and shifts $(\Delta_{max})_{max}$ toward higher pK^{XH} values. These effects are quite large; e.g., in the series D, E, F of Table VII, $(\Delta_{max})_{max}$

Table IX. "Hypothetical Model" Showing Effect of 50% Me_2SO-50% Water[a]

	$pK_1^{XH} = 0$ $pK_2^{XH} = 3$	$pK_1^{XH} = 2$ $pK_2^{XH} = 5$	$pK_1^{XH} = 4$ $pK_2^{XH} = 7$	$pK_1^{XH} = 6.5$ $pK_2^{XH} = 9.5$	$pK_1^{XH} = 9$ $pK_2^{XH} = 12$	$pK_1^{XH} = 11$ $pK_2^{XH} = 14$	$pK_1^{XH} = 13$ $pK_2^{XH} = 16$
DDD. $\alpha = 0.2, \beta = 0.5$, in 50% Me_2SO-50% H_2O							
pH range	0.2-3.9	0.5-5.7	0.8-7.2	1.3-9.1	1.8-10.9	2.3-12.2	none
pH_{max}	2.00	3.00	4.00	5.25	6.50	7.50	8.50
Δ_{max}	1.38	1.89	1.68	1.20	0.70	0.30	-0.10
EEE. $\alpha = 0.5, \beta = 0.5$, in 50% Me_2SO-50% H_2O							
pH range	0.9-8.7	1.9-9.7	2.9-10.6	4.1-11.9	5.4-13.1	6.3-14.1	7.3-15.1
pH_{max}	4.75	5.75	6.75	8.00	9.25	10.25	11.25
Δ_{max}	0.78	1.78	2.73	3.43	2.73	1.78	0.78
FFF. $\alpha = 0.8, \beta = 0.5$, in 50% Me_2SO-50% H_2O							
pH range	none	3.8-13.7	5.1-14.2	6.9-14.7	8.8-15.2	10.3-13.5	12.1-15.8
pH_{max}	7.50	8.50	9.20	10.75	12.00	13.00	14.00
Δ_{max}	-0.10	0.30	0.70	1.20	1.68	1.89	1.38

[a] See footnote *a* in Table II.

occurs at $pK_1^{XH} \approx 2$, $pK_2^{XH} \approx 5$ for $\alpha = 0.2$; at $pK_1^{XH} = 5.5$, $pK_2^{XH} = 8.5$ for $\alpha = 0.5$; and at $pK_1^{XH} \approx 9$, $pK_2^{XH} \approx 12$ for $\alpha = 0.8$. This corresponds to a total shift in pK^{XH} of ≈ 7 units.

(2) The value of $(\Delta_{max})_{max}$ depends strongly on α; it is highest for $\alpha = 0.5$ (e.g., 2.88 when $\beta = 0.5$) but much lower when α is close to zero or close to 1 (e.g., 1.34 for $\alpha = 0.2$ or 0.8 when $\beta = 0.5$).[52]

(3) The effect of increasing β is to slightly shift pH range and pH_{max} to *lower* values (opposite direction to change induced by α) and to shift $(\Delta_{max})_{max}$ toward higher pK^{XH} values (same direction as change induced by α). The effects induced by changing β are significantly smaller than those induced by changing α. E.g., in the series B, E, H of Table VII, $(\Delta_{max})_{max}$ occurs at $pK_1^{XH} \approx 4$, $pK_2^{XH} \approx 7$ for $\beta = 0.2$; at $pK_1^{XH} = 5.5$, $pK_2^{XH} = 8.5$ for $\beta = 0.5$; and at $pK_1^{XH} \approx 7$, $pK_2^{XH} \approx 10$ for $\beta = 0.8$. This corresponds to a total shift in pK^{XH} of only ≈ 3 units while a similar change in α shifts pK^{XH} by ≈ 7 units (see above).

