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Meisenheimer Complexes: A Kinetic Study of Water and Hydroxide Ion Attacks on 4,6-Dinitrobenzofuroxan in Aqueous Solution[1]

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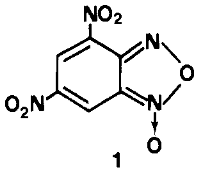
Abstract: In aqueous solution, 4,6-dinitrobenzofuroxan (**1**) gives a very stable Meisenheimer-type adduct **2**, which is completely formed at pH 5. The kinetics of formation and decomposition of **2** have been studied by the stopped-flow method between pH 1 and 13. At pH < 7, the formation of **2** appears to arise exclusively from the attack of a water molecule on the substrate **1**, which is apparently the first report of this kind in the field of Meisenheimer complexes. At pH > 7, the hydroxide-ion attack starts to compete with that of water; at pH > 9 the reaction $\mathbf{1} + OH^- \rightarrow \mathbf{2}$ is the only one observed. At pH > 10.6, the oscilloscope pictures reveal the existence of a fast equilibrium between **2** and a new species **3**, which is completely formed at pH 13 and identified as the dianion arising from the ionization of the hydroxyl group of the adduct **2**. The thermodynamic and kinetic parameters ΔH°, ΔS°, $\Delta H^{\neq}$, and $\Delta S^{\neq}$ for the various reactions have been determined. The formation and decomposition of **2** are subject to general base and general acid catalysis, respectively. Possible mechanisms for the reactions are discussed on the basis of the buffer catalysis effects and deuterium isotope effects. In particular, the abnormally high values obtained for the rate constants for base catalysis by carbonate and bicarbonate ions suggest a nucleophilic attack of these anions on **1** to give an unstable Meisenheimer-type intermediate.

Recently, nitrobenzofuroxans and benzofurazans have been reported to be potent in vitro inhibitors of nucleic acid synthesis in lymphocytes.[3-5] These antileukemic properties have been tentatively interpreted in terms of an easy Meisenheimer-type adduct formation[6] between the substrates and the essentially cellular SH and/or amino groups. In fact, such an explanation is not unreasonable, since some compounds of the series, such as 4,6-dinitrobenzofuroxan,[7,8] 4-nitrobenzofuroxan,[3] and 4-nitrobenzofurazan[3] are known to react with nucleophiles to give very stable Meisenheimer complexes. It was thus of interest to investigate kinetically the behavior of these compounds towards nucleophiles and, in particular, towards hydroxide and thiolate anions in order to get a better understanding of the reactions. Following a preliminary communication,[9] we report first a comprehensive study of the kinetics of formation and decomposition of the hydroxyl adduct **2** derived from 4,6-dinitrobenzofuroxan (**1**) in aqueous solution. Our results reveal some interesting and new features, which are due to the very strong electron-withdrawing character of the annelated furoxan ring. In particular, the fact that the adduct **2** may be formed from the attack of water on **1** is apparently the first report of this sort in the field of Meisenheimer complexes.



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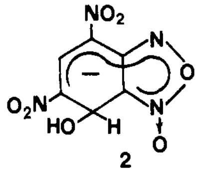

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Results

In aqueous solution, 4,6-dinitrobenzofuroxan (**1**, λ_{max} 415 nm, ϵ 7050 M^{-1} cm^{-1}) has been shown to give rapidly the yellow-colored adduct **2**, which was identified by NMR and visible spectroscopy[7-10] (λ_{max} 462.5 nm, ϵ 24 400 M^{-1} cm^{-1}) and which is completely formed at pH 5. To carry out a comprehensive study of the formation and decomposition of **2**, we have therefore investigated these reactions between pH 0.8 and 13, using dilute hydrochloric acid solutions, various buffer solutions, and dilute potassium hydroxide solutions. The ionic strength (μ) was always kept at 0.2 M by adding KCl as nec-

Table I. Experimental and Calculated Pseudo-First-Order Rate Constants k_{obsd}, k_f, and k_d for the Formation and/or Decomposition of the Adduct **2** in Water[a]

pH	k_{obsd}, s^{-1}	$k_f \times 10^2$, s^{-1}	k_d, s^{-1}	pH	k_{obsd}, s^{-1}	$k_f \times 10^2$, s^{-1}	k_d, s^{-1}
0.82[b]	20	2.45	20	5.98[g]	2.60×10^{-2}	2.58	1.46×10^{-4}
1.12[b]	9.8	2.40	9.8	6.72[g]	2.63×10^{-2}	2.63	2.68×10^{-5}
1.42[b]	5.05	2.47	5.05	7.05[g]	3.45×10^{-2}	3.45	1.65×10^{-5}
1.72[b]	2.59	2.52	2.57	7.38[g]	3.94×10^{-2}	3.94	8.85×10^{-6}
2.12[b]	0.98	2.44	0.96	7.52[h]	3.60×10^{-2}	3.60	5.85×10^{-6}
2.42[b]	0.515	2.40	0.49	7.89[h]	3.70×10^{-2}	3.70	2.57×10^{-6}
2.72[b]	0.27	2.41	0.246	8.23[h]	9.8×10^{-2}	9.8	3.1×10^{-6}
3.12[b]	0.126	2.48	0.101	8.38[i]	0.11	11	2.46×10^{-6}
3.12[c]	0.120	2.36	9.65×10^{-2}	9.12[j]	0.36	36	1.47×10^{-6}
3.30[c]	9.2×10^{-2}	2.50	6.7×10^{-2}	9.60[k]	1.50	150	2×10^{-6}
3.74[d]	4.86×10^{-2}	2.46	2.4×10^{-2}	10.90[l]	17.6	1760	1.19×10^{-6}
4.03[e]	3.59×10^{-2}	2.39	1.2×10^{-2}	11.05[l]	29	2900	1.38×10^{-6}
4.34[e]	3.01×10^{-2}	2.40	5.95×10^{-3}	11.23[l]	45	4500	1.42×10^{-6}
4.64[e]	2.79×10^{-2}	2.49	3.06×10^{-3}	11.45[l]	69	6900	1.31×10^{-6}
4.69[f]	2.56×10^{-2}	2.30	2.52×10^{-3}	11.65[l]	106	10600	1.28×10^{-6}
4.94[e]	2.64×10^{-2}	2.48	1.53×10^{-3}	11.83[l]	168	16800	1.35×10^{-6}
5.22[e]	2.52×10^{-2}	2.44	8.15×10^{-4}	12.05[l]	274	27400	1.31×10^{-6}
5.68[f]	2.37×10^{-2}	2.35	2.63×10^{-4}	12.23[l]	410	41000	1.30×10^{-6}

[a] At zero buffer concentration; $\mu = 0.20$ M; $t = 20$ °C. [b] HCl solutions (10^{-3}–0.2 M). [c] Citrate buffer. [d] Formate buffer. [e] Acetate buffer. [f] Succinate buffer. [g] Phosphate buffer. [h] *p*-Cyanophenoxide buffer. [i] Bicarbonate buffer. [j] Borate buffer. [k] Carbonate buffer. [l] KOH solutions (7×10^{-4}–1.5×10^{-2} M).

