

## Isotope Effects in Proton-transfer Reactions

### I. Base Catalyzed Racemization of 2-Methyl-3-phenylpropionitrile in Dimethyl Sulfoxide-Methanol Solutions

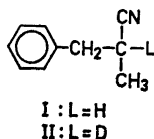
LARS MELANDER and NILS-ÅKE BERGMAN

*Department of Organic Chemistry, University of Göteborg and Chalmers Institute of Technology, Fack, S-402 20 Göteborg 5, Sweden*

The deuterium isotope effect has been measured in the racemization of 2-methyl-3-phenylpropionitrile in different mixtures of dimethyl sulfoxide and methanol with sodium methoxide as base. A smooth variation of the kinetic isotope effect has been observed. In pure methanol,  $k_D/k_H = 0.87 \pm 0.04$ , and in 90.2 % DMSO - 9.8 % methanol,  $k_D/k_H = 0.67 \pm 0.02$  at 60.0°C. The strength of the isotope effect and its variation are interpreted in terms of an unsymmetric transition state for the proton transfer.

Since it was suggested independently by Melander<sup>1</sup> and by Westheimer<sup>2</sup> that deviations from symmetry between donor and acceptor in the transition state could explain the observed weakness of the isotope effect of certain hydrogen transfer reactions, several experimental and theoretical investigations have lent support to this view. The recent review by Wolfsberg<sup>3</sup> could be consulted for references to the original literature.

In experimental studies of the variation of the isotope effect with symmetry, it is desirable to keep as much as possible constant. The racemization of 2-methyl-3-phenylpropionitrile, as studied by Cram *et al.*,<sup>4</sup> seemed to offer an interesting reaction for such studies. The proton donor and, to a first approximation, the accepting base remain the same, and still the reaction rate can be varied by a factor of about nine powers of ten, by changing the solvent from methanol to dimethyl sulfoxide. The strong interaction between the base, the methoxide ion, and methanol seems to be the main source of the difference in behavior in the two solvents. The interaction between the transition state and the solvent is much weaker, and this is favorable for an isotope effect study, because the hydrogen to be transferred is not strongly affected directly by solvation, either in the initial molecule, or in the transition state. A similar system has recently been studied by Bell and Cox,<sup>5</sup> who measured the hydrogen isotope effect in the inversion of (-)-menthone in mixtures of water and dimethyl sulfoxide.



In the present paper, we wish to report some results from the measurement of the rates of racemization of optically active 2-methyl-3-phenylpropionitrile (I) and its 2-*d* analogue (II) in different mixtures of dimethyl sulfoxide and methanol with sodium methoxide as base.

### EXPERIMENTAL

(+)-2-Methyl-3-phenylpropionic acid. Resolution of racemic 2-methyl-3-phenylpropionic acid (synthesized according to known methods) was accomplished by a modification of the procedure used in Ref. 6. Quinine (39.5 g, 122 mmol) was dissolved in 150 ml of a water : ethanol solution (2 : 3 by volume), and 20.0 g (122 mmol) of the acid was added. The solution was heated at 95°C for about 10 min on a water bath. The mixture was allowed to crystallize slowly at 30°C. The salt (48.3 g) collected by filtration was recrystallized three times from water : ethanol in the same proportions as above. After three recrystallizations, 15.6 g of salt was obtained. To liberate the acid, the salt (15.6 g) was decomposed with 2 N H<sub>2</sub>SO<sub>4</sub> and the mixture extracted with ether three times. The combined ether portions were washed with 2 N H<sub>2</sub>SO<sub>4</sub>, saturated sodium chloride solution, and with water. The ether solution was dried over anhydrous magnesium sulfate, and the ether was evaporated. The residue gave upon distillation *in vacuo* 4.2 g (25.6 mmol, 42 %) of acid, b.p.<sub>5</sub> = 120–121°C. The specific rotation of the acid was  $[\alpha]_{\text{D}}^{25} = +22.0^\circ$  (CHCl<sub>3</sub>), lit.<sup>7</sup>  $[\alpha]_{\text{D}}^{20} = +23.51^\circ$  (neat).

