187. Primary and Secondary Isotope Effects on Proton Transfers to Diazocarbonyl Compounds

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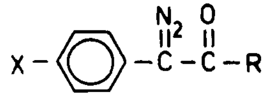
Summary

The primary solvent isotope effects on the AS_E-2 type hydrolyses of α-diazocarbonyl compounds p-$XC_6H_4CN_2CO_2CH_3$ ($X = NO_2, H, OCH_3$ and $C_6H_5CN_2CON(CH_3)_2$) are found to be identical despite large differences in their overall hydrolysis rates. The secondary solvent isotope effects diminish considerably with diminishing substrate reactivity, and for two substrates they are smaller than those normally anticipated for a simple proton transfer from the lyonium species. An analysis is presented of these and other abnormal secondary isotope effects found elsewhere, involving consideration of the solvation of the reaction complex.

Introduction. - The global solvent isotope effects on the acid-catalyzed hydrolysis of the α-diazo carboxylic esters **1a–1c** and the α-diazo carboxamide **2b**, have been shown to vary with substrate reactivity, from 1.46 for **1a** to 3.14 for **2b** [1]. Furthermore this variation has been taken not to represent a change in hydrolysis mechanism, but rather to reflect differences in the transition state structure for the protonation.



1 $R = OCH_3$
2 $R = N(CH_3)_2$

a $X = NO_2$
b $X = H$
c $X = OCH_3$

More detailed information on the transition state structure can be obtained by separating the overall solvent isotope effect into its primary and secondary components (equation (1)) [2], where $(k_D/k_H)_I$ is the contribution of isotopic substitution

$$k_{H_2O}/k_{D_2O} = (k_H/k_D)_I \times (k_H/k_D)_{II} \times \Phi^{\ddagger}/\Phi_S \qquad (1)$$

of the proton transferred in the reaction, and $(k_H/k_D)_{II}$ is that of the protons which remain bound to the solvent. The terms $\Phi^{\ddagger}$ and Φ_S are the transfer isotope effects of the transition state and initial substrate, and are given by the inverse of the ratio of the appropriate activity coefficients in H_2O and D_2O, respectively [3]. The individual isotope effects can further be expressed as

$$(k_H/k_D)_I = l/\phi_1 \qquad (2)$$

$$(k_H/k_D)_{II} = l^2/\phi_2^2 \qquad (3)$$

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where l is the fractionation factor for the hydronium-ion protons, and both ϕ_1 and ϕ_2 (the fractionation factors for the transferred and residual protons respectively [4]), vary predictably with the degree of proton transfer in the transition state [5].

The value of ϕ_1 has been measured in several hydrolyses by comparing the fraction of deuterium incorporated in the product relative to the fraction of deuterium in the solvent H_2O/D_2O mixtures. The critical assumption in this approach is that the isotopic composition of the product will reflect that of the transition state. This will be so if the protonation is irreversible [6]. So

$$\phi_1 = \frac{(D/H)\,\text{product}}{(D/H)\,\text{solvent}}. \tag{4}$$

Thus, if the values of Φ_S and $\Phi^{\ddagger}$ can be deduced or estimated, and l and ϕ_1 measured directly, the overall isotope effect can be used to calculate ϕ_2. Both fractionation factors give precious insight into the transition state structure. This approach is now applied to the hydrolysis of compounds **1a-1c** and **2b**.

Results. - *Determination of l.* The value of l, known to be 0.69±0.01 in water, increases with the dioxane content of dioxane/water mixtures [4] [7]. It has also been measured as 0.73±0.03 for the solution dioxane/water 60:40 (*v/v*), *i.e.* with dioxane mol fraction of 0.241 [8]. For our purposes we needed a more precise measure, and so we repeated the determination by the NMR. method described by *Gold* [9] and *Kresge* [10]. The effect of changing the acidity a, given by $a = [H^+]/([H]+[D])$ on the chemical shift of the water protons, is a function of the deuterium content n as expressed in equation (5); where v is the number of

$$\Delta\delta = \frac{a v \delta_j}{(1 - n + l n)} \tag{5}$$

equivalent protons having chemical shift δ_j. Hence l can be calculated from the ratio of the slopes of plots of $\Delta\delta$ against a for different values of n. This effect was measured in H_2O/D_2O mixtures using the dioxane peak as an internal reference for at least eight solutions of perchloric acid up to 0.53 M (solutions more concentrated than this gave noticable deviations from the correlation expression. The measurement was repeated for three solutions of differing deuterium content. Control experiments showed that the chemical shift dependence on perchlorate anion concentration was feeble and linear. The dioxane chemical shift, measured relative to an internal tetramethylammonium bromide reference was independent of the acid concentration up to 0.2 M. The values of l found using equation (5) *(Table 1)*, have a mean of 0.716±0.013[1]).

