Isotope Effects in Proton-transfer Reactions. VII.* Deuterium Solvent Isotope Effect and Primary Kinetic Isotope Effect on the Racemization of 2-Phenylpropionitrile in Methanol/Methanol-*O-d*

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The deuterium solvent isotope effect in mixtures of methanol and methanol-*O-d* has been determined for the methoxide-catalysed racemization of optically active 2-phenylpropionitrile at 25 °C. The limiting value of the ratio of the rate constants is $k_{MeOD}/k_{MeOH} = 2.10 \pm 0.03$. Application of the fractionation-factor theory leads to some discrepancy from the accepted solvation number of the methoxide ion. The primary kinetic isotope effect in different mixtures of methanol and methanol-*O-d* has been found to be constant, $k_D/k_H = 0.41 \pm 0.04$.

Solvent isotope effects are often considered useful in the investigation of reaction mechanisms.[1,2] In particular the information obtained from experiments in mixtures of light and heavy solvents has been considered to be of value in such studies.[2] A simple correlation between the solvent isotope effect and the involvement of solvent in the transition state has, however, been questioned.[3,4]

A rather strong solvent isotope effect was found in a recent investigation of the racemization of 2-methyl-3-phenylpropionitrile.[5] The limiting value of the ratio of the rate constants was $k_{CH_3OD}/k_{CH_3OH} = 2.11 \pm 0.05$ at 60 °C. The β-value derived from this ratio was somewhat low compared to the previously determined β which was obtained from a Brønsted plot based on an acidity function for methanol-dimethyl sulfoxide solutions. (The latter had been established by means of substituted anilines as indicator bases.) This together

with some collected literature data from other reactions strongly emphasized the apparent absence of a simple relationship between the solvent isotope effect and the transition-state symmetry.

In the present work we have investigated the variation of the kinetic solvent isotope effect and the primary kinetic isotope effect on the racemization of 2-phenylpropionitrile in mixtures of methanol and methanol-*O-d*. A comparison with the related results for 2-methyl-3-phenylpropionitrile [5] is made.

EXPERIMENTAL

2-Phenylpropionitrile. The preparation of optically active and isotopic nitriles has been described previously.[6] Both enantiomers of the nitriles were used.

Methanol and methanol-O-d. The purification of the methanol and the determination of the water content were carried out as before.[6] Commercial methanol-*O-d* (CIBA) with an isotopic purity > 99 % D was used without further purification.

Kinetic runs. The preparation of solutions and the kinetic runs were carried out as previously described.[6] In order to minimize the inter-experimental errors, an effort was made to evaluate the rate constants for the light and heavy nitrile from the same run using 2-phenylpropionitrile with a deuterium content at position 2 of about 50 %. The rate constants were calculated using the program PROGA-EXP.[7] Unfortunately the uncertainty in the rate constants obtained for the light nitrile was too large. Hence these rate constants were obtained from runs with undeuterated nitrile.

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* For Part VI of this series, see Ref. 6.

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RESULTS

Table 1 shows the kinetic solvent isotope effect in mixtures of methanol and methanol-O-d. The k_n values for $n = 0.00$, 0.20 0.40, 0.60, and 0.80 were obtained in solutions prepared from the same stock solution of sodium methoxide. Another stock solution prepared from methanol-O-d was used for $n = 0.99$. A small error in the determination of the stock base concentration could thus have caused an extra error in the $k_{0.99}/k_0$ ratio. To check this, one value in 80 % methanol/20 % methanol-O-d was measured using the latter stock solution. The values of k obtained by means of the two different solutions showed no significant difference.

The limiting kinetic solvent isotope effect has been determined by means of a polynomial expression, which represents the least-squares fit of the experimental values. This polynomial is: $k_n/k_0 = 1.00 + 0.72n + 0.38n^2$, giving $k_1/k_0 = 2.10 \pm 0.03$ when the accuracy of the determination in 99 mol % methanol-O-d is taken into account.