(4) In contrast to its dependence on α, the value of $(\Delta_{max})_{max}$ is little affected by changes in β. E.g., in series B, E, H $(\Delta_{max})_{max} = 2.73$, 2.78, and 2.73 for $\beta = 0.2$, 0.5, and 0.8, respectively.[53]

(5) When the difference $pK_2^{XH} - pK_1^{XH} = pK_2^{CH} - pK_1^{CH}$ is increased from 3 (series B, D, E, F, H, Table VII) to 5 (series BB, DD, EE, FF, HH, Table VIII), Δ_{max} increases significantly, indicating that the intramolecular pathway becomes more competitive with the external pathways. E.g., when the average of the pK^{XH} values is 7, the enhancement in Δ_{max} is 0.50 log unit with $\beta = 0.5$, 0.33 log unit with $\beta = 0.2$ or 0.8.

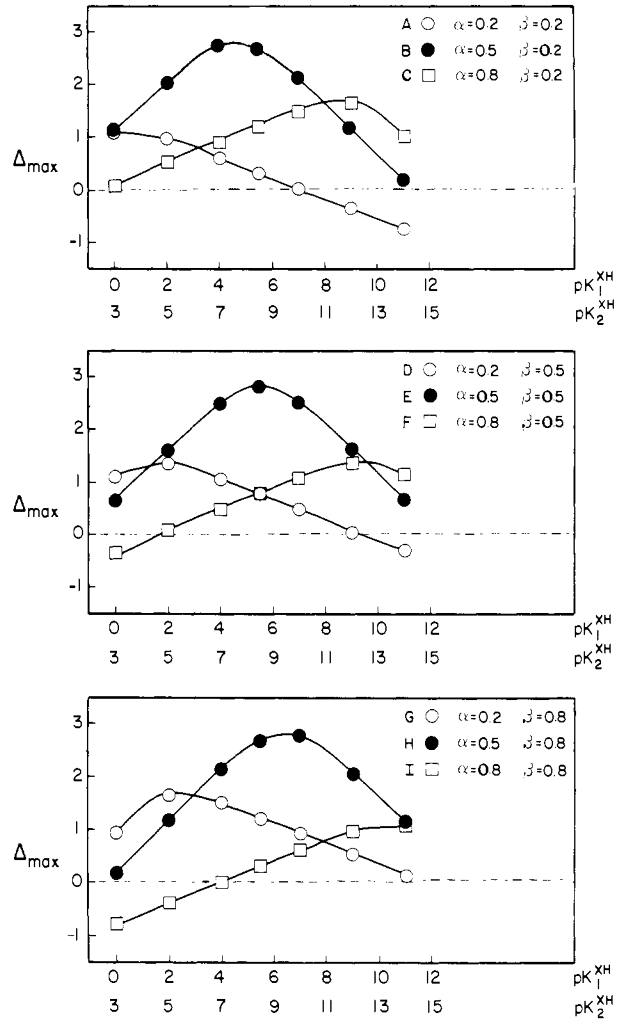

Figure 6. Δ_{max} vs. pK^{XH} for "hypothetical models".

(6) A comparison of the data summarized in Table IX with those in series D, E, and F of Table VII shows that the change to 50% Me_2SO-50% water shifts pH range and pH_{max} to slightly higher values and enhances Δ_{max}. The enhancement in Δ_{max} is largest near $(\Delta_{max})_{max}$ and can amount to as much as 0.65 log unit (e.g., for $\alpha = \beta = 0.5$, $pK_1^{XH} = 6.5$, $pK_2^{XH} = 9.5$). These effects are a consequence of an increase of $pK_a^{H_2O}$ to 17.44[54] which leads to a decrease in $k_1^{H_2O}$ and $k_2^{H_2O}$.

The above conclusions allow us now to make the following comments about the data generated for models II–V.