Table 1. *Values of the fractionation factor* l *for the hydronium ion, in dioxane/water 24:76 (mol/mol), measured by NMR.*

n	0.75	0.50	0.33	0.33[a])
l	0.705	0.733	0.706	0.722

[a]) Separate experiment.

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[1]) The errors quoted correspond to one standard deviation.

The value of l may also be derived, in principle, in a straightforward manner from the solvent isotope effect on the dissociation equilibria forming stabilized carbocations[2]).

$$\mathrm{Ar_3COL + L_3O^+ \overset{K}{\rightleftarrows} Ar_3C^+ + 2\,L_2O}. \tag{6}$$

Here

$$\frac{K_n}{K_H} = \frac{(1-n+n\Phi_{R^+})}{(1-n+n\Phi_{ROL})(1-n+n\phi_{ROL})(1-n+nl)^3} \tag{7}$$

where n is as before the atom fraction of deuterium. This expression can justifiably be simplified as Φ_{R^+} and Φ_{ROH}, the transfer isotope effects of the cation and the alcohol, should be very similar for triarylmethyl systems. Therefore

$$\frac{K_n}{K_H} = \frac{1}{(1-n+n\phi_{ROL})(1-n+nl)^3} \tag{8}$$

As equation (7) is linear in the fractionation factors Φ_{R^+}, Φ_{ROL}, and ϕ_{ROL} the solution for each is simple if the determination is made for several values of n, however extremely precise measurements would be necessary to allow estimation of factors very close to 1. In the present work we used as indicator tris(*p*-methoxyphenyl)methanol ($pK_{R^+} = 0.81$ in dioxane/water 60:40 (*v*/*v*) [11]), for which ϕ_{ROL} has been evaluated as 1.04 in water [12]. The ratio of absorbances at 486 and 283 nm (λ_{max} of R^+ and ROH respectively) were measured as a function of acid concentrations up to 0.4 M, in H_2O and in D_2O. The relations were linear in this concentration range as the ionic strength was maintained constant with sodium perchlorate. Comparison of the absorbance ratio in the isotopically different waters at any acid concentration gives directly the ratio of the dissociation constants, *i.e.* no evaluation of the extinction coefficients and hence individual concentrations is necessary. The data obtained are reported in *Table 2*. The small variation in n with acidity is due to the slight difference in deuterium content of the D_2O and $DClO_4$ solutions, and account of this was taken in the calculation of the values of l cited in the *Table*. The mean of these values 0.710 ± 0.008, is in good agreement with that estimated by the NMR. method (and involves much less fastidious experimentation). The mean value derived from both experimental approaches 0.713 ± 0.010.

Table 2. *Solvent isotope effects on the dissociation equilibria of tris(*p*-methoxyphenyl)methanol in dioxane/*L_2O *24:76 (mol/mol)*

$[L_3O^+]$M	X_H[a])	X_n	X_n/X_H	n	l
0.091	0.975	2.667	2.734	0.996	0.705
0.182	1.940	5.395	2.781	0.994	0.702
0.273	3.075	8.066	2.62	0.993	0.716
0.364	4.189	10.817	2.582	0.992	0.717

[a]) $X_H = \frac{\text{Absorbance at 486 nm}}{\text{Absorbance at 283 nm}}$ for n = 0.

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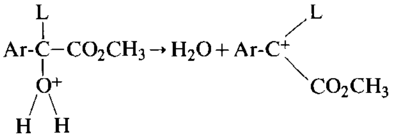
[2]) We are extremely grateful to Prof. *M. M. Kreevoy* for suggesting this method.

One may anticipate that the fractionation factors for H_3O^+ and OH^- differ only slightly between water and dioxane/water 24:76 (mol/mol) as the deuterium isotope effect on the autopyrolysis constant of water K_W is almost unchanged in the two media (despite large changes in the absolute value of K_W) [13].