The primary kinetic isotope effect in methanol and in mixtures of methanol and methanol-O-d

Table 1. Kinetic solvent isotope effect on the racemization of 2-phenylpropionitrile in mixtures of methanol and methanol-O-d. Temperature: 25.15 ± 0.05 °C. Concentration of substrate: 0.16 – 0.18 M. n = mol fraction of methanol-O-d.

n	[Base]/ mM	$k_n/$ 10^{-1} M^{-1} s^{-1} [a]	k_n/k_0 [b]
0	4.0	2.17 ± 0.03	1.00 ± 0.02
0.199	4.0	2.46 ± 0.03	1.13 ± 0.02
0.199	5.1	2.42 [c]	
0.399	4.0	2.93 ± 0.05	1.35 ± 0.03
0.599	4.0	3.40 ± 0.03	1.57 ± 0.02
0.799	4.0	3.92 ± 0.02	1.81 ± 0.02
0.99	5.1	4.53 ± 0.03	2.09 ± 0.03

[a] k_n is the mean of the second-order rate constants from at least 3 runs. Error limits are standard deviations of the mean values. [b] k_n/k_0 is the ratio between the second-order rate constants obtained in a solvent with a fractional content n of methanol-O-d and in ordinary methanol, respectively. [c] Obtained from one kinetic run using the same stock solution of sodium methoxide as for $n = 0.99$, (*cf.* Results).

Table 2. Primary kinetic isotope effect on the racemization of 2-phenylpropionitrile in mixtures of methanol and methanol-O-d. Temperature: 25.14 ± 0.05 °C. Concentration of base: 4.0 mM. Concentration of substrate: 0.15 − 0.18 M.

Mol fraction of methanol-O-d (n)	k_D/k_H [a]
0.0	0.42 ± 0.02
0.199	0.41 ± 0.01
0.399	0.41 ± 0.03
0.599	0.42 ± 0.02
0.99	0.40 ± 0.02

[a] k_D obtained from kinetic runs with a deuterium content in the nitrile of about 50 %. See Experimental.

is shown in Table 2. As can be seen from the table, k_D/k_H is constant within the experimental errors.

DISCUSSION

The interpretation of the experimental results obtained in the present investigation is given in terms of the fractionation theory.[8] According to this theory,

$$k_n/k_0 = (1 - n + n\phi^{\ddagger})^p/(1 - n + n\phi_{MeO})^m$$

where k_n is the rate constant for a reaction in a mixture of methanol-O-d and methanol with the fractional deuterium content n and k_0 is the rate constant for the corresponding reaction in methanol. $\phi^{\ddagger}$ and ϕ_{MeO} are the fractionation factors for the transition state and the methoxide ion, respectively. The number of methanol molecules solvating the methoxide ion and the transition state are denoted m and p, respectively.

The fractionation factor for the methoxide ion has been determined experimentally,[9,10] and we have started from the value $\phi_{MeO} = 0.73_8$ determined at 33.5 °C.[9] Assuming a pure zero-point energy effect, the value at 25.15 °C would be 0.73_9 which is the value used in the present paper.

In order to enable a comparison to be made, the results from our previous investigation on 2-methyl-3-phenylpropionitrile [5] are shown together with the results from the present in-
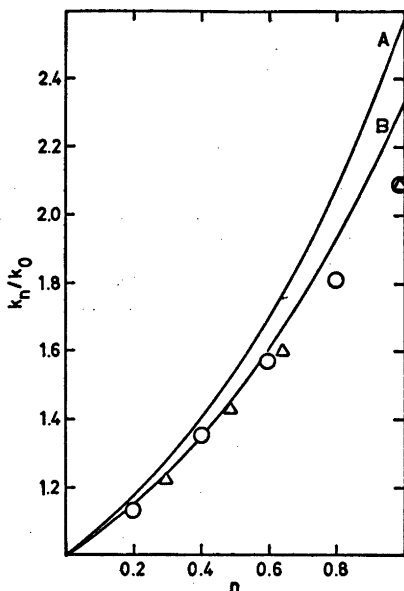
Fig. 1. Plot of k_n/k_0 *versus* n. O: 2-phenyl-propionitrile, experimental values at 25 °C. △: 2-methyl-3-phenylpropionitrile, experimental values at 60 °C. Solid curves: theoretical curves $k_n/k_0 = (1 - n + n\phi_{MeO})^{-3}$ for $\phi_{MeO} = 0.73_0$ (A) and $\phi_{MeO} = 0.75_4$ (B).

vestigation in Fig. 1, where k_n/k_0 is plotted *versus* the fractional deuterium content in the solution. The solvent isotope effect is rather strong in both cases, but as the two investigations refer to two different temperatures, it should be somewhat stronger for 2-methyl-3-phenylpropionitrile than for 2-phenylpropionitrile at comparable temperatures.