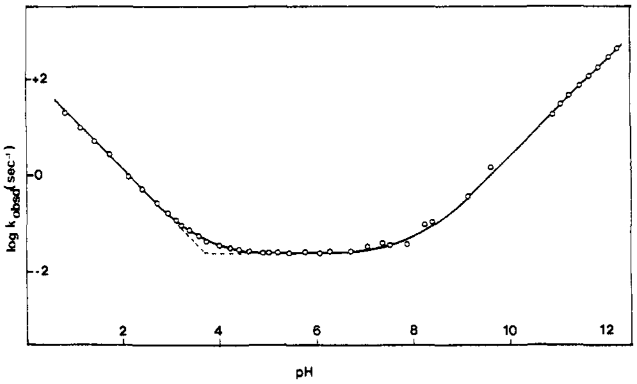


Figure 1. pH dependence of k_{obsd} (s^{-1}) for the formation and decomposition of the adduct **2** in water: 20 °C, $\mu = 0.20$ M.

essary. All pH values have been measured relative to the standard state in pure water, allowing the calculation of the hydrogen-ion concentration of the solutions from the hydrogen-ion activity by means of the relation $[H^+] = a_{H^+}/\gamma_{\pm}$, where $\gamma_{\pm}$ is the trace activity coefficient in 0.2 M KCl ($\gamma_{\pm} = 0.75^{11}$).

From the variations at 465 nm of the optical density obtained at the equilibrium as a function of pH, the adduct **2** appears to be half-formed at pH 3.73 at 20 °C. This $pH_{1/2}$ value, which denotes the pH at which the parent molecule **1** and the adduct **2** are present at equal concentrations, corresponds to the pK_a value for the reversible formation of **2** (eq 1) at $\mu = 0.2$ M. Although this latter is not a thermodynamic value, it compares fairly well with the pK_a values previously reported by Ghosh and Whitehouse[3] ($pK_a = 3.77$).

$$\mathbf{1} + H_2O \overset{K_a}{\rightleftarrows} \mathbf{2} + H^+ \tag{1}$$

Using the stopped-flow method, we could follow spectrophotometrically the kinetics of formation and/or decomposition of **2** at 465 nm. Under any given experimental condition, the appearance or the fading of color was in all cases an accurately first-order process. The logarithmic values of the observed first-order rate constant k_{obsd} for the combined formation and decomposition of **2** at 20 °C are plotted in Figure 1 as a function of pH. Since buffer catalysis of the reactions was sometimes observed, the k_{obsd} values used in this pH profile are those extrapolated to zero buffer concentration. As can be seen, a smooth pH-rate profile was so obtained despite the fact that buffers of varying chemical types were used.

The observed rate constant k_{obsd} reflects the rate of approach to equilibrium between **1** and **2** and is the sum of the pseudo-first-order rate constants k_f and k_d, respectively, for the formation and decomposition of **2**:

$$k_{obsd} = k_f + k_d \tag{2}$$

At equilibrium, we have

$$k_f[\mathbf{1}] = k_d[\mathbf{2}] \tag{3}$$

so that k_f and k_d are related to the thermodynamic equilibrium constant K_a for the formation of **2** (eq 1) by the relation

$$k_f/k_d = (K_a/a_{H^+})(\gamma_1/\gamma_2) \tag{4}$$

and therefoe, since $pH = pK_a + \log([\mathbf{2}]/[\mathbf{1}]) + \log(\gamma_2/\gamma_1)$ to the experimental $pH_{1/2}$ value corresponding to the half-formation of **2** ($pH_{1/2} = pK_a + \log(\gamma_2/\gamma_1)$)

$$k_f/k_d = \frac{a_{H^+_{1/2}}}{a_{H^+}} \tag{5}$$

Combining eq 2 and 5 leads to

$$k_d = \frac{k_{obsd}}{1 + (a_{H^+_{1/2}}/a_{H^+})} \tag{6}$$

$$k_f = \frac{k_{obsd}}{1 + (a_{H^+}/a_{H^+_{1/2}})} \tag{7}$$

Table I presents some values of k_f and k_d calculated in this way at 20 °C. Complete data are graphically represented in Figure 2, showing the pH dependence of k_f and k_d. These pH profiles are consistent with equations of the form

$$k_f = k_1^{H_2O} + k_2[OH^-] = k_1^{H_2O} + \frac{k_2 K_W}{a_{H^+}\gamma_{\pm}} \tag{8}$$

$$k_d = k_{-1}[H^+] + k_{-2} = \frac{k_{-1}a_{H^+}}{\gamma_{\pm}} + k_{-2} \tag{9}$$

Table II. Specific Rate and Equilibrium Constants for the Formation and Decomposition of Adduct **2** in Water at Different Temperatures[a]

Temp, °C	$k_1^{H_2O}$, s^{-1}	k_{-1}, $M^{-1}\ s^{-1}$	k_2, $M^{-1}\ s^{-1}$	k_{-2}, s^{-1}	pK_a	pK_b
9.5	1.12×10^{-2}	48.3	13 800	3.09×10^{-7}	3.76	−10.77
20	2.45×10^{-2}	100	27 400	1.35×10^{-6}	3.73	−10.44
29	4.62×10^{-2}	184	40 200	4.17×10^{-6}	3.72	−10.11
40	9.8×10^{-2}	432	72 000	1.66×10^{-5}	3.77	−9.76
50					3.68	−9.58

[a] $\mu = 0.20$ M.