Determination of the fractionation factors ϕ_l from the product isotopic compositions. The diazo compounds **1a**, **1b**, **1c** and **2b** were hydrolyzed in dioxane/water mixtures with a constant dioxane mol fraction of 0.241, but varying deuterium content. Control NMR. experiments established that the product mandelic esters and amide did not exchange their C-bound protons *a* to the carbonyl groups in deuteriated media under the reaction conditions. Quantitative analysis of the deuterium incorporation in the product was found to be more precise and reproducible by mass spectrometry than by NMR. spectroscopy. Chemical ionization was employed to limit fragmentation and its possible associated isotopic side effects. For the mandelic esters, the major, and almost unique fragmentation was $M^+ - 17$ ($= M^+ + 1 - 18$), corresponding to the formation of a stable benzylic cation.



$$\mathrm{Ar\text{-}\overset{L}{\underset{H\;\,H}{\underset{O^+}{C}}}\text{-}CO_2CH_3 \rightarrow H_2O + Ar\text{-}C^+{\scriptstyle\genfrac{}{}{0pt}{}{L}{CO_2CH_3}}}$$

For the phenyl and *p*-methoxyphenyl derivatives, this was the base peak, when methane was employed as reactant gas ($M+1 = 5$ and 13% resp.). Predictably use of isobutane as reactant gas diminished this fragmentation (by 50%), but was not used for the analysis as spectra with one predominent peak were preferred. The *p*-nitrophenyl analogue had $M+1$ as base peak ($M-17 = 10\%$). This probably represents not only a reduced stability of the benzyl cation, but also a predominant protonation on the O-atoms of the nitro group [14]. In this case both parent and fragment ions were monitored in the isotope analysis, and gave identical results (as did the electron impact (EI) and CI molecular ions for **1b**). Methane proved to be unsuitable as reactant gas for the analysis of the mandelamide, as it gave both $M+1$ (85%) and $M-1$ (50%) peaks as well as fragments at $M-15$ (100%) and $M-17$ (82%). In this case isobutane was used as only the $M+1$ peak was observed.

Introduction of the reaction products by GC. was employed to eliminate spurious peaks due to trace impurities, and to allow numerous scans under uniform conditions. The product isotope ratios and fractionation factors for several different H_2O/D_2O ratios are collected in *Table 3*. No correction for the breakdown of the rule of the geometric mean was included in the calculated fractionation factors, as there was no significant drift of the values of ϕ_l with solvent isotopic composition [15].

The values of ϕ_l found for each of the four compounds are identical within the limits of experimental error3). This result confirms the conclusion [1] that there

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3) It should be noted that the use of several solutions of different H_2O/D_2O ratio excludes the possibility that this constancy arises from a measurement artifact, due to exchange or scrambling in the mass spectrometer.

Table 3. *Fractionation factors for the proton transferred during the hydrolysis of diazocarbonyl compounds*

Substrate	$(H/D)_{L_2O}$	$(H/D)_{product}$	ϕ_l	ϕ_l (mean)	$(k_H/k_D)_l$[a]
1a	0.0209	0.112 ± 0.003[b]	0.187	0.213 ± 0.015	3.34
	0.176	0.802 ± 0.016	0.219		
	0.386	1.79 ± 0.05	0.216		
	0.687	2.98 ± 0.03	0.230		
1b	0.0209	0.106 ± 0.002[c]	0.197	0.201 ± 0.012	3.55
	0.176	0.874 ± 0.030[c]	0.201		
	0.256	1.36 ± 0.04	0.188		
	0.386	1.93 ± 0.03[c]	0.201		
	0.513	2.65 ± 0.08	0.194		
	0.687	3.49 ± 0.08[c]	0.197		
	1.03	4.52 ± 0.40	0.228		
1c	0.0209	0.097 ± 0.004	0.215	0.214 ± 0.004	3.33
	0.176	0.843 ± 0.020	0.209		
	0.386	1.80 ± 0.07	0.214		
	0.687	3.12 ± 0.10	0.220		
2b	0.256	1.39 ± 0.03	0.184	0.187 ± 0.007	3.81
	0.513	2.63 ± 0.10	0.195		
	1.03	5.71 ± 0.20	0.181		

[a] Calculated using equation (2).

[b] The errors quoted are the standard deviations from the mean.

