Proton Transfer from Cyanocarbon Acids. III.[1] Primary and Solvent Kinetic Isotope Effects in the Ionization of Malononitriles[2]

F. Hibbert and F. A. Long*[3]

*Contribution from the Department of Chemistry,
Cornell University, Ithaca, New York 14850.* *Received August 25, 1970*

Abstract: The slow proton-transfer reactions involved in the detritiation of malononitrile-*1-t* and *tert*-butylmalononitrile-*1-t* and in the bromination of the 1-H and 1-D malononitriles in the solvents H_2O and D_2O are characterized by unusual isotope effects. The primary isotope effects are $k^H/k^D = 1.49 \pm 0.03$ for reaction of both malononitriles with the catalyst H_2O and $k^H/k^D = 1.47$ for reaction of the *tert*-butyl derivative with acetate ion. Primary isotope effects can be calculated for the reverse reactions of the carbanions and are found to be very small. Both results are consistent with a transition state having the structure $RC^- \cdots HB^+$. In the water-catalyzed detritiation of *tert*-butylmalononitrile, the solvent isotope effect k_{H_2O}/k_{D_2O} has the value 3.48. When allowance is made for the secondary isotope effect on the base water, using fractionation factor theory, the large solvent isotope effect is shown to include an unusually large medium effect, which, however, can be understood in terms of the known structure of the transition state. The overall solvent isotope effect obtained when the malononitriles are allowed to exchange prior to bromination has the value $k_{H_2O}{}^H/k_{D_2O}{}^D = 5.4$. This more or less normal value results from the joint contributions of the very low primary kinetic isotope effect and the high solvent isotope effect.

Slow proton transfers in H_2O–D_2O mixtures have received considerable attention and two factors are now believed to determine the variation of rate with mole fraction in the mixed isotopic solvent.[4] The exchange effect allows for the fractionation of H or D between the solvent and all exchangeable sites in the reactants and transition state.[4f] Other possible consequences of changing the medium from H_2O to D_2O such as changes in solvation are included in the transfer or medium effect.[5] The exchange effect is normally so much more important that the medium effect is often neglected. This is not permissible, however, when there is considerable charge difference between reactants and transition state particularly when anionic species are involved.[6] In these cases change in structure of the solvent on forming the transition state can lead to differences between rates in H_2O and D_2O.[7]

The general-base-catalyzed detritiation and bromination of malononitrile and *tert*-butylmalononitrile have been shown to occur by a slow proton (or triton) transfer.[1] It was demonstrated that proton transfer to solvent water and to carboxylate species occurs through a transition state in which the proton is almost completely transferred from the carbon acid, the evidence for this being extremely low primary isotope effects, a Brønsted exponent β of almost unity, and reverse rates having properties characteristic of a diffusion-controlled reaction. This system provides the opportunity of understanding in detail the effect of changing solvent from H_2O to D_2O for a solvent-catalyzed proton transfer. Such catalysis has been subjected only to limited study in the context of H_2O–D_2O mixtures.[8]

Experimental Methods and Results

The preparation and purification of chemicals and the details of the kinetic and equilibrium measurements were described in the previous paper of this series.

The dissociation constant of *tert*-butylmalononitrile-*1-d* in D_2O at 25° corrected to infinite dilution was found to have the value $K_{D_2O}{}^{RCD} = 2.1 \pm 0.1 \times 10^{-14}$ compared with the value for its proton analog $K_{H_2O}{}^{RCH} = 7.9 \pm 0.4 \times 10^{-14}$. This gives a normal ratio of dissociation constants of 3.8 ± 0.3.

Rate coefficients at 25° and an ionic strength of 0.100 *M* for reactions in H_2O and D_2O are shown in Table I. The average deviations are shown and the number of determinations is given in parentheses after the rate coefficients. Catalytic coefficients for acetate ion were determined as the gradients of plots of rate coefficient *vs.* acetate concentration in the two solvents H_2O and D_2O. Two buffer ratios were studied in each case. Rate coefficients for hydroxide ion in H_2O and for deuterioxide ion in D_2O were calculated from the intercepts of these plots using the dissociation constants of acetic and deuterioacetic acids in H_2O and D_2O.[9] Bromination of *tert*-butylmalononitrile and its 1-D derivative in D_2O were initiated by introducing 0.05 ml of a solution of the carbon acid in dioxane into 10 ml of the D_2O solution. The bromination of the 1-D derivative in D_2O was also studied by introducing a solution of it in D_2O into the reaction mixture. The detritiation of malononitrile-*1-t* in D_2O is complicated by a possible secondary isotope effect, resulting from exchange of the proton

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[1] Part II: F. Hibbert, F. A. Long, and E. A. Walters, *J. Amer. Chem. Soc.*, **93**, 2829 (1971).