(a) The fact that $(\Delta_{max})_{max}$ for the 1,1-dinitroalkanes is found for $pK_1^{XH} \approx 4$, $pK_2^{XH} \approx 7$, i.e., substantially below the midpoint

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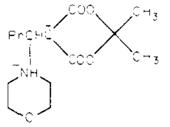
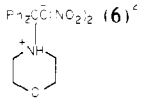
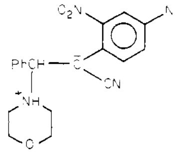
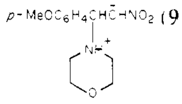
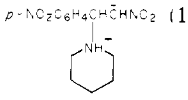
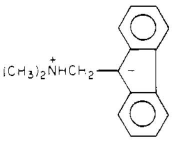
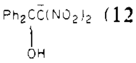
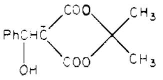
(52) Conclusions 1 and 2 can be understood qualitatively as follows. When α is very small, the rate constants depend little on pK_a^{BH} (pK^{XH}); in particular, $k_1^{H_2O}$ and $k_2^{H_2O}$ are not much smaller than k_1^H and k_2^H ($\log k_1^H/k_1^{H_2O} = \log k_2^H/k_2^{H_2O} = 14\alpha = 2.8$ for $\alpha = 0.2$). As a consequence the water pathways are the dominant external pathways over most of the pH range (at pH ≥ 2 for $\alpha = 0.2$, $\beta = 0.5$). Since k_i is not much larger than $k_1^{H_2O}$ or $k_2^{H_2O}$, Δ_{max} can never become very large but is relatively largest for low pK^{XH} (relatively largest k_i). This explains why $(\Delta_{max})_{max}$ is at low pK^{XH}. When α is very large the rate constants depend strongly on pK_a^{BH} (pK^{XH}) and k^H is very much larger than k^{H_2O} ($\log k_1^H/k_1^{H_2O} = \log k_2^H/k_2^{H_2O} = 14\alpha = 11.2$ for $\alpha = 0.8$). This makes "k_H" dominant over "k_{H_2O}" over most of the pH range (at pH ≤ 12 for $\alpha = 0.2$, $\beta = 0.5$). Since k_i is substantially smaller than k^H, "k_i" does not compete very well with "k_H" and Δ_{max} can again never be very large; it is relatively largest for high pK^{XH} because for high pK^{XH} "k_i" drops off only at high pH where "k_H" is very low. When α is intermediate the dependence of the rate constants on pK_a^{BH} (pK^{XH}) is intermediate ($\log k_1^H/k_1^{H_2O} = \log k_2^H/k_2^{H_2O} = 14\alpha = 7$ for $\alpha = 0.5$). "k_H" is dominant at pH ≤ 7.0, "k_{H_2O}" at pH ≥ 7.0 (for $\beta = 0.5$). Since "k_i" is significantly larger than k^{H_2O}, "k_i" competes quite well with "k_{H_2O}"; it also competes relatively well with "k_H" when pK^{XH} is in the midrange because the competition can occur at pH values in the midrange where "k_H" is much reduced.

(53) Conclusions 3 and 4 can be rationalized in the following terms. The relative magnitude of k_i compared to the other rate constants is given by equations like (17) and (18). For the case where $\alpha = 0.5$, the situation is then as follows. When pK^{XH} is low, Δ_{max} occurs at pH values where "k_i" competes mainly with the k_2^H pathway (e.g., for $pK_1^{XH} = 0$, $pK_2^{XH} = 3$, $pH_{max} = 4.75$ when $\beta = 0.2$; see Table VII, series B). As is apparent from eq 18, $\log k_i/k_2^H$ decreases with increasing β and thus Δ_{max} decreases as observed. When pK^{XH} is high, Δ_{max} occurs at pH values where "k_i" competes mainly with the $k_1^{H_2O}$ pathway (e.g., for $pK_1^{XH} = 11$, $pK_2^{XH} = 14$, $pH_{max} = 10.25$ when $\beta = 0.2$). According to eq 17, $\log k_i/k_1^{H_2O}$ increases with increasing β which leads to an increase in Δ_{max}, again as observed.

(54) Based on $pK_w \approx 16$ and $[H_2O] = 27.6$, $pK_a^{H_3O^+} = -1.44$.