[c] Measured on the molecular ion produced by electron impact.

is no change of hydrolysis mechanism with substituent, as such a change would primarily result in a change in ϕ_l. Furthermore the remarkable constancy of ϕ_l indicates that the variation of the solvent isotope effect with substrate reactivity is not associated with the proton 'in flight'. Therefore the primary kinetic isotope effect is insensitive to the change in transition state structure as indicated by the overall solvent isotope effect. Such an insensitivity is not rare. Whereas in principle the primary kinetic isotope effect for proton transfer to a series of bases is expected to pass through a maximum when the proton is half transferred in the transition state, the variation is not necessarily very marked [16]. In fact as *Albery* has indicated [17], the protonations of aliphatic diazo compounds of different reac-

Table 4. *Data for protonation of diazo compounds* $R^1R^2CN_2$ *by* H_3O^+

R^1	R^2	log k	ϕ_l	Ref.
H	CO_2^-	4.8	0.24	[18]
CH_3	$CO_2C_2H_5$	1.3	0.22	[19]
H	p-$NO_2C_6H_4$	1.12	0.20[a]	[8]
C_6H_5	$CON(CH_3)_2$	0.42	0.19[a]	
CH_3	$COCH_3$	−0.10	0.22	[19]
C_6H_5	C_6H_5	−0.10	0.20[b]	[20]
p-$OCH_3C_6H_4$	CO_2CH_3	−1.57	0.21[a]	
$CO_2C_2H_5$	CO_2^-	−1.7	0.27	[17]
C_6H_5	CO_2CH_3	−2.07	0.20[a]	
p-$NO_2C_6H_4$	CO_2CH_3	−3.58	0.21[a]	

[a] Dioxane/water 60:40 (*v/v*).

[b] DMSO/water 80:20 (*w/w*).

tivities by H_3O^+ all have remarkably constant fractionation factors for the proton 'in flight'. As can be seen from the assembled data in *Table 4*, the values of ϕ_l found for the protonation of substrates **1a**, **1b**, **1c** and **2b** correspond extremely well to those of other diazo compounds, covering in all 8 log units of protonation rate constant.

This phenomenon can be conveniently analyzed in terms of the *Marcus* theory of proton transfer [21] [22]. The activation free energy is dependent on three quantities: W^r, the energy invested in the formation of the 'reaction complex', which involves solvent and substrate reorganization leading to H-bond formation between the two reactants; $\Delta G_0'$, the standard free energy of proton transfer within this reaction complex; and $\Delta G_0^{\ddagger}$ the free energy of activation when $\Delta G_0'$ is zero. When $\Delta G_0'$ is zero the transition state will be symmetrical and the primary isotope effect a maximum. Furthermore when $\Delta G_0^{\ddagger}$ is large the variation of the primary isotope effect will be apparent only for large differences in $\Delta G_0'$ and $\Delta G^{\ddagger}$[23].

However this particular explanation is not appropriate for the substrates under study here, as *Albery* [24] and *Kreevoy* [20] [25] have shown that slow diazoalkane protonation is characterized by a large W^r term and a low $\Delta G_0^{\ddagger}$ term[4]). In the above analysis W^r is assumed to be isotopically insensitive, but *Kreevoy* has cautioned that this may not be so when strong H-bonds are formed [27] [2]. Normally strong H-bonds are not formed to C-atoms, and *Kresge* rightly points out that the loss of the solvational energy of the acid proton comprises a major part of the W^r term [28]. However an essential feature of the *Albery-Kreevoy* treatment is that the formation of the reaction complex involves much further solvent and electronic reorganization, leading to strong H-bond formation [20] [24][5]). Therefore the variation of ϕ_l with transition-state structure would not be from l (=0.69) for reactant-like transition states, *via* typically 0.15 for a symmetrical transition state, to 0.9 for a C-bound proton in a product-like situation, but a much less pronounced variation with limiting values as low as 0.27 corresponding to strongly H-bound complexes. As a further refinement *Albery & Kreevoy* suggest [30] that the energy barrier for proton transfers to diazo carbon be broad and low, hence diminishing any tunnel effect contribution to the primary isotope effect.

Secondary solvent isotope effects. The residual solvent isotope effects (after abstraction of the primary isotope effect) for the series **1a**, **1b**, **1c** and **2b** of 0.44, 0.45, 0.58 and 0.82 do testify to a change in the transition state structure. A decrease in reactivity (**2b**-**1a**) is associated with a more 'product-like structure' hence a smaller secondary isotope effect. The extremely small values obtained for **1a**, **1b** and **1c** indicate almost complete proton transfer, indeed two of the values are inferior to the minimum value of l^2 (=0.51 in this solvent), normally associated with the non-transferred protons of the lyonium species.

