Acta Chemica Scandinavica A 30 (1976) 411—417

Isotope Effects in Proton-transfer Reactions. VI.* Base-catalysed Racemization of 2-Phenylpropionitrile in Dimethyl Sulfoxide-Methanol Solutions

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The primary kinetic isotope effect in the racemization of 2-phenylpropionitrile with sodium methoxide as base has been determined in mixtures of methanol and dimethyl sulfoxide (DMSO) at +10 °C. A rather large increase in the strength of the isotope effect with increasing amount of DMSO has been observed. In methanol $k_D/k_H = 0.37 \pm 0.02$ and in 62 % methanol − 38 % DMSO $k_D/k_H = 0.18 \pm 0.01$. The variation and the magnitude of the primary kinetic isotope effect is believed to reflect an increasing symmetry of the transition state for the proton-transfer reaction with increasing concentration of DMSO in the solution. Brønsted's β determined by the acidity-function method equals 0.9. This, together with an observed curvature in the Brønsted plot, are facts which make it credible that 2-phenylpropionitrile does not behave as a Hammett base under the prevailing conditions.

The study of proton-transfer reactions has lately become a field of increasing interest, and efforts have been made to obtain detailed information on the transition-state structure in such reactions. A review of the work in the field has recently been published,[1] and can be consulted for references. The experimental quantities most frequently used as measures of the transition-state symmetry are the primary kinetic hydrogen isotope effect and Brønsted's β for the reactions. However, the validity of these quantities as indices of transition-state symmetry has recently been seriously questioned.[2,3] These doubts have mainly developed after the observation of anomalous Brønsted coefficients (see Ref. 2 and references cited there).

The compounds hitherto found to give rise to such deviations are all nitro compounds, and anomalies are observed when substituent changes are made in the substrate instead of in the catalysing base.[3] Brønsted β's less than zero as well as greater than unity are observed. Bordwell and Boyle[4] have suggested a two-step mechanism for the deprotonation of nitroalkanes to rationalize these effects.

For cyanocarbon acids, which in general are thought to behave as almost normal acids in the Eigen sense,[5,6] no anomalies have hitherto been reported, and we have now extended our investigations of proton transfers from cyanocarbon acids with an investigation of the base-catalyzed recemization of 2-phenylpropionitrile (I). In an earlier investigation,[7] a very weak kinetic isotope effect was found for the racemization of 2-methyl-3-phenylpropionitrile (II) in methanol. A Brønsted β equal to unity within the error limits was also determined by use of an acidity-function approach.

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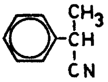

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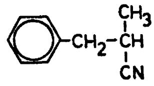

The present substrate, 2-phenylpropionitrile (I), is interesting from the point of view that there exists a possibility of delocalizing the negative charge into the phenyl group in the

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* For Part V of this series, see Bergman, N.-Å. and Melander, L. *Acta Chem. Scand. A 28* (1974) 747.

transition state and in the resulting carbanion, a possibility which is missing in II. The consequences of this for the magnitude and variation of the kinetic primary isotope effect seemed to be worth investigating.

EXPERIMENTAL

(±)-2-Phenylpropionitrile was synthesized according to Wideqvist,[8] b.p. 66–67 °C/0.27 kPa. Lit [8] b.p. 99.8 °C/1.06 kPa.

(±)-2-Phenylpropionic acid was prepared by hydrolysis of the nitrile to the acid. In a typical run, 29.5 g (225 mmol) of 2-phenylpropionitrile, 30 ml of water, 30 ml of glacial acetic acid and 30 ml of concentrated sulfuric acid were refluxed for 1 h. The mixture was poured onto ice. The oil layer was separated off and the aqueous layer was extracted with ether. The organic layers were combined and washed with water. The ether solution was dried over anhydrous magnesium sulfate. The solvent was evaporated and the residue gave upon distillation *in vacuo* 27.4 g (81 %) of the acid, b.p. 137–138 °C/0.87 kPa.

(−)-2-Phenylpropionic acid was obtained according to Pettersson.[9] The specific rotation of the acid was $[\alpha]_D^{25}$ −76.5° (*c* 0.0177, ethanol), lit.[10] $[\alpha]_D^{25}$ −79.1° (*c* 0.0157, ethanol).