Table III. Kinetic and Thermodynamic Parameters for the Formation and Decomposition of Complexes **2**, **6**, and **8** and Pseudobases **15** and **18** in Water ($T = 25$ °C)

	2[a]	**6**[b]	**8**[c]	**15**[d]	**18**[e]
$k_1^{H_2O}$, s^{-1}	3.45×10^{-2}			1.04	0.43
k_{-1}, $M^{-1}\ s^{-1}$	146			1.3×10^5	2.8×10^6
k_2, $M^{-1}\ s^{-1}$	33500	37.5	250	8.8×10^6	1.3×10^5
k_{-2}, s^{-1}	2.5×10^{-6}	9.8	0.225	1.1×10^{-2}	7.1×10^{-3}
$\Delta H^{\ddagger}_1$, kcal mol^{-1}	11.6 ± 0.4			11.8 ± 0.5	
$\Delta S^{\ddagger}_1$, eu	−26.3 ± 1.4			−17 ± 2	
$\Delta H^{\ddagger}_{-1}$, kcal mol^{-1}	12.3 ± 0.4			9.8 ± 0.5	
$\Delta S^{\ddagger}_{-1}$, eu	−7.3 ± 1.4			0 ± 2	
$\Delta H_1°$, kcal mol^{-1}	−0.7 ± 0.8			2 ± 1	
$\Delta S_1°$, eu	−19 ± 2.8			−17 ± 4	
$\Delta G_1°$, kcal mol^{-1}	4.95 ± 1.6			7.1 ± 2.2	
$\Delta H^{\ddagger}_2$, kcal mol^{-1}	9 ± 0.4	15.6 ± 0.8		4.1 ± 0.5	
$\Delta S^{\ddagger}_2$, eu	−7.75 ± 1.4	1.1 ± 2.7		−11 ± 2	
$\Delta H^{\ddagger}_{-2}$, kcal mol^{-1}	22 ± 0.6	7.3 ± 0.8		15.2 ± 0.5	
$\Delta S^{\ddagger}_{-2}$, eu	−10 ± 2.3	−29.4 ± 2.7		−14 ± 2	
$\Delta H_2°$, kcal mol^{-1}	−13 ± 1	8.3 ± 1.6		−11.1 ± 1	
$\Delta S_2°$, eu	2.25 ± 3.7	30.5 ± 5.4		3 ± 4	
$\Delta G_2°$, kcal mol^{-1}	−13.7 ± 2.1	−0.8 ± 3.2		−12 ± 2.2	
pK_a	3.75	13.43	9.96	5.11	6.82
pK_b	−10.25	−0.57	−4.04	−8.89	−7.18
pK_a'	11.30[f]			11.15	13

[a] This work, $\mu = 0.20$ M. [b] From ref 14, $\mu = 1$ M. [c] From ref 15, at zero ionic strength. [d] From ref 31a, $\mu = 0.10$ M. [e] From ref 31b, $\mu =$

Equations 10 and 11 show the reactions to which the various rate constants refer, viz. $k_1^{H_2O}$ and k_2 represent attack of **1** by water and hydroxide ion, respectively, while k_{-1} and k_{-2} refer to H^+ catalyzed and spontaneous decomposition of **2**, respectively.

$$\mathbf{1} + H_2O \underset{k_{-1}}{\overset{k_1^{H_2O}}{\rightleftharpoons}} \mathbf{2} + H^+ \tag{10}$$

$$\mathbf{1} + OH^- \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \mathbf{2} \tag{11}$$

At low pH, eq 8 and 9 reduce to

$$k_f = k_1^{H_2O} \tag{8a}$$

$$k_d = k_{-1}\,[H^+] = \frac{k_{-1}a_{H^+}}{\gamma_\pm} \tag{9a}$$

A plateau and a straight line of slope −1 are thus observed in Figure 2, allowing an easy determination of values of $k_1^{H_2O}$ and k_{-1}: $k_1^{H_2O} = 2.45 \times 10^{-2}\ s^{-1}$, $k_{-1} = 100\ M^{-1}\ s^{-1}$. At high pH, eq 8 and 9 reduce similarly to

$$k_f = k_2[OH^-] = \frac{k_2K_W}{a_{H^+}\,\gamma_\pm} \tag{8b}$$

$$k_d = k_{-2} \tag{9b}$$

thus leading in Figure 2 to a straight line of slope 1 and an other plateau, respectively, from which one can obtain values for k_2 and k_{-2}: $k_2 = 27\ 400\ M^{-1}\ s^{-1}$, $k_{-2} = 1.35 \times 10^{-6}\ s^{-1}$.

If one inserts these values into the expression for k_{obsd}

$$k_{obsd} = \frac{k_{-1}a_{H^+}}{\gamma_\pm} + k_{-2} + k_1^{H_2O} + \frac{k_2K_W}{a_{H^+}\,\gamma_\pm} \tag{12}$$

we see that, at low pH (pH < 3), $k_{obsd} = k_d$, i.e., only the reverse reaction $\mathbf{2} + H^+ \rightarrow \mathbf{1} + H_2O$ is important while, above pH 5, $k_{obsd} = k_f$, i.e., only the reaction $\mathbf{1} \rightarrow \mathbf{2}$ is important. This is in agreement with our experimental results. Note that the intersection in Figure 1 between the $k_1^{H_2O}$ plateau and the straight line of slope −1 yields $pK_a = 3.71$ at 0.2 M. This latter value agrees well with that determined thermodynamically.

Similar measurements were carried out at 9.5, 29, and 40 °C. Values of the various rate coefficients and equilibrium constants are collected in Table II. Table III gives the values at 25 °C of the corresponding enthalpies and entropies of activation as well as the enthalpy ($\Delta H°$), entropy ($\Delta S°$), and free enthalpy ($\Delta G°$) changes associated with the formation of adduct **2** in the equilibria in eq 10 and 11.

The rates of formation and decomposition of **2** have also been measured in deuterium oxide at 20 °C, allowing the calculation of the solvent isotope effects k_H/k_D. The data are summarized in Table IV.