[2] Work supported by the Atomic Energy Commission.

[3] To whom requests for reprints should be sent.

[4] (a) P. Gross, *Trans. Faraday Soc.*, **32**, 877 (1936); (b) E. Noonan and V. K. La Mer, *J. Phys. Chem.*, **43**, 247 (1939); (c) E. L. Purlee, *J. Amer. Chem. Soc.*, **81**, 263 (1959); (d) V. Gold, *Trans. Faraday Soc.*, **56**, 255 (1960); (e) C. G. Swain and E. R. Thornton, *J. Amer. Chem. Soc.*, **83**, 3884, 3890 (1961); (f) A. J. Kresge, *Pure Appl. Chem.*, **8**, 243 (1964); (g) R. Salomaa, L. L. Schaleger, and F. A. Long, *J. Amer. Chem. Soc.*, **86**, 1 (1964); (h) V. Gold, *Advan. Phys. Org. Chem.*, **7**, 259 (1969).

[5] (a) E. A. Halevi, F. A. Long, and M. A. Paul, *J. Amer. Chem. Soc.*, **83**, 305 (1961); (b) V. Gold and D. C. A. Waterman, *J. Chem. Soc. B*, 839, 849 (1968).

[6] D. M. Goodall and F. A. Long, *J. Amer. Chem. Soc.*, **90**, 238 (1968).

[7] (a) C. G. Swain and R. F. W. Bader, *Tetrahedron*, **10**, 182, 200 (1960); (b) V. Gold, *Trans. Faraday Soc.*, **64**, 2143 (1968).

[8] B. D. Batts and V. Gold, *J. Chem. Soc. A*, 984 (1969).

[9] V. Gold and B. M. Lowe, *ibid.*, *A*, 1923 (1968).

Table I. Solvent Isotope Effects[a]

Carbon acid	Base catalyst	Solvent	10^4k	k_{H_2O}/k_{D_2O}
		Detritiation		
tert-BuCT(CN)$_2$	H_2O	H_2O	3.27 ± 0.02 (4)	3.48
	D_2O	D_2O	0.94 ± 0.01 (5)	
CHT(CN)$_2$	H_2O	H_2O	83.7 ± 1.6 (7)	3.67
	D_2O	D_2O	22.8 ± 0.2 (2)	
			k'	
tert-BuCT(CN)$_2$	$CH_3CO_2^-$	H_2O	0.231 ± 0.003 (2)	1.12
	$CH_3CO_2^-$	D_2O	0.206 ± 0.002 (2)	
			$10^{-5}k'$	
tert-BuCT(CN)$_2$	OH^-	H_2O	2.48 ± 0.03 (2)	0.58
	OD^-	D_2O	4.28	
		Bromination		
			10^4k	
tert-BuCH(CN)$_2$	H_2O	H_2O	5.36 ± 0.14 (4)	3.70
	D_2O	D_2O	1.45 ± 0.05 (4)	
tert-BuCH(CN)$_2$	H_2O	H_2O	5.36 ± 0.14 (4)	5.42
tert-BuCD(CN)$_2$	D_2O	D_2O	0.99 ± 0.01 (2)	

[a] k and k' are pseudo-first-order (sec^{-1}) and second-order (M^{-1} sec^{-1}) rate coefficients at 25° and $I = 0.100$.

with the D_2O solvent during the course of the reaction. However, this secondary isotope effect must be small (<5%) since no curvature of the first-order plots could be detected. The ratio of rate coefficients for detritiation of *tert*-butylmalononitrile in H_2O and D_2O was studied at 35 and 45° as well as at 25°. The values were 3.41 and 3.05 compared with 3.48 at 25°.

Degenerate activity coefficients of transfer[6] for the malononitriles between H_2O and D_2O were determined by solubility and distribution methods. The malononitrile concentration in the aqueous (H_2O or D_2O) phase was measured in both methods by removing an aliquot and observing the absorption due to the malononitrile anion (at 2375 Å for the *tert*-butyl derivative and at 2240 Å for malononitrile anion) when this sample was added to a measured excess of 2 *N* NaOH.