Table X. Comparison between Theoretical Predictions and Experimental Results

compound	pK_1^{CH} or $pK_2^{CH_2}$	pK_1^{XH} or pK_2^{XH}	"k_i" expected	"k_i" observed	pH range investigated	pH range[r] expected (in H_2O)	Δ_{max} expected (in H_2O)
$EtOOC\bar{C}HCOOH$ (3)[a]	$pK_1^{CH} \sim 12.9$[i]	$pK_1^{XH} \sim 3.15$	yes	yes	7.08-10.44	~3.4-~8.0[j] ~1.9-~9.5[k]	~1.75[j] ~3.25[k]
 (7)[b]	$pK_2^{CH} \sim 3.5$-4.0	$pK_2^{XH} = 8.9$	yes	yes	8.03-9.27	~8.2-~11.7[j] ~6.7-~13.2[k]	~1.7[j] ~3.2[k]
 (6)[c]	$pK_2^{CH} \sim 5.0$	$pK_2^{XH} \sim 4.0$	yes	yes	8.41-9.41	~2.3-~9.2[l,n] ~1.3-~10.2[m,n]	2.9[l,n] 3.9[m,n]
 (8)[d]		$pK_2^{XH} = 7.5$	yes	yes	8.1-10.0	~3.9-~11.3	~2.0
 (9)[e]		$pK_2^{XH} \sim 6.0$	yes	yes	8.70-9.30	~3.5-~9.9[n,o] ~4.3-~10.8[n,p] ~5.1-~11.5[n,q]	~2.3[n,o] ~2.7[n,p] ~2.7[n,q]
 (10)[e]		$pK_2^{XH} \sim 7.3$	yes	yes	7.56-8.40	~4.1-~10.6[n,o] ~4.8-~11.5[n,p] ~5.7-~12.3[n,q]	~2.7[n,o] ~2.7[n,p] ~2.3[n,q]
 (11)[f]	$pK_1^{CH} \sim 15.0$	$pK_1^{XH} = 8.54$	yes	no	7.10->14.0	3.4-12.9	~2.5
 $Ph_2\bar{C}(NO_2)_2$ (12)[g]	$pK_1^{CH} = 5.5$	$pK_1^{XH} \sim 13.3$	no	no	1.56-14.36	none[l,n] ~5.5-~14.0[m,n]	~-0.92[l,n] ~0.08[m,n]
 (13)[h]	$pK_1^{CH} = 2.95$	$pK_1^{XH} \sim 14.1$	no	no	2.65-11.00	none[j] none[k]	~-3.1[j] ~-1.6[k]

[a] In 30% acetone-70% D_2O, ref 10. [b] In water, ref 15. [c] In 50% Me_2SO-50% water, ref 14. [d] In 50% Me_2SO-50% water, ref 16. [e] In 50% Me_2SO-50% water, ref 17. [f] In water, ref 18. [g] In 50% Me_2SO-50% water, ref 19. [h] In water, ref 20. [i] Estimated, based on the pK_a of diethyl malonate: Bell, R. P. *Trans. Faraday Soc.* 1943, *39*, 253. [j] Model Ia: EM = 3.3×10^{-3} M. [k] Model Ib: EM = 0.1 M. [l] Model IIb: EM = 0.1 M. [m] Model IIa; EM = 1 M. [n] In 50% Me_2SO-50% water which is the solvent used; pH range is somewhat wider and Δ_{max} somewhat larger (see text). [o] Model IIIA: $\beta = 0.1$. [p] Model IIIB: $\beta = -0.4$. [q] Model IIIC: $\beta = -0.9$. [r] pH range in which intramolecular dominance is expected.

($pK_1^{XH} = 5.5$, $pK_2^{XH} = 8.5$), must be mainly due to $\alpha = \beta = 0.30$ being lower than 0.50. If $k_1^{H_2O}$ and $k_2^{H_2O}$ were not reduced as much as they are, $(\Delta_{max})_{max}$ would occur at even lower pK^{XH} values.