While not having any apparent influence on the observed rate constant k_{obsd}, another process occurs in the more basic media, namely above pH 10.6. Thus, when a solution of the adduct **2**, for example at pH 5, is mixed in the stopped-flow apparatus with buffer or basic solutions so that the final pH of the mixture is greater than 10.6, an instantaneous spectral change is observed, leading to a final optical density which is lower than that of the pure adduct at 465 nm. Starting from

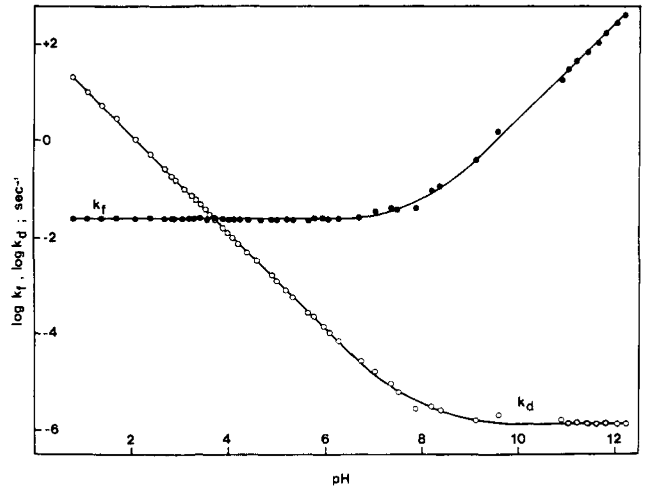
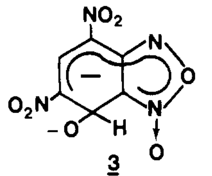


Figure 2. pH dependence of k_f (s^{-1}) and k_d (s^{-1}) for the formation and decomposition of the adduct **2** in water: 20 °C, μ = 0.20 M.

the molecule and working at the same final pH, we observed now pseudo-first-order kinetics leading to this new final optical density, but the value measured for k_{obsd} is always located on the straight line of slope 1 obtained at lower pH. The spectral changes are reversible and appear to be complete at pH 13. These observations, together with the existence of clean isosbestic points at λ 416 (ϵ 11 500 M^{-1} cm^{-1}) and 490 nm (ϵ 9550 M^{-1} cm^{-1}) in the group of spectra recorded at equilibrium and at various pH (Figure 3), clearly indicate a fast equilibrium between **2** and a new species. Although NMR measurements were not conclusive, owing to the relative insolubility of **2**, we suggest that this species is the dianion **3** (λ_{max} 450 nm, ϵ 16 200 M^{-1} cm^{-1}) resulting from the ionization of the hydroxyl group of the adduct **2**. This hypothesis is consistent with the absence of a similar spectral change in the corresponding methoxyl adduct **4**, where such an ionization cannot occur.[12] Furthermore, a somewhat similar behavior has recently been reported by Bunting and Meathrel[13] for neutral pseudobases derived from various quaternary ammonium heterocycles (see structures **14** and **17** in Discussion).



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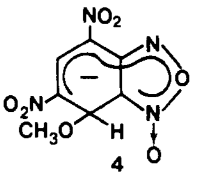

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Assuming the formation of **3**, the reaction now obeys eq 13 in basic medium.

$$1 + \mathrm{OH}^- \underset{k_{-2}}{\overset{k_2}{\rightleftarrows}} 2 \underset{\text{fast}}{\overset{\mathrm{OH}^-}{\rightleftarrows}} 3 + \mathrm{H_2O} \qquad (13)$$

$$\left(K_b' = \frac{a_3}{a_2 a_{\mathrm{OH}^-}}\right)$$

Here, the rate constant k_{obsd} is given by eq 14, which reduces to eq 15 because of the very low value of k_{-2}. Thus, the existence of this new equilibrium is not expected to affect the pH dependence of k_{obsd}, which is in agreement with the experimental observation. From the equilibrium measurements, the pK_a' for the formation of **3** has been found to be 11.80 at 0.2 M.

$$k_{obsd} = k_2[\mathrm{OH}^-] + \frac{k_{-2}}{1 + K_b'[\mathrm{OH}^-](\gamma_2\gamma_\pm/\gamma_3)} \qquad (14)$$

$$k_{obsd} = k_2[\mathrm{OH}^-] = \frac{k_2 K_W}{a_{\mathrm{H}^+}\gamma_\pm} \qquad (15)$$

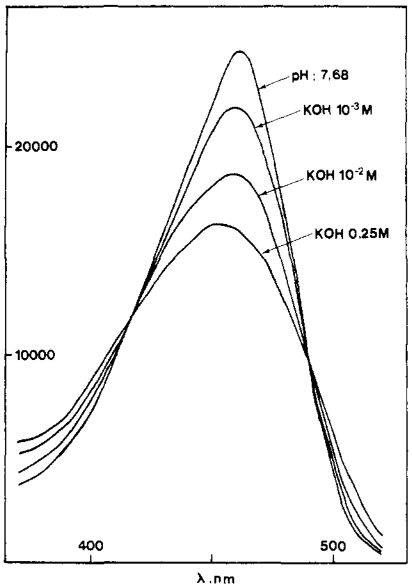


Figure 3. Absorption spectra of adduct **2** in various potassium hydroxide solutions.

Table IV. Deuterium Isotope Effects on the Kinetic and Thermodynamic Parameters for the Formation and Decomposition of **2**[a]

	H$_2$O	D$_2$O	k_H/ k_D	K_H/ K_D
$k_1^{\mathrm{H_2O}}$, s^{-1}	2.45×10^{-2}	1.47×10^{-2}	1.67	
k_{-1}, M^{-1} s^{-1}	100	264	0.38	
k_2, M^{-1} s^{-1}	27400	30200	0.905	
k_{-2}, s^{-1}	1.35×10^{-6}	8×10^{-7}	1.69	
K_a	1.86×10^{-4}	4.17×10^{-5}		4.4
K_b	2.75×10^{10}	4.7×10^{10}		0.585

[a] μ = 0.20 M, T = 20 °C.

As mentioned previously, the possibility of buffer catalysis had to be considered. In fact, although no appreciable catalysis occured with the more acidic buffers (citric acid, formic acid, chloroacetic acid), buffer catalysis was observed in less acidic buffers, as shown on Figure 4. This catalysis was investigated in some detail with the acetic acid-acetate system at 20 °C. As is apparent from Figure 5, slopes and intercepts of linear plots of k_{obsd} vs. the acetate anion concentration are dependent on pH, showing that the observed rate constant k_{obsd} can be fitted to the equation

$$k_{obsd} = k_1^{\mathrm{H_2O}} + k_{-1}[\mathrm{H}^+] + k_2[\mathrm{OH}^-] + k_{\mathrm{AcOH}}[\mathrm{AcOH}] + k_{\mathrm{AcO}^-}[\mathrm{AcO}^-] \qquad (16)$$