A factor which most certainly complicates the analysis is a possible change in the transfer-activity coefficients for the starting materials and the transition state.

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[4]) A differing interpretation of some of *Kreevoy*'s results has recently been presented [26].

[5]) This viewpoint is supported by the recent finding that the protonation of diazomethane by the hydronium ion has a rate constant close to the diffusion-controlled limit, in that little electron reorganization is necessary, and consequently the W^r term is small [29].

Normally most neutral or cationic organic substrates, with non-exchangeable H-atoms, have transfer isotope effects of the order of 1.0 [3], and a common simplification is to assume that the transition state effects will cancel those in the ground state. Such a simplification is inappropriate whenever the reaction in question generates or removes an anionic charge. Anions are less efficiently solvated in D_2O than in H_2O [3], and so their transfer activity coefficients are normally less than one.

The transfer coefficient can be usually found by measuring the solubility of the diazo compounds in dioxane/H_2O and in dioxane/D_2O. The measurement could not be made for **1b**, **1c** and **2b** as they separated from the saturated solution as dioxane-containing liquids. For **1a** which remained a non-solvated solid, no significant solubility difference was found ($\Phi = 1.04$). The transition state, with less negative charge should also have $\Phi \simeq 1.0$, so the low solvent isotope effect cannot, in this case, be attributed to an important transfer contribution.

Abnormal secondary isotope effects have also been noticed for the deprotonation of malononitriles [31] and disulfones [32] by water. In each of these reactions the proton transfer has been shown to be complete in the transition state, and is abnormally slow in D_2O relative to H_2O. In the study of the *t*-butylmalononitrile deprotonation (equation (9)), the primary isotope effect tends to confirm complete

$$\mathrm{RCL(CN)_2 + L_2O \rightarrow RC(CN)_2^- + L_3O^+} \qquad (9)$$
$$\mathrm{R} = t\text{-}\mathrm{C_4H_9}$$

proton transfer. However the anticipated limiting secondary isotope effect due to the non-transferred protons $= 1/l^2$ is surpassed by a factor of 1.78. *Long* recognized that the transfer-activity coefficient of the malononitrile was substantially reduced in the transition state, as a negatively charged species is being developed. Since

$$(k_\mathrm{H}/k_\mathrm{D})_\mathrm{II} = \left(\frac{l}{\phi_2}\right)^2 \times \frac{\Phi_\mathrm{RCL(CN)2}}{\Phi^\ddagger} \qquad (10)$$

a value of $\Phi^\ddagger = 0.55$ can be calculated, taking $\phi_2 = 0.7$ [31], and $\Phi_{\mathrm{RCL(CN)_2}} = 0.96$. However as *Albery* pointed out [33], this value is much smaller than that of the anion ($\Phi_{\mathrm{R(CN)2C^-}} = 0.77$), measured by the solvent isotope effect on the equilibrium with its conjugate acid. Hence the derived value is not intermediate between those of reactants and products, in contrast to analogous results for nitroalkane [34] and diketone [35] deprotonations, and furthermore indicates a solvation of the transition state entirely different from that which could be considered 'product-like'.

It is of interest that the above anomalies are not evident for deprotonations of malononitriles by carboxylate ions. In this case the value of 0.79 derived for $\Phi^\ddagger$ is, as expected close to that of the malononitrile anion, and is intermediate between this latter value and that of its conjugate acid. Thus the anomalous solvent isotope effects ascribed to the effects of transition state solvation concern only the L_2O and L_3O^+ reaction partners.

This phenomenon was analyzed by *Albery* in terms of the difference in self-diffusion coefficients of light and heavy water [36]. He proposed that for proton transfers that are extremely rapid, the rates may be limited not only by the diffusion together of the reactants to form the encounter complex, but also by reorganization of the solvent in the encounter complex to give a solvation pattern favourable to proton transfer. When the latter factor is rate-limiting, there could well be a substantial solvent isotope effect due to the 20% difference of self-diffusion coefficient of D_2O and H_2O, even though the reaction rate be not on the diffusion-controlled limit.