(+)-2-Phenylpropionic acid was also obtained according to Pettersson.[9] The specific rotation of the acid was $[\alpha]_D^{25}$ +75.5° (*c* 0.0849, ethanol). lit.[10] $[\alpha]_D^{25}$ +79.0° (*c* 0.0167, ethanol).

(−)-2-Phenylpropionamide and (+)-2-phenylpropionamide were prepared according to Pettersson.[9]

(+)-2-Phenylpropionitrile. The optically active nitriles used in this investigation were all prepared by dehydration of the corresponding amide, and in a typical run 3.7 g (24.8 mmol) of the (−)-2-phenylpropionamide and 8 g (56.35 mmol) of P_2O_5 were mixed and heated *in vacuo*. The optically active nitrile distilled at 85 °C/0.4 kPa and the yield was 2.1 g (64.6 %). The specific rotation was $[\alpha]_{436}^{25}$ +39.7° (*c* 0.035, methanol).

(−)-2-Phenylpropionitrile. The nitrile was prepared in the same way as described for (+)-2-phenylpropionitrile. The specific rotation was $[\alpha]_{436}^{25}$ −43.4° (*c* 0.025, methanol).

(±)-*2-Phenylpropionitrile-2-*d was prepared according to Cram and Uyeda.[11] Deuterated nitrile was hydrolyzed to acid in the same way as the undeuterated nitrile.

The *(+)-* and *(−)-2-phenylpropionic-2-*d *acids* were obtained by resolution[9] of the racemic deuterated acid. The specific rotations were $[\alpha]_D^{25}$ +75.1° (*c* 0.0225, ethanol) and −75.3° (*c* 0.0278, ethanol), respectively.

*(+)-2-Phenylpropionitrile-2-*d and *(−)-2-phenylpropionitrile-2-*d were prepared in the same way as described above for the undeuterated optically active nitriles. The specific rotations were $[\alpha]_{436}^{25}$ +42.6° (*c* 0.0059, methanol) and −42.7° (*c* 0.0508, methanol), respectively.

Purity of optically active nitriles. The products were all pure according to gas-liquid chromatography. The analyses were performed on a Perkin-Elmer 900 gas chromatograph fitted with a flame ionization detector. The outer diameter of the column used was 3 mm and the length 2 m. The stationary phase was 3 % of SE-30 silicon gum rubber on Gaschrom Q 100–120 mesh and the flow rate of nitrogen was 30 ml/min.

IR analysis of the neat liquid in a sodium chloride cell on a Beckmann IR 9 instrument showed a strong absorption at 2240 cm^{-1}.

^1H NMR analysis on a Varian A 60 (CCl_4): δ 7.25 (5 H, s), 3.80 (1 H, q), 1.50 (3 H, d).

Mass spectrometry on an AEI MS 902 instrument using the glass heated inlet system showed 95 % D in position 2 in the deuterated nitriles. The following conditions were used: sample temp. 100 °C, source temp. 200–300 °C, electron energy 10 eV, accelerating voltage 8 kV and emission 20 μA.

Methanol. Commercial methanol with a water content less than 0.05 % (Merck Methanol zur Analyse) was dried in the following way. Clean dry magnesium turnings were warmed with methanol in a flask until all of the magnesium had been converted into methoxide. More methanol was added, and after refluxing the methanol was distilled into a receiver equipped with a syringe needle which made it possible to transfer the methanol to a glass bottle closed with a rubber plug and metal closure. The entire procedure was performed under an atmosphere of nitrogen and in dried glassware. The bottles with purified methanol were stored in a desiccator.

In later kinetic runs commercial methanol (May & Baker Methanol anhydrous) was used without further purification. The water content in each batch of the methanol was determined by gas chromatography [12,13] using a Perkin-Elmer F11 instrument fitted with a hot wire detector. The outer diameter of the column used was 9 mm and the length 2 m. The column was filled with Porapak Q: column temp. 120 °C, carrier gas helium, flow rate 50 ml/min. The water content in the methanol was always less than 0.033 % by weight.