Neglecting the $k_2[\mathrm{OH}^-]$ term in the pH range studied, eq 16 simplifies to eq 17, which upon some rearrangement affords eq 18

$$k_{obsd} = k_1^{\mathrm{H_2O}} + k_{-1}[\mathrm{H}^+] + k_{\mathrm{AcOH}}[\mathrm{AcOH}] + k_{\mathrm{AcO}^-}[\mathrm{AcO}^-] \qquad (17)$$

$$k_{obsd} = k_1^{\mathrm{H_2O}} + k_{-1}[\mathrm{H}^+] + \left[k_{\mathrm{AcOH}}\frac{[\mathrm{H}^+]\gamma_\pm^2}{K_a^{\mathrm{AcOH}}} + k_{\mathrm{AcO}^-}\right][\mathrm{AcO}^-] \qquad (18)$$

As expected, a plot of the intercepts vs. the hydrogen-ion concentration affords a straight line with an intercept equal to $k_1^{\mathrm{H_2O}} = 2.48 \times 10^{-2}$ s^{-1} and a slope equal to k_{-1} = 92 M^{-1} s^{-1} (Figure 6). Within experimental error, these values agree well with the one previously determined from the pH profile.

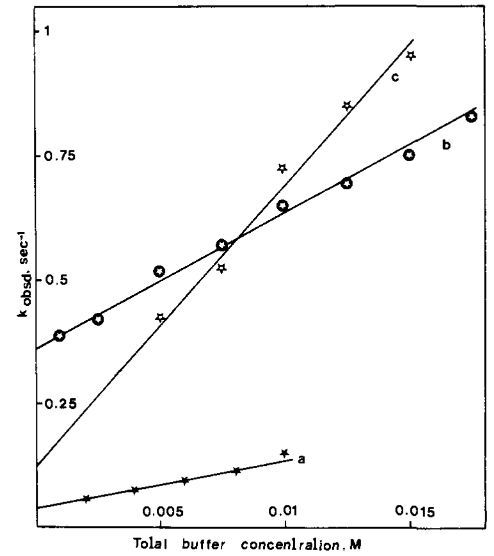


Figure 4. Dependence upon total buffer concentration of k_{obsd} (s^{-1}): 20 °C, μ = 0.20 M: (a) *p*-cyanophenoxide buffer (pH 7.89); (b) borate buffer (pH 9.12); (c) bicarbonate buffer (pH 8.38).

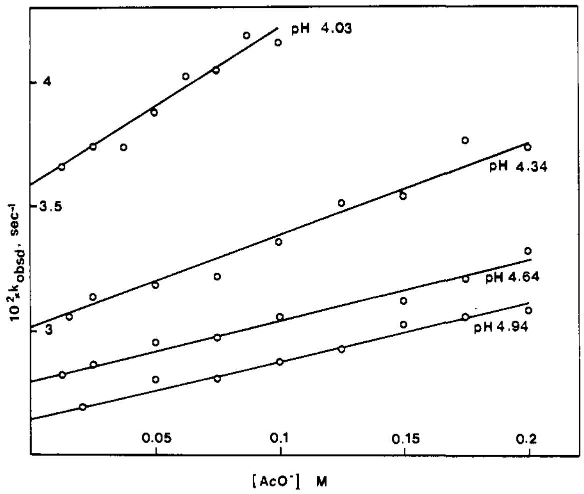


Figure 5. Effect of acetate concentration and pH on k_{obsd} for the reaction of **1** with water: 20 °C, μ = 0.20 M.

Furthermore, a plot of the slopes vs. $[H^+]$ is also linear, allowing the determination of the second-order rate constants k_{AcO^-} and k_{AcOH} for catalysis by the buffer species AcO^- and AcOH: $k_{AcO^-} = 1.75 \times 10^{-2}\ M^{-1}\ s^{-1}$, $k_{AcOH} = 1.11 \times 10^{-2}\ M^{-1}\ s^{-1}$.

In the more basic buffers, we could detect only catalysis by the basic species B^-, as expected since here only the forward reaction contributes significantly to the rate of equilibration. On the other hand, the failure to detect catalysis by the acidic species BH in the more acidic buffers is probably due to the fact that the contribution of the term $k_{-1}[H^+]$ is then much higher than that of the term $k_{BH}[BH]$. Table V summarizes the various second-order rate constants k_{BH} and k_{B^-} determined.

Discussion

General Features of the Reaction of Water and Hydroxide Ion with 1. As is clearly apparent from the pH profile of Figure 1, the formation of adduct **2** arises exclusively from the attack of a water molecule on 4,6-dinitrobenzofuroxan (**1**) as long as the pH is lower than 7. At pH greater than 7, the attack of hydroxide ion begins to compete significantly with that of water and the reaction **1** + $OH^- \rightleftharpoons$ **2** is the only one observed above pH 9. The fact that water reacts efficiently with the neutral compound **1** to give the anionic σ complex **2** is, to the best of our knowledge, the first report of this kind in the field of Meisenheimer complexes. Such a reaction was not found to occur, not even to a small extent, in the formation of the most stable hydroxyl adducts which have so far been studied, namely the adducts **6**, **8**, and **10** derived from 1,3,5-trinitrobenzene

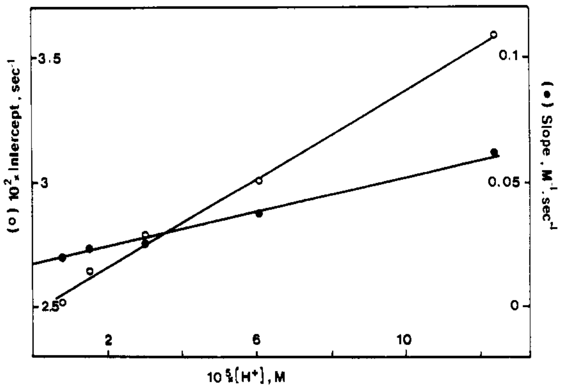
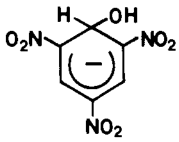


Figure 6. Plots of the slopes and intercepts of lines in Figure 5 against the hydrogen-ion concentration: 20 °C, μ = 0.20 M.