(+)-2-Methyl-3-phenylpropionitrile (+I). The nitrile was obtained by conversion of the acid to the nitrile, according to Ref. 6. Optically active acid (3.9 g, 23.8 mmol) gave 1.90 g (13.1 mmol, 55 %) of nitrile. The specific rotation of +I was  $[\alpha]_{\text{D}}^{25} = +27.3^\circ$  (ethanol), lit.<sup>6</sup>  $[\alpha]_{\text{D}}^{25} = +37.4^\circ$  (neat).

(-)-2-Methyl-3-phenylpropionic acid. Optically impure (-)-2-methyl-3-phenylpropionic acid was obtained by shaking the mother liquor from the recrystallizations of the above quinine salt with dilute sulfuric acid and extracting with ether. The optically impure acid (10.1 g, 61.5 mmol) was dissolved in 45 ml of ethyl acetate and treated with a solution of (+)- $\alpha$ -phenylethylamine (7.45 g, 61.5 mmol) in 20 ml of ethyl acetate.<sup>7</sup> The mixture was heated to dissolve the salt. After crystallization, 12.4 g of salt was obtained and was recrystallized twice from ethyl acetate. The salt (7.1 g) was shaken with 2 N H<sub>2</sub>SO<sub>4</sub> and ether. After further extraction with ether, the combined extract was washed with 2 N H<sub>2</sub>SO<sub>4</sub>, saturated sodium chloride solution and with water. The ether solution was dried over anhydrous magnesium sulfate, and the ether was evaporated. The residue gave upon distillation *in vacuo* 3.0 g (18.3 mmol, 30 %) of acid, which had b.p.<sub>5</sub> = 124–125°C. The specific rotation was  $[\alpha]_{\text{D}}^{25} = -26.0^\circ$  (CHCl<sub>3</sub>), lit.<sup>7</sup>  $[\alpha]_{\text{D}}^{25} = -24.56^\circ$  (neat).

(-)-2-Methyl-3-phenylpropionitrile (-I). The nitrile was obtained according to the procedure for +I. Optically active acid (2.7 g, 16.4 mmol) gave 1.55 g (10.7 mmol, 65 %) of optically active nitrile with specific rotation  $[\alpha]_{\text{D}}^{25} = -32.9^\circ$  (ethanol).

2-Methyl-3-phenylpropionic-2-*d* acid-*d*. Deuterated 2-methyl-3-phenylpropionic acid was obtained by equilibrating methylbenzylmalonic acid (synthesized according to known methods) with deuterium oxide, followed by decarboxylation. Methylbenzylmalonic acid (39.0 g, 187 mmol) was dissolved in 150 ml of benzene in a 250 ml flask, equipped with a modified type of water separator. Deuterium oxide (altogether 17.3 g, 864 mmol) was added in twelve small portions. After each added portion, the mixture was refluxed, and before a new portion was added, the water was separated. After the last addition, the benzene was distilled off, and the temperature in the oil bath was

raised to about 170°C. At that temperature, methylbenzylmalonic acid-*d*<sub>2</sub> decarboxylated, to give 2-methyl-3-phenylpropionic-2-*d* acid-*d*. Distillation *in vacuo* gave 27.3 g (165 mmol, 88 %) of acid with b.p.<sub>s</sub> = 106–107°C. The NMR spectrum of the acid showed no protons in the 2-position indicating an isotopic purity better than 98 %.

(+)-2-Methyl-3-phenylpropionic-2-*d* acid. Resolution of the deuterated acid was accomplished in the same way as for the undeuterated one. Racemic 2-methyl-3-phenylpropionic-2-*d* acid-*d* (21.4 g, 130 mmol) gave 4.8 g (29.1 mmol, 45 %) of (+)-2-methyl-3-phenylpropionic-2-*d* acid. The specific rotation was  $[\alpha]_{\text{D}}^{25} = +22.3^\circ$  (CHCl<sub>3</sub>).

(+)-2-Methyl-3-phenylpropionitrile-2-*d* (+II). This nitrile was obtained in the same way as previously described for +I. (+)-2-Methyl-3-phenylpropionic-2-*d* acid (4.5 g, 27.2 mmol) gave 2.25 g (15.4 mmol, 57 %) of +II. The specific rotation was  $[\alpha]_{\text{D}}^{25} = +32.4^\circ$  (ethanol).