The solubility of *tert*-butylmalononitrile in H_2O and D_2O was determined by shaking the solid with an aqueous phase for several hours at 25°. In H_2O the solubility is 3.0×10^{-2} *M* and the ratio of solubilities $S_{H_2O}/S_{D_2O} = 1.04$. In two distribution experiments for water–cyclohexane and deuterium oxide–cyclohexane, the ratio of partition functions for *tert*-butylmalononitrile $D_{H_2O}/D_{D_2O} = 1.04$ was obtained. A similar experiment for malononitrile using ether as the nonaqueous reference phase gave $D_{H_2O}/D_{D_2O} = 1.02$. The resulting degenerate activity coefficients for transfer of *tert*-butylmalononitrile and malononitrile between H_2O and D_2O are 1.04 and 1.02, respectively.

According to the convention used in earlier papers,[6] we define the fractionation factor φ applicable to the Gross–Butler equations as the equilibrium constant of (I). This is the medium-independent constant. The fractionation factor φ' defined by (II) is more commonly used. The two are related by the degenerate activity coefficients of transfer γ (III), assuming H_2O and D_2O to be ideal and assuming no secondary isotope effect on eq III.

$$HA^{H_2O} + {}^1\!/_2D_2O^{H_2O} \rightleftharpoons DA^{H_2O} + {}^1\!/_2H_2O^{H_2O} \qquad \varphi \qquad \text{(I)}$$

$$HA^{H_2O} + {}^1\!/_2D_2O^{D_2O} \rightleftharpoons DA^{D_2O} + {}^1\!/_2H_2O^{H_2O} \qquad \varphi' \qquad \text{(II)}$$

$$HA(\text{or } DA)^{D_2O} \rightleftharpoons HA(\text{or } DA)^{H_2O} \qquad \gamma \qquad \text{(III)}$$

The relationship is

$$\varphi = \varphi'\gamma$$

This last equation clearly illustrates the way in which pure exchange effects and medium or transfer effects contribute to the effect of changing solvent.

Discussion

Primary Kinetic Isotope Effects. The rates of detritiation and the rates of bromination of the two malononitriles and their 1-D derivatives in water can be combined to give primary kinetic isotope effects for proton transfer from the carbon acids to water. Kinetic results for the bromination of *tert*-butylmalononitrile and detritiation of the 1-T derivative in acetate buffer solutions give primary isotope effects for catalysis by acetate ion. The rate coefficients are given in the previous paper;[1] the isotope effects calculated from these data are shown in Table II.

Table II. Primary Kinetic Isotope Effects

Carbon acid	Base catalyst	Exptl k^H/k^T	Exptl k^H/k^D	Calcd[a] k^H/k^D
Malononitrile	H_2O	1.71 ± 0.10	1.51	1.45
tert-Butylmalononitrile	H_2O	1.64 ± 0.05	1.46	1.41
tert-Butylmalononitrile	$CH_3CO_2^-$	1.74 ± 0.05[b]		1.47

[a] Calculated from the k^H/k^T values by the Swain relationship, $k^H/k^T = (k^H/k^D)^{1.442}$: C. G. Swain, E. C. Stivers, J. F. Reuwer, Jr., and J. L. Schaad, *J. Amer. Chem. Soc.*, **80**, 5885 (1958). [b] The bromination data (k^H) refer to $I = 0.200$, but the detritiation data refer to $I = 0.100$.

As previously noted,[1] these primary isotope effects are the lowest observed for proton transfer from carbon. This can be understood in terms of a transition state in which the proton is almost completely transferred from the carbon acid. The large p*K* difference between substrate and catalyzing base is expected to lead to a very low primary isotope effect.[10] The small isotope effect also fits in nicely with a comparison made earlier by Bell[11] of the variation in Brønsted exponents and primary isotope effects along a series of carbon acids. For this series of esters and ketones, as the Brønsted exponent measured for catalysis by carboxylate species increases from 0.42 to 0.79, the primary isotope effect (k^H/k^D) with H_2O as the base catalyst decreases from 4.5 to 2.0 in a reasonably smooth manner. The isotope effect here, $k^H/k^D = 1.48$, together with $\beta = 0.98$ extends this correlation and is consistent with Bell's proposal that the Brønsted exponent, treated as a measure of the degree of proton transfer, is closely related to the primary isotope effect.[12]