Table V. Rate Constants for Catalysis by Buffer Species[a]

Buffer (basic species)	pK_a[b]	k_{BH}, $M^{-1}\ s^{-1}$	k_{B^-}, $M^{-1}\ s^{-1}$
Water	−1.74	100	4.45×10^{-4}[c]
Acetate	4.64	1.11×10^{-2}	1.75×10^{-2}
Bicarbonate	6.34		58
PO_4H^{2-}	6.72		0.185
p-Cyanophenoxide	7.89		19.8
Borate	9.12		27.5
Carbonate	9.98		2370
Hydroxide ion	15.66		27400

[a] μ = 0.20 M, t = 20 °C. [b] pK_a at μ = 0.20 M. [c] Obtained from $k_1^{H_2O}/55.5$.



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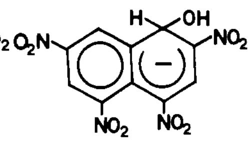

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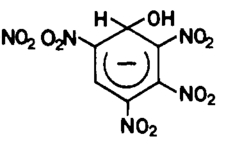

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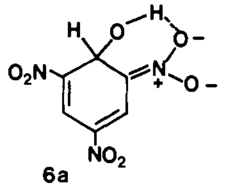
(**5**),[14] 1,3,6,8-tetranitronaphthalene (**7**),[15] and 1,2,3,5-tetranitrobenzene (**9**).[16] This interesting result is largely the consequence of the very strong electron-withdrawing character of the furoxan ring, which is demonstrated by the very high thermodynamic stability of adduct **2**. The pK_a for the formation of **2** is 3.75 at 25 °C, as compared with pK_a of 9.96 and 9.62, respectively, for the formation of **8** and **10** and a pK_a of 13.43 for the formation of **6**, which is frequently used as a model for comparison of reactions involving monohydroxyl adducts.

Increasing the temperature from 10 to 50 °C does not result in an appreciable change in the pK_a value for the formation of **2**, which is in agreement with the very weak enthalpy change $\Delta H_1{}^\circ$ associated with the reaction **1** + $H_2O \rightleftharpoons$ **2** + H^+. Values of pK_b calculated from $pK_b = pK_a - pK_w$ are included in Table II. As can be seen, K_b is strongly temperature dependent and decreases with increasing temperature. Since we have the relation $K_a = K_b \times K_w$ and recalling that K_a is only slightly temperature dependent, this temperature dependence of K_b mainly reflects that of the autoprotolysis product of water

(K_w). The absolute value of the enthalpy change $\Delta H_2°$ associated with the reaction **1** + $OH^- \rightleftarrows$ **2** is, indeed, fairly close to the value of the enthalpy for the ionization of water[17] ($\Delta H_w°$ = 13.1 kcal mol^{-1}).

As shown in Table III, the much greater stability of the adduct **2** with respect to its benzenic analogue **6** comes primarily from its slower rate of decomposition: the ratio $k_{-2}^{\mathbf{2}}/k_{-2}^{\mathbf{6}}$ is equal to 2.5×10^{-7}, compared with a ratio $k_2^{\mathbf{2}}/k_2^{\mathbf{6}}$ of 900 for the rates of the hydroxide attack. The same holds true with respect to **8** ($k_2^{\mathbf{2}}/k_2^{\mathbf{8}} = 134$, $k_{-2}^{\mathbf{2}}/k_{-2}^{\mathbf{8}} = 1.11 \times 10^{-5}$), which is consistent with general features reported in comparing other Meisenheimer complexes.[14,18,19] Looking at the activation parameters for **2** and **6**, the enormous differences in the k_2 and k_{-2} values appear to be due both to large entropy and enthalpy changes with a domination of enthalpy effects. The much higher value of $\Delta H_{-2}^{\ddagger}$ for **2** relative to that for **6** is particularly significant ($\Delta H^{\ddagger}{}_{-2}{}^{\mathbf{2}} - \Delta H^{\ddagger}{}_{-2}{}^{\mathbf{6}} = 14.7$ kcal mol^{-1}). The entropy of activation for the decomposition of **2** is also much less negative than that for the decomposition of **6** ($\Delta S^{\ddagger}{}_{-2}{}^{\mathbf{2}} - \Delta S^{\ddagger}{}_{-2}{}^{\mathbf{6}} = 19.4$ eu), suggesting that intramolecular hydrogen bonding as described by Bernasconi for **6**[14] (structure **6a**) would not be significant in **2**.

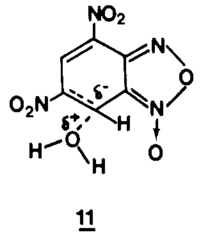


6a

The very high electron-withdrawing ability of the furoxan ring is further demonstrated by the formation at high pH of the dianion **3**. This reaction is unique in that it is the first time that the ionization of a hydroxyl group attached to an sp^3 carbon of a Meisenheimer complex is observed in aqueous solution. This result may be understood in terms of intensive delocalization of the negative charge of **2** over the furoxan ring and the nitro groups, which thereby renders the ionization of the OH group much easier.

Buffer Catalysis and Isotope Effects. The present work shows the existence of general base catalysis of the reaction of water with 4,6-dinitrobenzofuroxan (**1**). As required for the reverse reaction, formation of **1** from adduct **2** is seen to be subject to general acid catalysis. The solvent isotope effect $K_a^{H_2O}/K_a^{D_2O}$ on the ionization constant of **1** is 4.4, a value which is in the same range as the isotope effects measured for a number of acids of similar strength.[20-22]

Our kinetic solvent isotope effect of $k_1^{H_2O}/k_1^{D_2O} = 1.67$ for water attack on **1** is somewhat smaller than those usually observed for typical general base-catalyzed reactions (with proton transfer from oxygen to the general base catalyst $k^{H_2O}/k^{D_2O} \simeq 2.3$[21,23]). Nevertheless, this effect seems to be too large to be consistent with a transition state such as **11**, which does not involve a rate-limiting proton transfer and tends to favor **12**, which represents general base catalyzed water attack with a second water molecule acting as base catalyst. Cases of authentic general base catalysis, where the solvent isotope effect is only 1.2 or even lower have, in fact, been reported.[24,25] We believe that the large negative entropy of activation ($\Delta S^{\ddagger}{}_1 = -26.3$ eu) is also better consistent with **12** than with **11**. Negative entropies of activation of this order of magnitude have been reported in the general base-catalyzed hydrolysis of a number of activated acyl compounds.[26-29] More interesting is the fact that large negative entropies of activation have also been found by Ritchie[30] in the reactions of water with crystal violet and malachite green cations and by Bunting[31a] in the reactions of water with some quaternary ammonium heterocycles such as **14**.