Indeed the reverse protonation of malononitrile anion by H_3O^+ has a rate constant of $2.6 \times 10^9 \text{M}^{-1}\text{s}^{-1}$ [37], lower than those measured for reactions controlled by translational diffusion (typical values 1.5×10^{10}-$3.0 \times 10^{10} \text{M}^{-1}\text{s}^{-1}$) [38]. Some reorganization, either of reactants or solvent must occur. The validity of the model is in no doubt, although it does imply that the proton transfer itself will be completely uncoupled to *polar*-solvent-molecule realignment - a matter on which informed opinions differ [39]. However the model does not fit *Long*'s data, as analysis reveals that an 'anomalous' factor of 1.4 ($= \Phi_{R(CN)_2C^-}/\Phi^+$) has to be rationalized. This is substantially greater than the ratio of self-diffusion coefficients which form the basis of the argument, and which have been measured by several methods as being only 1.2 [40]. It should be noted that the 40% difference of translational-diffusion coefficients between H_3O^+ and D_3O^+ is not of relevance here, as the diffusion differences that concern us are those in the solvent cage after encounter has occurred.

So we are left with several examples - protonation of α-carboxymethyl diazoalkanes **1a** and **1b** by L_3O^+, deprotonation of malononitrile, *t*-butylmalononitrile, and probably disulfones by L_2O, in which the secondary isotope effects fall outside the commonly accepted limits. The question naturally arises of to what extent the commonly accepted limits are valid. For the protonations of **1a** and **1b** the values of ϕ_2 calculated according to equation (3) are 1.07 and 1.06; for the malononitrile deprotonations, introduction of $\Phi^+ = \Phi_{R(CN)_2C^-} = 0.77$ into equation (10) yields $\phi_2 = 0.59$. The fractionation factor for the non-transferred protons in the transition state for protonation by L_3O^+ is intermediate between those of L_2O and L_3O^+. These are 1.0 (by definition) and 0.69, *in the bulk solvent*. In the reaction complex the environment, as regards solvent organization and association is certainly different from that in the solvent as a whole. It is reasonable that the dipolar solvent molecules will be more extensively oriented and associated around the H-bonded reaction and product complexes[6]. The values of ϕ_2 for protonation of **1a** and **1b** would then indicate that D_2O molecules prefer an associated state relative to H_2O molecules (here we are obliged to ignore the unpredictable effect of the dioxane co-solvent on the transition state fractionation factors). This conclusion is amply borne out experimentally, as differences in density, melting point, specific heat and viscosity show that D_2O is more structured than H_2O (at and around room temperature) [41].

The results for deprotonation of malononitrile by L_2O indicate that the fractionation factor for L_3O^+ in these reaction complexes is 0.59, *i.e.* inferior to the

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[6] The coupling of the motion of polar solvent molecules to the actual proton transfer, and the timing thereof [39], is not under consideration here. Rather we distinguish between the solvation of the transition state - be it similar to the reaction complex or product complex situations, and the solvent distribution after relaxation of the product complex.

normal value. This is difficult to verify independently, but can be rationalized in terms of the broadening of the potential wells of the H-bonds of L_3O^+ with the solvent molecules which are more tightly bound in the reaction complex [27] [2]. Introduction of further fractionation factors for the solvating L_2O molecules, for which no evidence exists in the bulk solvent, would also lower the overall value. In view of this ambiguity of interpretation caution should be applied in attributing quantitative significance to this value.

Gold [42] has already recognized that in the transition state for proton transfer, fractionation factors may not be intermediate in character between reactants and products, because of solvation effects. He was concerned with anomalous fractionation factors in hydroxide-ion reactions which he considered would not necessarily exist for hydronium ions. The experimental evidence for anomalous isotope effects on protonation by hydronium ions [33], was not then available, but the essential idea of fractionation factors peculiar to the reaction complex is applicable in both cases.

It should be noted that if the limits $1 > \phi_2 > l$ are retained the resultant values of a_i defined by equation (11) are 1.2 and 0.42 for protonations of **1a** and *t*-butyl-

$$\phi_2 = l^{(1-a_i)} \qquad (11)$$

malononitrile anion respectively. These values are irreconciliable with the well-founded interpretation of a_i as an index of the degree of proton transfer in the transition state, by analogy to the *Brönsted*-a_B [43]. It is now recognized that those cases of anomalous values of the *Brönsted*-a_B found for deprotonation of substituted nitroalkanes are due to the differences, in electronic distribution and solvation, between the nascent nitroalkane anions *in the reaction complex*, and the product nitronate anions. The 'anomalous' a_i-values noted above result from a similar disparity between the situation in the reaction complex and in free solution - in this case as regards the L_3O^+ and L_2O species.