(-)-2-Methyl-3-phenylpropionic-2-*d* acid. The (-)-antipode was obtained in the same way as described for the undeuterated acid. Optically impure (-)-2-methyl-3-phenylpropionic-2-*d* acid (11.4 g, 69.0 mmol) gave with (+)- $\alpha$ -phenylethylamine 4.1 g (24.8 mmol, 38 %) of optically pure acid. The specific rotation was  $[\alpha]_{\text{D}}^{25} = -24.7^\circ$  (CHCl<sub>3</sub>).

(-)-2-Methyl-3-phenylpropionitrile-2-*d* (-II). Optically pure (-)-2-methyl-3-phenylpropionic-2-*d* acid (3.8 g, 23.0 mmol) gave 1.45 g (9.9 mmol, 43 %) of -II in the same way as described for the other nitriles. The specific rotation was  $[\alpha]_{\text{D}}^{25} = -30.1^\circ$  (ethanol).

*Purity of nitriles.* The different nitrile products were all pure, according to gas chromatography (GLC) and NMR. The NMR spectra of +II and -II showed no protons in the 2-position. An isotopic purity of at least 98 % seems therefore warranted.\*

*Methanol.* Commercial methanol with a water content less than 0.05 % was dried over molecular sieves Linde type 4 A and stored under an atmosphere of nitrogen.

*Sodium methoxide.* A stock solution of sodium methoxide (0.2–0.3 M) was made by dissolving a proper amount of clean sodium metal in the above methanol under an atmosphere of nitrogen. The solution obtained was stored under an atmosphere of nitrogen.

*Dimethyl sulfoxide.* Commercial DMSO was dried over molecular sieves Linde type 4 A and distilled under reduced pressure. After a long period of drying over molecular sieves, the DMSO was distilled once more, and then stored over molecular sieves under an atmosphere of nitrogen.

*Solutions for kinetic runs.* All solutions for kinetic runs were made by mixing methanol, DMSO, and sodium methoxide solutions in the proper proportions (by weight). The kinetic base solutions were stored under an atmosphere of nitrogen in glass bottles, equipped with a rubber plug and a metal closure so arranged that a proper amount of the solution could be withdrawn with a gas-tight syringe. All titrations in order to determine the concentration of the base in the solutions (after dilution with water) were made with a Radiometer Titrigraph.

*Kinetic runs.* All measurements were made on a Perkin-Elmer 141 polarimeter, which has an accuracy of  $\pm 0.002^\circ$ . All kinetic runs were performed in thermostated polarimeter tubes of 1 dm length, and a volume of 1 ml. The temperature was maintained at  $60.0 \pm 0.1^\circ\text{C}$  in each run, except one, which was performed in a solution containing 98.4 % DMSO. In spite of the high dilution of the base, the racemization was so fast in the latter case, that the principal part of the material had racemized before measurements could begin. Hence the temperature had to be lowered, and the run was made at  $30.0 \pm 0.1^\circ\text{C}$ . In every case, one run for the heavy compound in one cell was made simultaneously with one for the light compound in another cell. The two cells were connected in parallel with the thermostat. The two parallel runs gave the first-order rate constants, and as the base concentration was the same in the two runs, the ratio of the rate constants gave the magnitude of the kinetic isotope effect.

At least two runs were made in each medium.

The evaluation of the rate constants was made on an Olivetti Programma 101 desk-top computer by a least-squares-method program.

\* Note added in proof. It has later been shown by means of mass spectrometry that the deuterium content of position 2 was only 94 %.

## RESULTS

That the rate of racemization is a true measure of the proton transfer can be seen in Table 1, which shows that the racemization rate is the same as the exchange rate. The percentage exchange was measured by NMR, and the percentage racemization was measured polarimetrically. The discrepancy between the percentages found in the 50.5–49.5 mixture can be estimated to lie within the experimental errors.

*Table 1.* Racemization rate, compared with exchange rate for 2-methyl-3-phenylpropionitrile-2-*d* in mixtures of dimethyl sulfoxide and methanol with sodium methoxide as base. Temperature  $60.0 \pm 0.1^\circ\text{C}$ .

Weight % DMSO	Substrate	[Substrate] mol l <sup>-1</sup>	[Base] mol l <sup>-1</sup>	Time h	Racem. %	Exch. %
90.2	-II	0.167	0.0127	0.417	47	46
50.5	+II	0.234	0.179	23	61	57
0.0	+II	0.242	0.287	49	33	33

As measurements were made on both the (+)- and the (-)-form of the substrates, it was also shown that the two forms racemized at the same rate. These two rates should be the same, and that they undoubtedly were so can be seen from Table 2. The results in Table 2 show that no optically active impurities could have been present, and this was also checked by running some reactions to completion. No residual optical activity could be detected.