Dimethyl sulfoxide (DMSO) was dried over Linde type 4 A molecular sieves, distilled under reduced pressure and stored under an atmosphere of nitrogen.

Sodium-methoxide. A 20–100 mM stock solution of sodium methoxide was made by dissolving clean sodium metal in the above methanol under an atmosphere of dry nitrogen. The solution was titrated using a Radiometer Titrigraph, diluted with dry methanol and used for the kinetic runs. The error in the base concentration was less than 3 %. Titration of some of the solutions before and after the kinetic run gave good agreement, within the experimental error.

All kinetic runs were performed on a Zeiss Old 5 digital polarimeter using the wave length 436 nm and with an accuracy in the reading of ±0.001°. The reactions were performed in a thermostated 10 cm polarimeter cell, equipped with vacuum windows. The temperature measurements were made, just outside and after the cell, in the circulating water from the thermostat, using a calibrated thermistor connected to a FLUKE 8300 A digital voltmeter. The thermistor was calibrated against a Hewlett Packard 2801 A quartz thermometer to a precision of 0.1 °C and was capable of measuring temperature changes of less than 0.002 °C. The temperature was maintained by a Hetofrig cooling bath, type CB6, together with a Hetotherm Ultrathermostat O2 Pt 623 UO. The temperature fluctuation within each run was less than 0.1 °C at 0 °C and less than 0.02 °C at higher temperatures. A Compucorp 425 G Scientist calculator, interfaced on line with the polarimeter and the voltmeter, collected polarimeter data, temperatures, and times, and evaluated rate constants using a least-squares program.

In a typical run, 0.023 g (0.176 mmol) of the nitrile and 1 ml of the pre-thermostated sodium methoxide solution were mixed and added to the polarimeter cell by means of a syringe. In the case of the fastest reactions, the polarimeter cell was first charged with methoxide solution by means of a syringe. Using another syringe, charged with a proper amount of the nitrile, the methoxide solution was withdrawn from the cell. The syringe was rapidly shaken and the mixture added to the cell. The reactions were followed for 2 – 3 half-lives and readings were made every two seconds.

Both the (+)- and (−)-form of the nitriles was used, and no difference was found between the racemization rates of the two forms.

Some of the kinetic runs were examined to completion, and no residual optical activity could be detected. After some of the kinetic runs the reaction mixture from the polarimeter cell was poured into aqueous HCl solution. Extraction with pure pentane and analysis of the pentane layer with gas chromatography showed no other products than the nitrile.

The base concentrations were corrected to the kinetic temperatures using published data on the density of methanol at different temperatures.[14]

RESULTS

Table 1 gives the results of a comparison between the racemization rate and the exchange rate for the nitrile in methanol solution. Deuterated optically active nitrile was allowed to react for about 10 min. The reaction was quenched with aqueous HCl solution and the nitrile isolated and analysed for the deuterium content by mass spectrometry and for the optical activity by polarimetry. Within the experimental errors the racemization rate is the same as the exchange rate. Thus the rate of racemization is a true measure of the rate of the proton transfer in methanol, and the same should be still more likely to hold in the mixtures containing DMSO.

Table 1. Comparison between racemization and exchange rates for (+)-2-phenylpropionitrile-2-*d* ($[\alpha]_{436}^{25}$ initially +43.48°, deuterium content initially 95 %) in methanol with sodium methoxide (0.012 M) as base. Reaction time about 10 min. Concentration of substrate: 0.06 – 0.15 M. Temperature: 25 °C.

$[\alpha]_{436}^{25}$ [a]	Racem. %	Deuterium content in substrate [b] %	Exch. %	Racem./Exch.
23.17	47	52	45	1.04
25.51	41	54	43	0.95
24.80	43	55	42	1.02
25.42	42	58	39	1.08
27.35	37	59	38	0.97
			Mean value	1.01

[a] Obtained from recovered (+)-2-phenylpropionitrile-2-*d*, dissolved in methanol. [b] The initial and final deuterium contents of 2-phenylpropionitrile-2-*d* were determined by mass spectrometry. See Experimental.