Conclusion. - The variation of the kinetic solvent isotope effect on the hydrolysis of 2-aryl-2-diazocarboxylic esters and *N,N*-dimethyl-2-phenyl-2-diazoacetamide with substrate reactivity is a consequence of differing transition-state geometry. The primary isotope effect is shown to be, once again, an insensitive measure of this change, whereas the secondary effects are more informative.

Extensive solvent reorganization in the reaction complex prior to proton transfer, may be responsible not only for holding constant the primary isotope effect, for a spectrum of transition state geometries, but also for enlarging the limits of possible secondary isotope effects. The latter effect will only be discernable when proton transfer is (almost) complete in the transition state.

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Experimental Part

Generalities: see [1]. UV. spectra were measured on a *Pye Unicam* 8-1000 spectrophotometer. $HClO_4$ was *Merck p.a.* grade 70%. Standard solutions were titrated with *Merck* Titrisol NaOH. $NaClO_4$ was the *Merck p.a.* grade. Tetramethylammonium bromide was the *Fluka purum* product. Compounds **1a**, **1b**, **1c** and **2b** were synthetized as described previously [1].

The residual solvent-proton content of solutions in D_2O was monitored by NMR. calibration with a known quantity of sodium acetate. D_2O contained 99.5% deuterium. $DClO_4$ was prepared by five successive cycles of addition of D_2O 10 ml to $HClO_4$ (70%) 10 ml, followed by distillation of the excess water. The 2M solution obtained by dilution contained 98.5% deuterium. Dioxane/L_2O

Table 5. *Variation of Chemical Shift of H_2O protons with acidity* a[a])

n[b])	$a \cdot 10^3$	$\Delta\delta$ Hz	n	$a \cdot 10^3$	$\Delta\delta$ Hz
0.0	0.00	35.24	0.33	9.05	58.97
0.0	1.94	39.77	0.33	10.61	62.85
0.0	2.17	40.10	0.33	11.58	65.88
0.0	3.80	44.82	0.50	0.00	35.18
0.0	4.23	45.92	0.50	1.63	41.11
0.0	5.46	48.36	0.50	3.91	47.52
0.0	6.39	50.72	0.50	5.43	52.23
0.0	7.47	53.75	0.50	7.19	57.12
0.0	8.30	55.35	0.50	8.56	60.83
0.0	9.13	57.29	0.50	9.97	64.20
0.0	10.18	59.99	0.50	11.71	68.75
0.0	11.85	63.86	0.50	12.91	72.18
0.33	0.00	34.37	0.50	13.26	73.30
0.33	1.91	39.93	0.66	0.00	34.54
0.33	2.25	40.48	0.66	1.11	38.59
0.33	3.17	42.96	0.66	2.12	41.62
0.33	3.79	44.82	0.66	2.94	44.31
0.33	4.38	46.10	0.66	3.86	46.93
0.33	5.78	49.57	0.66	5.69	52.74
0.33	5.88	50.55	0.66	6.17	54.00
0.33	6.06	50.23	0.66	6.60	55.44
0.33	7.04	53.58	0.66	7.35	57.79
0.33	8.50	56.83			

[a]) Defined by equation $a = [H^+]/([H]+[D])$.

[b]) The small progressive deviation from the quoted value (max. 1%), with increasing acidity (see *Table 2*), is neglected in these experiments as two regression lines are compared.

Table 6. *Dependence of the H_2O chemical shift in dioxane/H_2O 60:40 (v/v) on concentration of the perchlorate ion*

$[ClO_4^-]$ M^{-1}	$b \cdot 10^4$ [a])	$\Delta\delta$ Hz	$[ClO_4^-]$ M^{-1}	$b \cdot 10^4$ [a])	$\Delta\delta$ Hz
0.028	6.4	34.37	0.198	44.7	33.19
0.045	10.2	34.37	0.231	52.1	32.03
0.089	20.0	34.04	0.275	61.8	32.86
0.074	17.6	34.20	0.292	70.0	32.52
0.117	26.4	33.70	0.314	78.9	32.44
0.158	35.6	33.70			

[a]) Defined by equation $b = ClO_4^-/(2[H_2O]+[ClO_4^-])$.

mixtures, both acidic and neutral, were prepared by addition of the appropriate weight of dioxane to give a constant mol ratio of 0.241:0.759 relative to L_2O (corresponding to dioxane/H_2O 60:40 (*v/v*)).