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(10) A. V. Willi and M. Wolfsberg, *Chem. Ind.* (*London*), 2097 (1964); R. P. Bell and D. M. Goodall, *Proc. Roy. Soc.*, *Ser. A*, **294**, 273 (1966); J. L. Longridge and F. A. Long, *J. Amer. Chem. Soc.*, **89**, 1292 (1967); A. J. Kresge, D. S. Sagatys, and H. L. Chen, *ibid.*, **90**, 4174 (1968); J. E. Dixon and T. C. Bruice, *ibid.*, **92**, 905 (1970).

(11) R. P. Bell, *Discuss. Faraday Soc.*, **39**, 16 (1965); J. E. Crookes and R. P. Bell, *Proc. Roy. Soc.*, *Ser. A*, **286**, 285 (1965).

(12) Recent studies and analyses [F. G. Bordwell, *et al.*, *J. Amer. Chem. Soc.*, **91**, 4002 (1969); A. J. Kresge, *ibid.*, **92**, 3210 (1970); F. G. Bordwell, personal communication] raise doubts about the general validity of equating a Brønsted exponent with the degree of proton transfer in the transition state. However, in the present limiting case of virtually complete proton transfer the correlation appears to be relatively firm.

The isotope effects for catalysis by the solvent water and acetate ion can be converted by equilibrium data to primary isotope effects for proton transfer from hydronium ion and acetic acid to the anions of malononitrile and *tert*-butylmalononitrile. For catalysis by water

$$\mathrm{RCH + H_2O \underset{-1}{\overset{1}{\rightleftharpoons}} RC^- + H_3O^+}$$

$$\mathrm{RCD + H_2O \underset{-2}{\overset{2}{\rightleftharpoons}} RC^- + DH_2O^+} \qquad \text{(IV)}$$

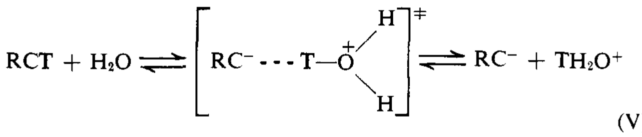
Hence for this case the reverse isotope effect is given by

$$k_{-1}/k_{-2} = (l/\varphi_{\mathrm{RCH}})(k_1/k_2) \qquad (1)$$

We can set $l = 0.69 \pm 0.02$,[4h] and can approximate φ_{RCH} by the value 1.0. This gives $k_{-1}/k_{-2} = 1.02$, with an estimated error of ± 0.15. The conclusion of a negligible primary kinetic isotope effect for reaction of hydronium ion and carbanion implies a process which involves little change in the force constants of the isotopic bond as the transition state is formed. This is as expected for a reaction that from other evidence appears to be diffusion controlled, *i.e.*, involves formation of a transition state which is virtually an "encounter" ion pair of $\mathrm{H_3O^+ \cdots RC^-}$. A different way of relating these facts is to note that in the forward direction the kinetic isotope effect is identical with the equilibrium isotope effect, and this also implies a transition state that is virtually the same as the ionic products.

A similar analysis to (1) above can be made for the reactions where acetate ion is the catalyst. In this case the reverse reactions are of $\mathrm{RC^-}$ with the species HOAc and DOAc in the solvent water. Here the reverse primary kinetic isotope effect calculates to the low value 1.40, employing the firmly established result[9] $\varphi_{\mathrm{HOAc}} = 0.96$ and $k_1/k_2 = 1.47$ for reaction of acetate ion. This small isotope effect is again consistent with earlier conclusions on mechanism.