*Table 2.* Racemization rate for (+)- and (-)-form of 2-methyl-3-phenylpropionitrile and 2-methyl-3-phenylpropionitrile-2-*d* in methanol with sodium methoxide as base. Temperature  $60.0 \pm 0.1^\circ\text{C}$ .

Substrate	[Substrate] mol l <sup>-1</sup>	[Base] mol l <sup>-1</sup>	$k_2 \times 10^6$ <sup>a</sup> l mol <sup>-1</sup> sec <sup>-1</sup>
+I	0.337	0.273	$7.55 \pm 0.27$
-I	0.254	0.255	$7.57 \pm 0.28$
+II	0.335	0.273	$6.60 \pm 0.19$
-II	0.249	0.255	$6.67 \pm 0.22$

<sup>a</sup> Second-order racemization rate constant; error includes uncertainty in base concentration.

It is natural to assume that the racemization process is first-order also in the base.<sup>4</sup> The observed first-order rate constant for the racemization could then be divided by the base concentration to obtain the second-order rate constant ( $k_2$ ). This has been done in Tables 2 and 3. The vast increase in the racemization rate when the concentration of methanol was diminished is clear from Table 3 (last column). It is seen that the rate constants cover a

Table 3.\* Summary of the isotope effect data in the racemization of 2-methyl-3-phenylpropionitrile in mixtures of dimethyl sulfoxide and methanol with sodium methoxide as base. Concentration of substrate 0.2–0.3 mol l<sup>-1</sup>.

Weight % DMSO	Temp. °C <sup>a</sup>	[Base] mol l <sup>-1</sup>	$k_H^b$ sec <sup>-1</sup>	$k_D^b$ sec <sup>-1</sup>	$k_D/k_H$	$k_{2H}^c$ l mol <sup>-1</sup> sec <sup>-1</sup>
0.0	60.0	0.273	$(2.06 \pm 0.05) \times 10^{-6}$	$(1.80 \pm 0.02) \times 10^{-6}$	$0.87 \pm 0.04$	$(7.55 \pm 0.27) \times 10^{-6}$
24.8	60.0	0.203	$(4.28 \pm 0.01) \times 10^{-6}$	$(3.73 \pm 0.01) \times 10^{-6}$	$0.87 \pm 0.01$	$(2.11 \pm 0.03) \times 10^{-6}$
50.5	60.0	0.170	$(1.20 \pm 0.02) \times 10^{-5}$	$(1.03 \pm 0.02) \times 10^{-5}$	$0.86 \pm 0.04$	$(7.06 \pm 0.20) \times 10^{-6}$
75.5	60.0	0.0220	$(2.86 \pm 0.05) \times 10^{-5}$	$(2.21 \pm 0.02) \times 10^{-5}$	$0.77 \pm 0.02$	$(1.30 \pm 0.04) \times 10^{-5}$
90.2	60.0	0.0127	$(6.33 \pm 0.07) \times 10^{-4}$	$(4.26 \pm 0.07) \times 10^{-4}$	$0.67 \pm 0.02$	$(4.98 \pm 0.18) \times 10^{-3}$
98.4	30.0	0.0049	$(1.65 \pm 0.02) \times 10^{-4}$	$(0.99 \pm 0.01) \times 10^{-4}$	$0.60 \pm 0.01$	$(3.37 \pm 0.11) \times 10^{-3}$

\* Note added in proof. As it was later shown that the deuterium content of position 2 of the nitrile was as low as 94 %, some recalculation has been undertaken. It shows that the figures in the  $k_D/k_H$  column should be decreased by 0.01 to 0.02, the largest deviation corresponding to the strongest isotope effect (0.60).

<sup>a</sup> Accuracy  $\pm 0.1^\circ\text{C}$ .

<sup>b</sup> First-order racemization rate constant.

<sup>c</sup> Second-order rate constant; error includes uncertainty in base concentration.

range of about four powers of ten, and probably considerably more, if the difference in temperature is taken into consideration.