The results from the measurements of the racemization rate for the nitrile in methanol using different base concentrations are shown in Table 2. Two different temperatures have been used in order to cover a base-concentration range as large as possible. The second-order rate constant (k_2), obtained by dividing the racemization rate constant (pseudo first-order rate constant) by the corresponding base concentration, is given. A small increase in k_2 with increasing base concentration is observed, and a plot of the logarithm of the pseudo first-order rate constant of the racemization *versus* the logarithm of the base concentration gives a straight line with a slope of 1.14±0.02 (25.02 °C) and 1.05±0.01 (0.05 °C), *i.e.*, the reaction order in methoxide ion deter-

Table 2. Racemization rates for 2-phenylpropionitrile in methanol with sodium methoxide as base. Concentration of substrate: 0.15 – 0.18 M.

[Base]/ mM	k_{obs}/ 10^{-4} s^{-1}	k_2/ 10^{-3} M^{-1} s^{-1} [a]
$t = 25.02$ °C		
10.8	25.0[b]	23.1
8.3	19.1[b]	23.0
5.3	11.4[b]	21.5
5.3[c]	11.3[b]	21.3
5.3[d]	11.4[b]	21.5
2.8	5.50[b]	19.6
$t = 0.05$ °C		
103	15.6[e]	1.51
68	10.2[e]	1.50
35	4.92[e]	1.41
35[f]	4.88[e]	1.39
17.3	2.36[e]	1.36

[a] Second-order rate constant. Error limits are less than 3 % including uncertainty in the base concentration. [b] Mean value obtained from two or three runs. The maximum deviation from the quoted mean values is less than 1.5 %. Standard deviation in each run is less than 0.5 %. [c] 0.24 mol % water added to the solution. [d] 1.10 mol % water added to the solution. [e] Obtained from only one run. Standard deviation in this run is less than 0.5 %. [f] Solution was 65 mM in NaCl.

mined in this way is somewhat above unity. This observation can be rationalized by assuming that the methoxide probably exists partly as ion-pairs in methanol at the concentrations concerned and that the ion-pairs is a more effective catalyst than the free ion.

Evidence for ion-pair formation in methanol solutions at very low base concentrations (0.4 – 6.7 mM) has also been given by Leffek and Suszka,[15] but their conclusion was that the reactivity of the ion pair was much less than that of the free methoxide ion in the combination of sodium methoxide with 4,4′-bis(dimethylamino)triphenylmethyl tetrafluoroborate in methanol.

On the contrary, Cram *et al.*[16] assumed that the base is completely dissociated at low concentrations (5.5 – 37.6 mM) and that the methoxide ion is the active catalytic species in the racemization of (–)-2-phenylbutyronitrile in methanol.

Evidently the idea put forward in the present investigation should be investigated further.

Changing the ionic strength of the reaction solution by the addition of NaCl has no significant influence on the racemization rate, as can be seen in Table 2.

Addition of small amounts of water to the

Table 3. The primary kinetic isotope effect in the racemization of 2-phenylpropionitrile in mixtures of DMSO and methanol with sodium methoxide as base. Concentration of the substrate: 0.15 – 0.18 M. Temp. 10.0 ± 0.1 °C; difference between any runs maximum 0.01 °C (*cf.* EXPERIMENTAL).

[DMSO]/ mol %	[Base]/ mM	Substrate[a]	k_2/ 10^{-3} M^{-1} s^{-1} [b]	k_D/k_H
0	5.8	D H	1.53 ± 0.05 4.1 ± 0.1	0.37 ± 0.02
0	50	D H	1.69 ± 0.05 4.6 ± 0.1	0.37 ± 0.02
8.9	5.3	D H	3.5 ± 0.1 10.6 ± 0.3	0.33 ± 0.02
21.6	5.3	D H	14.3 ± 0.4 48 ± 1	0.30 ± 0.02
38.0	5.3	D H	74 ± 2 411 ± 13	0.18 ± 0.01

[a] H = 2-phenylpropionitrile, D = 2-phenylpropionitrile-2-*d*. [b] Second-order rate constant. Weighted average from at least two runs.

sodium methoxide solution has likewise no significant effect on the reaction rate (Table 2).