Solvent Isotope Effects. The last column of Table I gives deuterium solvent isotope effects for three catalysts, acetate ion, hydroxide ion, and water itself. For acetate, where no exchange terms enter, the value $k_{\mathrm{H_2O}}/k_{\mathrm{D_2O}} = 1.12$ is very similar to values found for related reactions[13] and indicates a modest medium effect. In complete contrast, when water is the catalyst the solvent isotope effect is usually large, varying with substrate from 3.5 to 3.7. The detailed analysis of these effects turns out to relate closely to the reaction mechanism.



$$\mathrm{RCT + H_2O \rightleftharpoons \left[RC^- \cdots T{-}\overset{+}{O}H_2 \right]^{\ddagger} \rightleftharpoons RC^- + TH_2O^+} \qquad \text{(V)}$$

$$\frac{k_{\mathrm{H_2O}}}{k_{\mathrm{L_2O}}} = \frac{(1 - n + n\varphi_2)^2(1 - n + n\varphi_1)}{(1 - n + n\varphi_2{}^{\ddagger})^2(1 - n + n\varphi_1{}^{\ddagger})}\left(\frac{\gamma^*}{\gamma_{\mathrm{RCT}}\gamma_{\mathrm{H_2O}}}\right)^n \qquad (2)$$

Water-Catalyzed Reaction. Our remarks will apply equally to detritiation and bromination except for the last reaction shown in Table I which will be discussed separately. The solvent isotope effect in these reactions can be thought of as comprising two terms: a medium or transfer effect and a secondary isotope effect on the base water. In the light of our previous study, the transition state in (V) is written with almost complete triton transfer and closely resembles an ion pair between carbanion and hydronium ion. The solvent isotope effect can be expressed as in eq 2, where φ_2 and $\varphi_2{}^{\ddagger}$ are fractionation factors for the "water" protons in the reactant and transition state, respectively, φ_1 is the fractionation factor for the reactant malononitrile (RCT), and γ is the degenerate activity coefficient for transfer of the species from $\mathrm{H_2O}$ to $\mathrm{D_2O}$. The exchange terms φ_2 and $\varphi_2{}^{\ddagger}$ involve the secondary isotope effect on water and the term with γ the medium effect. Since we are measuring detritiation and bromination, the proton corresponding to φ_1 is prevented from fractionating in reactants and transition state and can be ignored. By definition, φ_2 and $\gamma_{\mathrm{H_2O}}$ are unity. The degenerate activity coefficients of transfer for the malononitriles have been determined. Hence for the ratio of rate coefficients in the pure solvents

$$\frac{k_{\mathrm{H_2O}}}{k_{\mathrm{D_2O}}} = \frac{1}{(\varphi_2{}^{\ddagger})^2}\,\frac{\gamma^{\ddagger}}{\gamma_{\mathrm{RCT}}} = \frac{1}{(\varphi_2{}^{\ddagger})^2}\,\frac{\gamma^*}{1.04} \qquad (3)$$

For proton transfer *from* hydronium ion, Kresge[4f] has suggested that the two protons not undergoing transfer should be given a fractionation factor (φ) in the transition state intermediate between that of the reactant (hydronium ion, for which $\varphi = 0.69$) and that of the product (water, where $\varphi = 1.0$), the precise value depending upon the degree of proton transfer. Kresge used the Brønsted exponent α as a measure of the degree of proton transfer in the transition state. Hence $\varphi = l^{1-\alpha}$. When $\alpha = 0$, corresponding to zero proton transfer, the protons have a fractionation factor identical with those in hydronium ion; when $\alpha = 1$, corresponding to complete proton transfer, the protons have a fractionation factor of unity as in water. These ideas have received experimental support.[4f,5b] The present example involves proton transfer *to* water to form hydronium ion; hence applying this concept leads to $\varphi_2{}^{\ddagger} = l^{\beta} = 0.69^{0.98} = 0.70$. This is an explicit statement of our view that the transition state protons closely resemble those in the hydronium ion. Setting $\varphi_2{}^{\ddagger} = 0.70$ implies that the secondary isotope effect on water as a base has reached a maximum value for this reaction.[14]

Putting $k_{\mathrm{H_2O}}/k_{\mathrm{D_2O}} = 3.6$ (the mean value from Table I) and $\varphi_2{}^{\ddagger} = 0.70$ into (3) gives $\gamma^{\ddagger} = 1.83$. This very high value for the degenerate activity coefficient of transfer of the transition state from $\mathrm{H_2O}$ to $\mathrm{D_2O}$ is unexpected; it accounts for almost half of the observed solvent isotope effect, the remainder coming from the secondary isotope effect on the base catalyst water. In favorable circumstances, the analysis of a solvent isotope effect into its various components can be verified by using it to predict the solvent isotope effect at intermediate mole fractions of $\mathrm{H_2O}$ and $\mathrm{D_2O}$. For the present case, however, the intermediate isotope

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(13) F. A. Long and D. Watson, *J. Chem. Soc.*, 2019 (1958).