The isotopic rate ratios are obtained directly from the racemization rates for the light and heavy compounds, and are found in Table 3. The errors given are the maximum deviations from the mean values. The value of  $k_D/k_H = 0.60$  obtained at 30.0°C cannot directly be compared with the other values obtained at 60.0°C. The effect of the temperature decrease will be a strengthening of the isotope effect, and the value of  $k_D/k_H$  at 60.0°C could be expected to be somewhat higher than 0.60, but still lower than the one obtained in 90.2 % DMSO.

### DISCUSSION

The results of the measurements of the isotope effect show that it is weak, but that the strength increases with an increasing fraction of dimethyl sulfoxide in the solvent. This seems to be what would be expected from our present picture of a simple hydrogen cation transfer.<sup>1-3</sup>

The proton transfer from the substrate SH to the base B<sup>-</sup> can be represented by the solid-line potential-energy curve in Fig. 1. In the present case, SH is represented as a weaker acid than BH, which certainly agrees with the properties of the compounds concerned in this investigation.

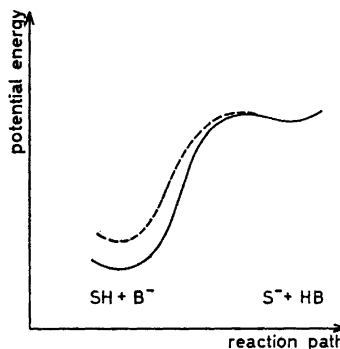


Fig. 1. Potential-energy diagram for the proton transfer. SH denotes the substrate, and HB methanol.

When the fraction of dimethyl sulfoxide in the solvent is increased, the small anion B<sup>-</sup>, in particular, is desolvated, resulting in a higher potential-energy level for the left-hand part of the curve (dashed line). (The solvation effect on all molecules and ions other than B<sup>-</sup> is neglected in the simplest picture.) The result is a smaller activation energy and a slightly increased symmetry in the energetics of the reaction. In the present investigation, we are still far from the symmetric case, the proton being close to the base in the transition state, which can be written S<sup>-</sup>⋯HB under all conditions studied.

The limiting value of  $k_D/k_H$  for an extremely unsymmetric transition state need not be exactly unity in a reaction like the present one. The reason is that the transition state is similar to the products, not to the reactants. For reasons discussed below, it seems likely that the rate of the reverse reaction is close

to the limit of diffusion control, and for this direction, the transition state is reactant-like. In such a case, the isotope effect may vanish, and hence the kinetic isotope effect of the forward reaction has to be equal to the equilibrium isotope effect. The variation of the kinetic isotope effect observed in the present investigation may then simply reflect a variation in the equilibrium isotope effect, *e.g.* caused by the different degree of hydrogen bonding of the product methanol molecule in the different solvent mixtures.

In the recent study by Bell and Cox<sup>5</sup> of the inversion of menthone in mixtures of water and dimethyl sulfoxide, a maximum, in the strength of the isotope effect,  $k_H/k_D = 6.5$ , was observed in the vicinity of equal strength of the two acids. These authors devised a method to calculate the difference  $\Delta pK$  for the two acids under the prevailing conditions in each medium, and the outcome enabled them to plot the logarithm of the second-order rate constant versus  $\Delta pK$ , and thus finding the Brønsted exponent  $\beta$ . The latter was found to be 0.48, in good agreement with the other findings.

According to the same kind of reasoning,<sup>5</sup> the  $\Delta pK$  under the prevailing conditions in the present experimental system can be written

$$\Delta pK = pK_{SH} - pK_{CH_3OH} = pK_{SH}^\circ - H_- + \log[CH_3O^-] - \log[CH_3OH]$$

provided that the substrate may be assumed to behave like a true Hammett indicator, the thermodynamic dissociation constant of which is  $K_{SH}^\circ$ . If  $H_-$  was determined in a solution with the same  $[CH_3OH]$  as the solution used in the kinetic experiments, but with a somewhat different  $[CH_3O^-]$ , it is still approximately correct to introduce that  $H_-$  once the  $[CH_3O^-]$  introduced refers to a solution of the same composition as that for which  $H_-$  was determined.