(b) For the 9-substituted fluorenes $(\Delta_{max})_{max}$ occurs just slightly below the midpoint ($pK_1^{XH} = 4.5$, $pK_2^{XH} = 9.5$) despite the fact that $\alpha = 0.33$ is almost as low as for the 1,1-dinitroalkanes. Apparently the higher β value of 0.51 helps in shifting $(\Delta_{max})_{max}$ closer to the midpoint. As with the 1,1-dinitroalkanes it should be noted that $(\Delta_{max})_{max}$ would occur at lower pK^{XH} values were it not for the large reduction applied to $k_1^{H_2O}$ and $k_2^{H_2O}$.

(c) For the nitroalkanes one would expect, based on $\alpha = 0.45$ and $\beta = 0.1$ for model IIIA, that $(\Delta_{max})_{max}$ is located somewhat on the acidic side, but, in fact, it lies virtually at the midpoint. Once again this is due to the large reductions applied to $k_1^{H_2O}$ and $k_2^{H_2O}$. However, as β is lowered still more ($\beta = -0.4$ and -0.9) $(\Delta_{max})_{max}$ definitely moves toward lower pK^{XH} values; e.g., for $\beta = -0.9$ it is at $pK_1^{XH} \approx 2$, $pK_2^{XH} \approx 5$.

(d) In comparing the magnitude of $(\Delta_{max})_{max}$ for the various models, we note that it is considerably larger for the fluorenes (3.67) compared to the 1,1-dinitroalkanes (2.94 for the same EM). This enhancement must be mainly due to the larger $pK_2^{XH} - pK_1^{XH}$ (5 for fluorenes, 3 for 1,1-dinitroalkanes) since α, the other factor found to affect $(\Delta_{max})_{max}$ significantly, is virtually the same (0.33 and 0.30, respectively) in both systems. Conversely, $pK_2^{XH} - pK_1^{XH}$ is the same for the mono- and dinitroalkanes, but the larger $\alpha = 0.45$ for the nitroalkanes is expected to enhance $(\Delta_{max})_{max}$ for these compounds. However, $(\Delta_{max})_{max}$ is found to be about the same for mono- and dinitroalkanes. This is because the enhancement predicted for the former is compensated for by smaller reductions applied to k^H and k^{H_2O} (see Table I).

Limitations of the Proposed Models. The models developed in this paper and the conclusions drawn from them need to be applied with a grain of salt. They should mainly be used in a qualitative rather than a strictly quantitative sense because the quantitative aspects depend on various approximations and assumptions which introduce unavoidable uncertainties. For example, a 10-fold error in the assumed EM will change all Δ_{max} values by one unit and change the pH range by one unit on both sides. An error in the assumed value for $pK_2^{CH} - pK_1^{CH} = pK_2^{XH} - pK_1^{XH}$ has also an effect which, albeit not very large, would change Δ_{max} somewhat. The various corrections applied in calculating the different rate constants were based on averages but in a given case may be off by perhaps as much as a factor of 10.

Another assumption which is a potential source of error is that α and β for the intramolecular pathway are the same as for the intermolecular pathway. This assumption was made for the sake of simplicity and in the absence of experimental data which bear on this question. It could well be that inasmuch as the transition state for the intramolecular pathway includes a water molecule

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while this is probably not the case for the intermolecular one, this could have a significant effect on α and/or β. Work on this question is in progress in our laboratory.

Somewhat related to this is the uncertainty in $pK_{\ddagger}^{XH}$ and $pK_{\ddagger}^{CH}$. Our assumption that they lie halfway between their values in the reactant and the product state is certainly not completely correct in every situation and may seriously break down in some cases, particularly for nitroalkanes where C–H bond cleavage/formation and charge development/distribution are very much out of step with each other.[36,38]

Finally, our treatment of carbonyl compounds does not take into consideration the possibility of keto–enol isomerism and is therefore only valid when the enol form is a minor component. A treatment which takes enols into account would lead to a modification of eq 5–7 by changing the denominators ($K_2^{XH} + [H^+]$) into ($K_2^{XH} + [H^+] + K_E^{XH}[H^+]/K_E^{OH} + [H^+]^2/K_E^{OH}$) where K_E^{OH} and K_E^{XH} are the acidity constants of the enol for the OH and the XH group, respectively.