Determination of factor 1. - By *NMR. method.* Chemical-shift differences were measured on a *Perkin-Elmer* R-248 (no deuterium lock necessary), and traced on a scale of 3.37 Hz/cm. Five measures were made for each solution. The data obtained are reported in *Table* 5. The dependence of H_2O chemical shift on perchlorate ion concentration was measured with solutions of $NaClO_4$ up to 0.3 M (corresponding to a $HClO_4$ '*a*' value of 7.9×10^{-3}. The independence of the dioxane chemical shift on acidity was measured relative to $(CH_3)_4NBr$ 0.2 M internal standard, for acid solutions up to 0.2 M (at higher concentrations crystallization of $(CH_3)_4NClO_4$ occurred).

By *indicator method.* Solutions of varying acidity in differing dioxane/L_2O mixtures were prepared by dilution of stock solutions of $LClO_4$ 0.5 M in each dioxane/L_2O mixture with $NaClO_4$ in the same mixture. For the UV. measurement 10% by volume of solutions of the indicator, 6×10^{-4} M in each solvent mixture were added.

Determination of product-fractionation factors. Generally the diazo compound (30 mg) was added to a solution of $HClO_4$ 0.5 M in dioxane/L_2O 241:759 (mol/mol) (10 ml). When all the diazo compound had reacted (followed by TLC.), the medium was neutralized with $NaHCO_3$-solution, and extracted with CH_2Cl_2 (5 × 10 ml). The CH_2Cl_2 extract was washed with water (5 × 20 ml) and dried over $MgSO_4$. The solution were directly analyzed by GLC./MS.; retention times on OV (17, 3%, 1 m) column with flow rates (methane, 7.5 ml/min): **1a** 4.5 min at 180°; **1b** 1.4 min at 145°; **1c** 3.2 min at 170°; **2b** 5.2 min at 180°.

MS. analyses (Spectra Chemical Ionization, CH_4 source, pressure 1 Torr, ionization energy 300 eV, *m/z*). - **1a**: 252 (2), 240 (5), 212 (100, $M+1^+$), 194 (10); **1b**: 177 (5), 167 (2, $M+1^+$), 149 (100); **1c**: 219 (2), 207 (5), 197 (13, $M+1^+$), 179 (100); **2b**: 192 (20), 180 (85, $M+1^+$), 178 (50), 164 (100), 162 (82). - Chemical Ionization ($^iC_4H_{10}$): **1b**: 167 (100, $M+1^+$), 149 (60); **2b**: 180 (100, $M+1^+$).

Technique. A window of three mass units (m.u.) was repetitively scanned at 10 m.u./s. Only the spectra corresponding to the summit of the GLC. peak (typically two per GLC.) were retained, as the relative peak intensities were not falsified by concentration differences during sampling; peak surfaces were accurately proportional to their heights. Samples of non-deuteriated material were run to exactly determine the contribution of the ^{13}C-isotopes in protonated material to the intensity of the peak for deuteriated material. The product isotope ratio D/H) prod. is given by D/H) prod. = A/(B-AC), where A = intensity of RH peak, B = intensity of RH + 1, C = ratio of (RH + 1)/RH in undeuterated material. Each product ratio reported in *Table 3* is the mean of between 15 and 50 determinations run on samples from three separate hydrolyses.

Determination of the transfer isotope effect for **1a**. After shaking **1a** (30 mg) with basic solutions (pL = 10) of dioxane/H_2O and dioxane/D_2O (5 ml) under N_2 and in the dark, the suspension were sampled by filtration followed by dilution of 10 µl of filtrate to 10 ml in ethanol. These dilute solutions had to be carefully kept in the dark as photodecomposition was found to be rapid. Each dilution was repeated twice and the absorbance at 345 nm was measured immediately. The mean absorbance ratio of samples from protic and deuteriated solutions were 1.025, 1.007, 1.051 and 1.036, sampled after 2, 4, 24 and 36 h.

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