The racemization rate and k_D/k_H at different concentrations of DMSO in the solvent are given in Table 3.

The observed increase in the second-order rate constant in the experiments using different base concentrations indicates that a nearly constant base concentration is necessary if different experiments are to be compared. In any case, the isotopic nitriles in the same solvent mixture should be racemized with the same base concentration to minimize the errors in k_D/k_H. Hence, most of the runs in Table 3 refer to almost the same base concentration. However, a nearly tenfold increase in the base concentration in methanol has no measurable effect on k_D/k_H.

The rate constants for the heavy nitrile were obtained by using 2-phenylpropionitrile-2-*d* with a deuterium content at position 2 of 95 %. No correction for the protium content has been applied.

The large increase in the racemization rate with increasing concentration of DMSO in the solutions made measurements impossible in mixtures with more than 38 mol % DMSO. Thus, a reaction with a half-life of about 30 s was obtained at 10 °C in a solvent with 38 % DMSO and 62 % methanol. This is close to the lower limit for measurable rates with the present method. The increased viscosity of DMSO – methanol solutions complicated measurements at lower temperatures.

DISCUSSION

As can be seen from Table 3 the isotope effect is rather weak in methanol. The strength of the isotope effect increases rather rapidly with increasing proportion of DMSO in the solution. In 38 mol % DMSO an almost "normal" isotope effect is obtained. We have not been able to demonstrate the existence of a possible maximum in the strength of the isotope effect owing to the difficulty of measuring racemization rates for the present substrate in media still richer in DMSO.

The rather rapid strengthening of the isotope effect observed in the present investigation differs from what was obtained earlier with 2-methyl-3-phenylpropionitrile.[7] A comparison of the two investigations is made in Fig. 1. As can be seen, k_D/k_H for 2-methyl-3-phenylpropionitrile is closer to unity and varies considerably less than that for 2-phenylpropionitrile in the same composition range for the solvent.

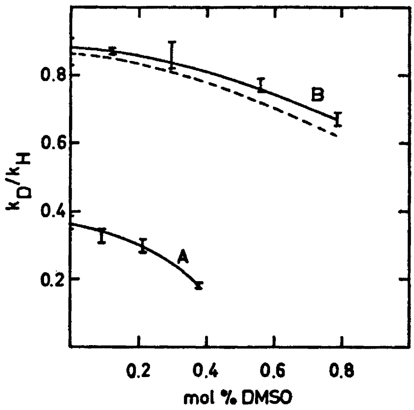

Fig. 1. Comparison between k_D/k_H obtained for 2-phenylpropionitrile at 10 °C (A) and for 2-methyl-3-phenylpropionitrile at 60 °C (B). Dashed curve indicates the effect of a temperature correction (assuming a pure zero-point-energy isotope effect) to 10 °C applied to curve B.

Taking the magnitude of k_D/k_H as a measure of the symmetry of the transition state and ignoring a possible contribution from tunnelling, the results mean that the proton abstraction from 2-phenylpropionitrile by methoxide ion in 38 % DMSO – 62 % methanol is likely to have a nearly symmetrical transition state.

We have also tried to determine a Brønsted's β for this reaction. Although sometimes questioned as a reliable measure of the transition-state structure, it would be of interest to compare this magnitude with the β-value obtained for 2-methyl-3-phenylpropionitrile.[7]

The method of determining β when the free-energy change for the reaction is controlled by a solvent variation was devised by Bell and Cox,[17] and later used in determining β for the racemization of 2-methyl-3-phenylpropionitrile.[7]

The result for 2-phenylpropionitrile can be seen in Fig. 2. The points are more likely to be situated on a curved line than on an expected straight line, which was the case for 2-methyl-3-phenylpropionitrile. The best straight line