(14) Further support for this assumption is provided by the value of the primary isotope effect. In terms of fractionation factor theory, $k^{\mathrm{D}}/k^{\mathrm{H}} = \varphi_1{}^{\ddagger}/\varphi_1 = 0.68$, where φ_1 and $\varphi_1{}^{\ddagger}$ are fractionation factors for the proton in malononitrile and the transferred proton, respectively. If we assume φ_1 to have a value close to unity, $\varphi_1{}^{\ddagger} = 0.68$. This is entirely compatible with the value $\varphi_2{}^{\ddagger} = 0.70$ for the outer protons in the transition state and indicates that the transition state resembles an ion pair with all the protons in the hydronium moiety being identical.

effects are not sensitive to the precise values given to the medium and fractionation factor terms, and we must therefore accept our conclusions of a maximum secondary isotope effect and a large medium effect term. In our subsequent discussion we will attempt to understand this large effect in terms of the transition state structure and medium effects observed for other proton-transfer transition states.

Acetate- and Hydroxide-Ion-Catalyzed Detritiation. We have already commented upon the solvent isotope effect observed for the acetate-catalyzed reaction. It can be accounted for by the degenerate activity coefficients of transfer for the species involved.

$$k_{\mathrm{H_2O}}/k_{\mathrm{D_2O}} = \gamma^{\ddagger}/\gamma_{\mathrm{RCT}}\gamma_{\mathrm{OAc^-}} = 1.12 \qquad (4)$$

Since $\gamma_{\mathrm{RCT}} = 1.04$, $\gamma^{\ddagger}/\gamma_{\mathrm{OAc^-}} = 1.16$. This low value is not inconsistent with the previous discussion. With full proton transfer, the transition state $\mathrm{RC^- \cdots TOAc}$ is virtually a carbanion and considerable cancellation of the medium effect for it and acetate ion is quite reasonable.

For hydroxide-ion- compared with deuterioxide-ion-catalyzed detritiation the expression for the rate ratio involves an additional term to allow for the exchange of the hydroxide proton; this is a secondary isotope effect on the base, hydroxide ion. φ_2 and $\varphi_2^{\ddagger}$ are fractionation factors for the "hydroxide protons" in reactants and transition state. The expression is

$$\frac{k_{\mathrm{H_2O}}{}^{\mathrm{OH^-}}}{k_{\mathrm{D_2O}}{}^{\mathrm{OD^-}}} = \frac{\varphi_2}{\varphi_2{}^{\ddagger}} \frac{\gamma^*}{\gamma_{\mathrm{OH^-}}\gamma_{\mathrm{RCT}}} = 0.58 \qquad (5)$$

The value $\varphi_2 = 0.50$ will be used in this discussion. It is the mean of the value of 0.46 measured by Heinzinger and Weston[15] and that, 0.53, which can be deduced from the ionic products of H_2O and D_2O.[16] The size of the medium effect term shown in (5) can be deduced from previous data. Kingerley and La Mer determined the equilibrium constant $K = 1.53$ for[17]

$$\tfrac{1}{2}\mathrm{H_2O} + \mathrm{OD^-}{}^{\mathrm{D_2O}} + \mathrm{Br^-}{}^{\mathrm{H_2O}} = \tfrac{1}{2}\mathrm{D_2O} + \mathrm{OH^-}{}^{\mathrm{H_2O}} + \mathrm{Br^-}{}^{\mathrm{D_2O}} \qquad \mathrm{(VI)}$$

Using this value, $(1/\varphi_{\mathrm{OH^-}})(\gamma_{\mathrm{OH^-}}/\gamma_{\mathrm{Br^-}}) = 1.54$, together with the measurement by Goodall and Long[6] of $\gamma_{\mathrm{Cl^-}}/\gamma_{\mathrm{OAc^-}} = 1.19$ and of $\gamma_{\mathrm{Br^-}}/\gamma_{\mathrm{Cl^-}} = 1.10$ by Greyson,[18] we can deduce that

$$(1/\varphi_{\mathrm{OH^-}})(\gamma_{\mathrm{OH^-}}/\gamma_{\mathrm{OAc^-}}) = 2.02 \quad \gamma_{\mathrm{OH^-}}/\gamma_{\mathrm{OAc^-}} = 1.01 \qquad (6)$$