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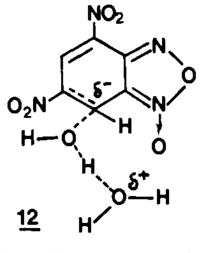

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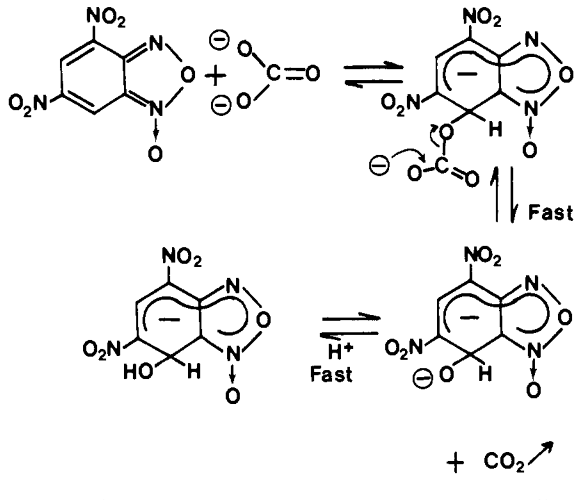
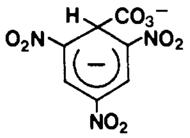
Just as for the forward reaction, the isotope effect k_{-1}^H/k_{-1}^D in the reverse reaction is not as conclusive as one could hope. In the earlier literature, a value in that range was commonly associated with a mechanism of specific acid catalysis.[32] However, a number of examples of authentic general acid catalysis whose solvent isotope effect is in the range of 0.40–0.70 have been reported, e.g., in the hydrolysis of ortho esters and of some acetals and ketals.[32,33] More recently, a ratio of 0.61 has been reported for the general acid-catalyzed decomposition of the pseudobase **15**.[31a] Since this latter reaction is closely related to the decomposition of the hydroxyl adduct **2**, a similar solvent isotope effect might be expected.

We tried to correlate our data on general base catalysis by the Bronsted equation (Figure 7). Because the various bases belong to different structural types it is not surprising that the various constants do not lie on a single Bronsted line. However, it appears to us that the rate constants referring to catalysis by bicarbonate and carbonate ions are higher than can be accounted for by any "reasonable" Bronsted line. A possible interpretation of this extra reactivity could be in terms of nucleophilic catalysis, which is known to manifest itself by positive deviations from Bronsted plots.[34,35] The mechanism of this nucleophilic catalysis can be visualized as can be seen in Scheme I.

Scheme I



The fact that **1** is known to readily displace carbon dioxide from bicarbonate solutions[7,36-38] is in accord with such a mechanism which is supported by two additional arguments. First, Butler has recently reported a visible spectrum, indicating the formation of the adduct **13** from the attack of carbonate ion on 1,3,5-trinitrobenzene in benzene containing dicyclohexyl crown-6.[39] On the other hand, we have observed that **1** reacts very easily with phenoxide ions more basic than *p*-cyanophenoxide ion as well as with most amines to give de-



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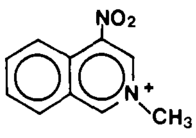
tectable Meisenheimer-type intermediates.[40] This behavior, which precluded the use of these compounds as buffers in the present study, is currently under further investigation in the laboratory.

Whether hydroxide ion attacks **1** directly or reacts as a general base catalyst for the reaction of water with **1** is an interesting question. According to the rule formulated by Jencks,[41] general base catalysis is not expected to occur, since the reaction of hydroxide ion with water in a simple proton exchange does not involve an unfavorable free-energy change. However, Ritchie et al.[30] have recently argued that this reasoning might not apply to a number of cases, such as those of carbonium or quinolinium cations previously mentioned,[30,31] where the simple proton transfer between water and OH^- can be visualized as follows

$$[HO^- \; H_2O \; E] \rightleftharpoons [H_2O \; HO^- \; E]$$

where E is the electrophile. The reason is that this exchange would place the electrophile E in a position originally occupied by the solvation shell of the hydroxide ion, a process which is, in fact, expected to involve a very unfavorable free-energy change. Therefore, general base catalysis could be a more favorable pathway, since it would avoid the formation of the unstable intermediate $[H_2O \; HO^- \; E]$. Our data do not permit an unequivocal choice between these two mechanisms. On the one hand, the small inverse isotope effect, $k_2^{OH^-}/k_2^{OD^-} = 0.905$, suggests a direct attack by OH^-.[42] On the other hand, the fact that the point for OH^- lies on the same Bronsted line as that defined by borate, *p*-cyanophenoxide, and water may be taken to suggest that the OH^- reaction is in fact a general base (OH^-) catalyzed attack of water. However, as pointed out before, due to the limited number of buffers and the fact that they belong to different structural classes, the mentioned Bronsted line (Figure 7) is somewhat arbitrary. Hence we do not claim that the argument for general base catalysis based on it is a very strong one. It is nevertheless interesting that the observed solvent isotope effect for the reverse direction ($k_{-2}^{H_2O}/k_{-2}^{D_2O} = 1.69$) also suggests that a proton transfer may be part of the rate-limiting transition state.

Adduct Formation vs. Pseudobase Formation. The occurrence of water attack on **1** as well as of formation of the dianion **3** makes the behavior of 4,6-dinitrobenzofuroxan formally similar to that of some quaternary nitrogen heterocycles, such as 2-methyl-4-nitroisoquinolinium and 1-methyl-3-nitroquinolinium cations **14** and **17**.[31] On the one hand, water attack competes significantly with hydroxide-ion attack in the formation of neutral pseudobases **15** and **18** from cations **14** and **17**, the reactions involving, as those giving **2**, a rehybridization of the carbon atom located at the entering site of the nucleophile. On the other hand, the ionization of the hydroxyl group of **15** and **18** occurs at high pH to give the monoanions **16** and **19**. This makes an interesting comparison of kinetic and thermodynamic data for the formation and decomposition of these species.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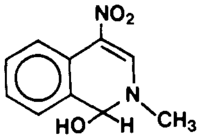
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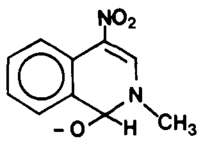
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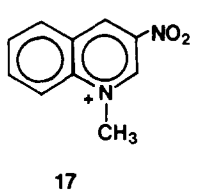
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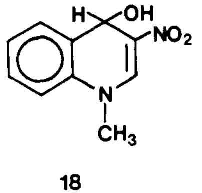
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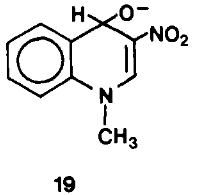
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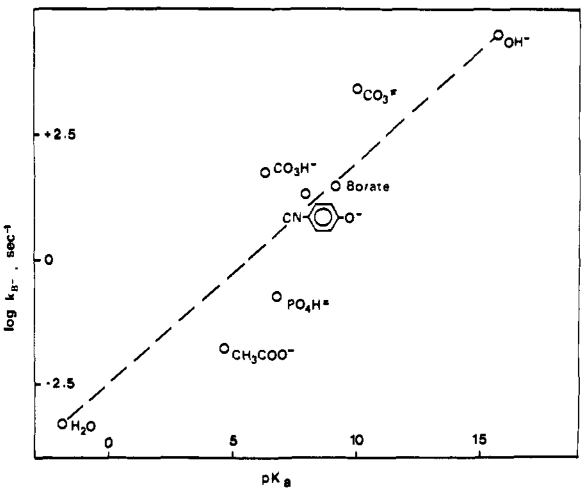