In spite of these limitations we believe that our models are very useful in predicting whether an intramolecular pathway should be definitely observable or definitely not observable or whether the situation might be ambiguous; they also predict whether the contribution by the intramolecular pathway would be large or small, and in what approximate pH range this pathway would be most easily detectable. The predictive power of these models is tested in the next section where prediction and experimental observation is compared for nine compounds.

Comparison of Theory with Experimental Results

Table X summarizes the relevant data for **3** and **6**–**13**. It is apparent from the table that in all cases except for **11** (**11** will be discussed below) the theoretical predictions match with the experimental results. This is true regardless of what EM was chosen (e.g., **3**, **6**, **7**, **12**, **13**) or, in the case of **9** and **10**, regardless of which β value was used.

For **12**, model Ia (EM = 1 M) predicts a slightly positive Δ_{max} of 0.08 which for 50% Me_2SO–50% water is expected to increase to $\Delta_{max} \approx 0.3$. Thus, if EM were 1 M the intramolecular pathway would, in principle, be expected to make a contribution. However, the effect is too small to be detected unequivocally because for definite experimental proof that the intramolecular pathway is significant one usually likes to see at least a 5- to 10-fold rate enhancement (Δ_{max} = 0.7 to 1.0) over the rate which can be accounted for by the external pathways above.

The discrepancy between theory and experiment for **11** is puzzling. The model, based on an EM of 0.1 M, predicts a rather large Δ_{max} of ~2.5 which occurs well within the pH range investigated, and therefore experimental detection should have been easy. We are forced to conclude that perhaps EM is much smaller than assumed and thus much smaller than for most of the other compounds. The reasons for it are not immediately obvious; it might be worthwhile to reinvestigate this compound.

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Supplementary Material Available: Table S1, Model I: Carbonyl Compounds, and Figure S1, Δ_{max} vs. pK^{XH} for benzyl cyanides (4 pages). Ordering information is given on any current masthead page.

S_N2 Substitution with Inversion at a Cyclopropyl Carbon Atom: Formation of 9-Oxatetracyclo[6.2.1.$0^{1,6}$.$0^{6,10}$]undecane

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Abstract: The stereoisomeric chlorohydroxypropellanes **2a** and **2b** were prepared by chlorocarbene addition to 4,5,6,7-tetrahydro-2-indanol. The stereochemistry of **2a** and **2b** was established by chemical correlation and by X-ray crystal structure determination of the tosyl derivative **3** of **2b**. On treatment with *t*-BuOK in Me_2SO, **2a** yielded the tetracyclic ether **1**. This remarkable reaction was shown to be an unambiguous case of a genuine S_N2 reaction with inversion at a cyclopropane carbon atom. Alternative mechanisms could be excluded; in particular, a carbene mechanism was excluded by the observation that the stereoisomer **2b** is unchanged under the reaction conditions and that, starting from **2a**-*10-d*, deuterium is retained (inverted) at the carbon atom that undergoes the substitution.

Nucleophilic substitution at cyclopropane rings continues to be an intriguing process. It shows remarkable differences with analogous substitutions at other saturated carbon atoms, cyclopropyl halides being in general much less reactive than normal alkyl halides. This was first observed by Gustavson in 1891[2] and explained by Brown in 1951 by the concept of I strain,[3] i.e., the increase of bond-angle strain at the carbon center when going from the tetracoordinate ground state to the transition state, in which this carbon atom is either tricoordinate and trigonal (S_N1) or pentacoordinate and trigonal bipyramidal (S_N2).

Substitution at cyclopropane rings under solvolytic (S_N1) conditions, first observed by Roberts and Chambers in 1951,[4] has since been intensively investigated and shown to be a concerted process in which ionization is accompanied and assisted by disrotatory ring opening.[5,6]

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