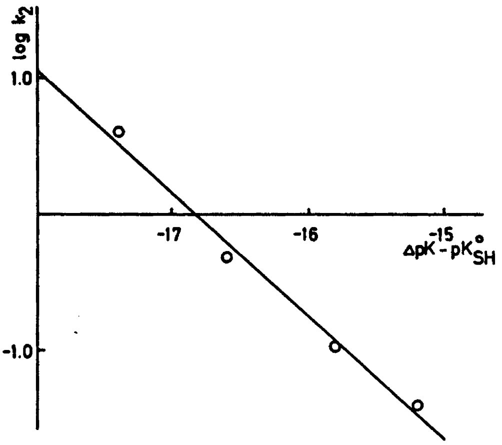

Fig. 2. Plot of the logarithm of the second-order rate constant for the racemization of 2-phenylpropionitrile in mixtures of methanol and DMSO at 10 °C *versus* $\Delta pK - pK^\circ_{SH}$, obtained as in Ref. 7.

for the present results found by a least-squares treatment gives $\beta = 0.9$. This is a rather high value considering the strength of the kinetic isotope effect, and this together with the observed trend toward a curvature probably indicates that the underlying assumption in this treatment fails, *i.e.*, that the substrate (2-phenylpropionitrile) does not behave as the substituted anilines used in establishing the H_- acidity function.

The acidity-function method of determining Brønsted's β used here has recently been claimed to give abnormal β-values.[18] The addition of DMSO to a protic solvent is suggested[18] to raise the activity of the catalysing ion as well as the carbanion resulting from the carbon acid by similar amounts relative to the larger and perhaps also more polarisable transition-state anion. The result will be a large increase in the rate of the reaction when DMSO is added, but not necessarily a large change in ΔpK (difference in pK_a of the substrate and the conjugate acid of the catalysing base). This has been shown to be the case in, for instance, acetate-catalysed proton transfers from nitroparaffins.[18] The catalysing ion (acetate ion) and the nitronate ion have rather similar structures, and it is difficult to say what the effect would be if the resulting ion is a carbanion with a more or less localized charge, as with our compound. In any case it is evident that a reliable simple relationship between rate and equilibrium is difficult to obtain in this way.

The only safe way to test the validity of the acidity-function method is to directly determine the pK's concerned. Unfortunately, such a determination has not been made for the present case, but the following estimates could be made.

The use of the acidity-function method to determine ΔpK is founded on the assumption that the substrate (in the present case 2-phenylpropionitrile) behaves as the indicators used to establish the H-scale. This also means that no dramatic change in the pK of the nitrile should be observed when the medium is changed from pure methanol to DMSO.[19] Assuming a constant pK of 2-phenylpropionitrile between 0 and 38 mol % DMSO means that the whole change in $\Delta pK - pK^\circ_{SH}$ (2.2 units according to Fig. 2) is ascribed to an increase in pK for methanol. Such an increase does not seem unlikely in view of the fact that pK for methanol is known [20] to increase from 18.3 in methanol to 27.0 in pure DMSO.

However, the assumption of a constant pK for the nitrile, being a consequence of an assumed similarity to certain Hammet bases, is worth some consideration.

It is known [20] that 9-cyanofluorene becomes more acidic by almost 6 pK units when the medium is changed from methanol to DMSO. 2-Phenylpropionitrile very much resembles 9-cyanofluorene with respect to the possibility of delocalizing the negative charge of the anion into the phenyl group. On structural grounds it seems probable therefore that 2-phenylpropionitrile will become more acidic when the DMSO content of the medium is increased. As an example, a decrease in pK for 2-phenylpropionitrile by some 2 units together with some 2 units increase in pK for methanol over the composition range 0 – 38 mol % DMSO would be sufficient to make $\beta = 0.5$. A somewhat less rapid decrease in pK for 2-phenylpropionitrile would correspond to a somewhat higher β, of course.

At the present stage, when the pK_a of 2-phenylpropionitrile in different mixtures of methanol and DMSO is unknown, it is impossible to determine a definite value of β. It does not seem unlikely, however, that the true β could be reconcilable with the isotope-effect evidence concerning the symmetry of the transition state.

Acknowledgements. We wish to thank Professor Lars Melander for his interest in this work and for many useful suggestions during the preparation of the manuscript. Many thanks are due to Mr. W. Pimlott (Department of Medical Biochemistry, University of Göteborg) for technical aid in the determination of the mass spectra. Financial support from the Swedish Natural Science Research Council is gratefully acknowledged.

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Received January 13, 1976.