Figure 7. Log k_{B^-} for general base catalysis vs. pK_a values (not statistically corrected) of the corresponding bases: 20 °C, $\mu = 0.20$ M.

As can be seen in Table III, the most noteworthy feature is that for a roughly comparable thermodynamic stability of the addition products relative to the starting materials, the rates of formation and decomposition of the pseudobases **15** and **18** are much higher than those for **2**. This may have something to do with the fact that the transformation between **1** and **2** is accompanied by a large electronic reorganization, whereas the transformations **14** → **15** and **17** → **18** are not. This is reminiscent of the contrasting behavior between normal acids and C–H acids, which lead to anions whose charge is strongly delocalized (e.g., acetylacetone).[43] The deprotonation of the former is very fast, that of the latter very slow and has been explained along similar lines.

An additional factor which may play some role in accelerating nucleophilic attack on **11** and **14** is the positive charge. One would expect this factor to be more important when the attack is by OH^- ion, i.e., one expects the ratios k_{OH}/k_{H_2O} to be larger for **14** and **17** compared to **1**. This is in fact the case, but the effect is not dramatic: $k_{OH}/k_{H_2O} = 10^6$ M^{-1} for **1**, 8.5×10^6 M^{-1} for **14** and 3×10^6 M^{-1} for **17**.

Another noteworthy result is the fact that the ionization of the hydroxyl group of the anionic adduct **2** occurs at approximately the same pH as that of the –OH group of neutral pseudobases **12** and **15** ($pK_a'^2 = 11.30$, $pK_a'^{15} = 11.15$, $pK_a'^{18} = 13$). This result may only be accounted for if the negative charge is largely delocalized, thus confirming our earlier suggestion.

Experimental Section

Materials. 4,6-Dinitrobenzofuroxan was prepared by the procedure of Drost;[33] mp 172 °C (lit.[36] 172 °C). HCl and KOH solutions were prepared from Titrisol. Buffer solutions were made up from the best available commercial grades of reagents. Buffers used were: citrate, chloroacetate (pH < 3.3); formate (pH 3-4); succinate (pH 4-5.7); benzoate (pH 3.6-4.3); acetate (pH 4-5.2); phosphate (pH 6-7.5); bicarbonate (pH 8.38); borate (pH 8.5-9.5); carbonate (pH 9.5-10.5).

Rate and pH Measurements. Stopped-flow determinations were performed on a Durrum stopped-flow spectrophotometer, the cell compartment of which was maintained to ±0.5 °C. Other kinetic measurements were made using a Beckman DB-G spectrophotometer. All kinetic runs were carried out under pseudo-first-order conditions with a substrate concentration of about 3×10^{-5} M. Rate constants are accurate to ±3%.

The pH was measured on a Radiometer Model pH meter according to standard methods. The pH values are relative to the standard state in pure water. The pD values were obtained by adding 0.40 to the pH meter reading.[44]

Acknowledgment. We thank Professor C. F. Bernasconi (University of California, Santa Cruz) for criticism and assistance in the preparation of the manuscript. One of us (W.P.N.) thanks Professor J. F. Bunnett (University of California, Santa Cruz) for providing facilities and supplies for part of the work.

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Characterization of the Solvent Dependence of the Nonbonded Atom Interaction Energy by the Stereoselectivity of Asymmetric Reactions

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Abstract: The stereoselectivity of bromide displacement from D- or L-α-bromophenylacetic acid (BPAA) or its methyl ester (MBPA) by L-tyrosine ethyl ester or L-proline derivatives was measured in water and in aqueous solutions of methanol, dioxane, urea, and $NaNO_3$. The results were interpreted in terms of the difference in the free energies of the diastereomeric transition states which reflect nonbonded atom interaction energies in the various solvent media. The stereoselectivity was found to be much higher for processes involving the conformationally rigid proline derivatives, and, in the case of the proline amide reaction in water solution, it exhibited large temperature coefficients which had opposite signs for the reaction with BPAA and MBPA. A much smaller temperature dependence of stereoselectivity was observed in aqueous solutions containing methanol or dioxane as cosolvents. At 35 °C, reactions of L-proline derivatives with L-MBPA were always faster than those with the D isomer, although conformational analysis shows that the transition-state complex formed from L-MBPA is sterically more hindered. Large additions of methanol or dioxane always sharply reduced the stereoselectivity but in some systems the stereoselectivity passed through a maximum on addition of small concentrations of these cosolvents. Addition of urea and of $NaNO_3$ had generally little effect on the stereoselectivity.

In calculating the potential energies characterizing the various conformations accessible to synthetic polymers, it is generally assumed that the role of the solvent has to be taken into account only insofar as it affects dipole–dipole interaction energies.[2] Such interactions have been shown to be particularly important in predicting the unperturbed dimensions of polypeptides.[3] Yet, while this approach has led to valuable results in a variety of systems, it has clearly some important limitations. A striking demonstration of the anomalies that may be encountered is provided by the study of the trans–gauche conformational equilibrium of 1,2-dichloroethane.[4a] This is a particularly simple case, and the conventional analysis would have predicted that the fraction of the molecules in the gauche conformation should increase with an increasing dielectric constant of the solvent. Such a correlation is, in fact, observed with a number of media, but in benzene and dioxane solution the content of the gauche conformer is much higher than expected from the dielectric constant of these solvents. This