In Fig. 1 two curves, A and B, are also drawn corresponding to $m = 3$ and $\phi^{\ddagger} = 1$ at 25 and 60 °C, respectively. These curves correspond to the assumption that the methoxide ion is solvated by three methanol molecules and that the transition state contains no methanol molecules with properties different from those in the bulk of the solution. In other words, the interaction between the transition state and the solvent would be negligible for a reaction which gives a curve like A or B. The only interaction with the solvent would be that of the methoxide ion. The experimental results for the two compounds, although referring to different temperatures, show a remarkable conformity, but the corresponding

limiting curves deviate rather much due to the different values of ϕ_{MeO} at 25 °C (0.73_0) and 60 °C (0.75_4). From this comparison it can be concluded that the interaction between the solvent and the transition state is weaker in the reaction of 2-methyl-3-phenylpropionitrile than for 2-phenylpropionitrile. This idea of a rather weak interaction between the transition state and the solvent in the reaction of 2-methyl-3-phenylpropionitrile has previously been suggested.[5]

In the previous investigation of 2-methyl-3-phenylpropionitrile, $\phi^{\ddagger}$ (at 60 °C) was computed from k_1/k_0 for different combinations of m and p,[5] but in the present paper we have adopted a somewhat different method and applied it to the experimental data obtained with both nitriles.

The expression for k_n/k_0 can be transformed into:

$$[(1 - n + n\phi_{MeO})^m k_n/k_0]^{1/p} = 1 + n(\phi^{\ddagger} - 1)$$

As we know ϕ_{MeO}, we are able to calculate the left-hand member for each experimental k_n/k_0 value and each set of m and p and plot it *versus* n. The best straight line through the points gives $\phi^{\ddagger}$. The results for some combinations of m and p are given in Table 3 together with the correlation coefficients obtained from the least-squares treatment.

Table 3. Transition-state fractionation factors $\phi^{\ddagger}$ for different numbers of methanol molecules solvating the methoxide ion (m) and the transition state (p). Numbers in italics are the correlation coefficients obtained from the least-squares treatment. I denotes 2-phenyl-propionitrile, II 2-methyl-3-phenylpropionitrile. (Primary data for the latter have been taken from Ref. 5.)

$m = 1$		$m = 2$		$m = 3$	
I	II	I	II	I	II
$p = 1$					
1.549	1.592	1.136	1.202	0.831	0.907
0.998	*0.997*	*0.954*	*0.994*	*0.967*	*0.951*
$p = 2$					
1.246	1.262	1.066	1.097	0.911	0.953
0.998	*0.999*	*0.953*	*0.993*	*0.965*	*0.949*
$p = 3$					
1.158	1.168	1.044	1.063	0.940	0.968
0.998	*0.999*	*0.953*	*0.993*	*0.964*	*0.949*

It has been shown in other investigations [5a,b,10] that $m = 3$ is a very reasonable assumption. We have thus to confine ourselves first-hand to $m = 3$ and different values of p. As can be seen in Table 3, the fit is rather poor (to judge from the correlation coefficient) for at least 2-methyl-3-phenylpropionitrile independently of the value of p. A slightly better fit is obtained for 2-phenylpropionitrile. The reverse is true for $m = 2$ but for both compounds the fit becomes best with $m = 1$. However, a value of m less than 3 results in $\phi^{\ddagger} > 1$ which is somewhat difficult to interpret as we expect $\phi^{\ddagger}$ to lie between the value of ϕ_{MeO} and 1.

Fractionation factors greater than unity have been called upon recently to explain experimental evidence in amide methanolysis.[11] A fractionation factor $\phi^{\ddagger} = 1.2$ for the methanol molecules in the solvation shell of the transition state was found to be consistent with the experimental values. The methanol molecules in the solvation shell were thought to be trapped in a "gas-like" state during the existence of the transition state.

Due to the rather limited experimental data in the present investigation and also to the demand for very high accuracy of the data it is not easy to decide whether the present results could be explained in such terms. On the other hand, a definite discrepancy seems to exist between the results obtained and the predictions from a conventional application of the fractionation-factor theory. The deviations seem to be somewhat larger for 2-phenylpropionitrile. Whether the difference between the two carbon acids is caused by their different ability of delocalizing the developing negative charge in the transition state is a question which must be further investigated.

Provided that the number of methanol molecules solvating the transition state is the same for both compounds, the fact that the limiting solvent isotope effect for 2-methyl-3-phenylpropionitrile is probably stronger than that for 2-phenylpropionitrile at comparable temperatures means that the value of $\phi^{\ddagger}$ must be greater for the former substrate than for the latter.

The primary kinetic isotope effect has been found to be independent of the deuterium content of the solvent. This was also the case for 2-methyl-3-phenylpropionitrile.[5] A finding deviating from this behavior has been reported for the proton transfer from 2-nitropropane to hydroxide ion or methoxide ion. In these cases a weak interdependence was found.[4,9b]

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