Assuming the γ^* values for the transition states involving acetate ion and hydroxide ion to be identical, eq 4 and 6 can be combined to give the medium effect for the hydroxide-ion-catalyzed reaction

$$\gamma^*/\gamma_{\mathrm{OH^-}}\gamma_{\mathrm{RCT}} = 1.12/1.01 = 1.11 \qquad (7)$$

We can therefore calculate a value for the fractionation factor ($\varphi_2{}^{\ddagger}$) for the hydroxide proton in the transition state, the result being $\varphi_2{}^{\ddagger} = 0.96$. The value of $\varphi_2{}^{\ddagger}$ can be related to the degree of proton transfer in the transition state **1** by an analogous argument to the one used to deduce $\varphi_2{}^{\ddagger}$ in eq 3. It should have a value between that for water ($\varphi = 1.00$) and that for hydroxide ion ($\varphi = 0.50$). The observed value, 0.96, indicates that this proton closely resembles the protons in water and points to a transition state in which the proton is largely transferred from the carbon acid (**1**). In the previous paper[1] it was not possible to deduce the exact transition state structure for hydroxide-ion-catalyzed detritiation, but the conclusion here, although very approximate, is at least compatible with our earlier results.

$$\mathrm{RC^- \cdots T{-}OH}$$

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Overall Solvent Isotope Effect for Water Catalysis. The solvent isotope effect of 5.42 from the last two rows of Table I is the ratio of rates of proton transfer in H_2O to deuteron transfer in D_2O. It has a normal value. This is still consistent with our earlier discussion of the water-catalyzed reactions since the overall isotope effect is, as usual, composed of two effects: a primary isotope effect and a solvent effect measured as, for example, in the bromination of *tert*-butylmalononitrile-*1-h* in H_2O and D_2O. The only unusual feature is that here it is the primary effect which is small and the solvent effect which is large. Combination of the independently measured primary ($k^{\mathrm{H}}/k^{\mathrm{D}} = 1.46$) and solvent ($k_{\mathrm{H_2O}}/k_{\mathrm{D_2O}} = 3.7$) isotope effects gives good agreement with the overall solvent effect. This normal value suggests the following useful generalization for isotope effects in proton transfers where the solvent water is acting as the base catalyst. When the primary isotope effect is low because of a high degree of proton transfer, the solvent contribution (which itself is a combination of two factors as discussed) is likely to be large and the overall solvent effect will be quite large. However, when the primary effect is small because of little proton transfer, both contributions to the solvent effect will be low and the overall solvent isotope effect will correspondingly have a small value. Intermediate cases with intermediate degrees of proton transfer can be envisaged.

The overall isotope effect can be related through the equilibrium to the isotope effect on the reverse reaction (8), where K_1 and K_2 are acid dissociation constants in

$$\mathrm{RCH + H_2O} \xrightleftharpoons[-1]{1} \mathrm{RC^- + H_3O^+} \qquad K_1$$

$$\mathrm{RCD + D_2O} \xrightleftharpoons[-2]{2} \mathrm{RC^- + D_3O^+} \qquad K_2$$

$$k_{-1}/k_{-2} = (k_1/k_2)(K_2/K_1) = 5.4/3.8 = 1.4 \qquad (8)$$

H_2O and D_2O. The observed effect is close to the ratio of proton and deuteron mobilities in H_2O and D_2O,[19] that is, close to the effect expected if the reverse reactions are diffusion controlled, and therefore consistent with our earlier conclusions.[1]

Medium Effects on Proton-Transfer Reactions in H_2O–D_2O Solvents. There are very few examples of studies in H_2O–D_2O solvents in which the solvent acts as a base catalyst and in these, no reliable values for the medium effect contribution are given.[8,20] This study provides the first example. There are, however, many other proton transfers in which medium effects have been calculated and these are of interest in attempting to explain the present very large value.

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(15) K. Heinzinger and R. E. Weston, Jr., *J. Phys. Chem.*, **68**, 2179 (1964).

(16) V. Gold and B. M. Lowe, *J. Chem. Soc. A*, 936 (1967).

(17) R. W. Kingerley and V. K. La Mer, *J. Amer. Chem. Soc.*, **63**, 3256 (1941).

(18) J. Greyson, *J. Phys. Chem.*, 71, 2210 (1967).

(19) G. Ertl and H. Gerisher, *Z. Elektrochem.*, **66**, 560 (1962).

(20) H. H. Huang, R. R. Robinson, and F. A. Long, *J. Amer. Chem. Soc.*, **88**, 1866 (1966).

Studies of medium effects in proton transfers from hydronium ion have been discussed by Gold,[4h] who concluded that the effects were small. However, as pointed out by Gold, these low values could result from cancellation of sizable activity coefficients between reactants and transition states. For example, in the proton transfer from hydronium ion to 2-dichloromethylene-1,3-dioxolane,[5b] cancellation of activity coefficient terms gives a negligible overall medium effect, that is, the term $\gamma_S\gamma_{H_3O^+}/\gamma^* = 1.0$, where S is the dioxolane. An independent measure of γ_S gave 1.17; hence γ^* is probably significantly different from unity. This sort of cancellation only occurs when there is little difference in charge between reactants and transition state. For the water-catalyzed proton transfer from malononitriles, neutral reactants lead to a highly polar ion-pair transition state; hence a large medium effect could be anticipated. For all reactions of this type the size of the medium effect should depend upon the degree of proton transfer, *i.e.*, upon the degree of charge separation; a maximum effect is expected for the nearly complete proton transfer observed for malononitriles.

In the neutralization of nitroalkane anions by acetic acid in H_2O–D_2O mixtures, Goodall and Long[6] analyzed contributions to the rate from fractionation and medium effects. Their analysis indicated a kinetic medium effect of 13%, which when split into its individual components gave $\gamma_{S^-}/\gamma_{Ac^-} = 1.27$ and $\gamma^*/\gamma_{Ac^-} = 1.18$, where S^- is the nitroalkane anion, Unfortunately, it is not possible to make individual measurements of γ^*, but it is clear that its value is different from unity and that considerable cancellation in the ratio $\gamma_{LAc}\gamma_{S^-}/\gamma^*$ results in the medium effect of 13%.

Some idea of the magnitude of the transfer effects to be expected for an ion pair can be obtained from studies of salts in H_2O and D_2O solutions. The values $\gamma_{MX} = 1.46$ and 1.53 for potassium and silver chlorides have been measured.[6,21] In addition, S_N1 and S_N2 solvolysis reactions in H_2O–D_2O media exhibit solvent isotope effects as large as 1.5.[22]

The large transfer isotope effect could alternatively be accounted for by the inclusion in the transition state of further water molecules with fractionation factors less than unity. Such molecules could be involved in general solvation, but it is questionable whether this essentially parametric approach adds much to the present treatment.[7b] A more specific possibility is that proton transfer occurs through a bridging water molecule. This could give a term in which two additional φ values differing from unity could replace the medium effect in the expression for the solvent isotope effect (2). Evidence from other reactions is against this possibility.[23] In the present case the difference in medium effects for catalysis by the bases water and acetate would imply that if the water-bridge mechanism operates for water as a base, it does not operate for acetate. Such a difference in proton-transfer mechanism would surely be reflected in the primary isotope effects for catalysis by water and acetate ion; these isotope effects, however, are identical. The difference between medium effects for catalysis by these two bases is apparently best explained as due to a difference in free energies of transfer for the transition states and the bases acetate ion and water. The implication of all of this is that the transfer isotope effect for an extreme ion-pair transition state is sufficiently large that incorrect mechanistic conclusions from studies in H_2O–D_2O media could result from its neglect.

Acknowledgment. We wish to thank Mrs. Sue Garcia and Mrs. Diane Parchomchuk for technical assistance.

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(21) V. K. La Mer and E. C. Noonan, *J. Amer. Chem. Soc.*, **61**, 1487 (1939); P. Salomaa and V. Aalto, *Acta Chem. Scand.*, **20**, 2035 (1966).

(22) R. E. Robertson, *Progr. Phys. Org. Chem.*, **4**, 213 (1967); C. G. Swain and E. R. Thornton, *J. Amer. Chem. Soc.*, **84**, 822 (1962); P. M. Laughton and R. E. Robertson, "Solute-solvent Interactions," Marcel Dekker, New York, N. Y., 1969, Chapter 7, p 399.

(23) W. J. Albery, *Progr. React. Kinet.*, **4**, 353 (1967); M. M. Kreevoy and J. M. Williams, Jr., *J. Amer. Chem. Soc.*, **91**, 6809 (1969).