In Fig. 2, the logarithms of the second-order rate constants, determined and normalized to 25°C by Cram *et al.*,<sup>4\*</sup> have been plotted *versus*  $\Delta pK - pK_{SH}^\circ$ , obtained by means of the  $H_-$ , tabulated by Stewart *et al.*<sup>8</sup> for solutions 0.025 M in sodium methoxide. The value introduced for  $[CH_3O^-]$  is thus 0.025. The slope of this Brønsted plot gives  $\beta = 1.1$ . In view of the assumptions and approximations, all that can be said is that the Brønsted exponent seems to be close to unity, a result consistent with the very weak isotope effect and the ideas expressed in Fig. 1. It would be of interest to know whether the slight variation in the strength of the isotope effect is accompanied by a curvature in the Brønsted plot. Such a curvature is not indicated by the plot in Fig. 2, but, on the other hand, the accuracy should not be overestimated. It should also be borne in mind that the observed isotope effect and the plot refer to different temperatures.

According to a very recent preprint by Long *et al.*,<sup>9</sup> a Brønsted exponent  $\beta = 0.98 \pm 0.02$  has been observed for the hydrogen cation abstraction from *tert*-butylmalononitrile by carboxylate anions in aqueous solution. According to another preprint by Hibbert and Long,<sup>10</sup> the primary isotope effect for the abstraction from the same substrate by acetate ion is very weak,  $k_D/k_H = 0.68$  at 25°C. Similar isotope effects were observed with water as the base, and malononitrile as well as its *tert*-butyl derivative as substrates.

\* Relative values were taken from Table VI of Ref. 4 and put on an absolute scale by means of the results from runs 37, 42, and 47, as found in Table II of the same reference.

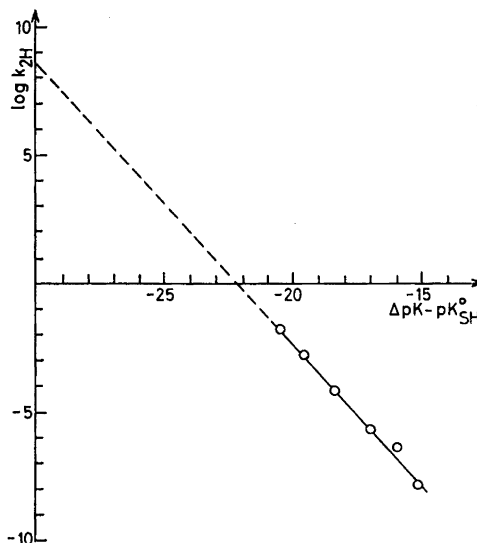


Fig. 2. Plot of the logarithm of the second-order rate constants determined and normalized to 25°C by Cram *et al.*<sup>4</sup> versus  $\Delta pK - pK_{SH}^{\circ}$ , obtained by means of the  $H_{-}$ , tabulated by Stewart *et al.*<sup>8</sup>

The conclusions from our present results and those of Long *et al.*<sup>9</sup> are obviously the same, *i.e.* that the transition state is very unsymmetric, the hydrogen cation being almost completely transferred to the base.

By means of equilibrium data, Long *et al.*<sup>9</sup> computed the rates of the reverse reaction in their system, and also discussed the reversal of the closely related hydrogen cation abstraction from 1,4-dicyano-2-butene, studied by Walters and Long.<sup>11</sup> The results indicate that the protonation rate is close to the diffusion limit. An extrapolation of the Brønsted plot of Fig. 2 would reach the diffusion limit in the neighborhood of  $\Delta pK - pK_{SH}^{\circ} = -30$ . If this point is assumed to correspond to  $\Delta pK = 0$ , as in a symmetric Eigen plot,<sup>12</sup> the conclusion should be that  $pK_{SH}^{\circ} = 30$ , a rather reasonable approximate value for the present substrate. Thus it seems natural to believe that the protonation (on carbon) of the carbanion of 2-methyl-3-phenylpropionitrile is also diffusion controlled under the conditions used by Cram *et al.*<sup>4</sup> in determining the rate of deprotonation. The reason is that if we admit that in the interval concerned, the deprotonation rate constant,  $k_{2H}$ , follows the relation

$$\log k_{2H} = \log k_{\text{diff}} - \Delta pK$$

the rate constant of protonation,  $k_{-}$ , must be equal to  $k_{\text{diff}}$ , because

$$\log (k_{2H}/k_{-}) = -\Delta pK$$

The group of substrates investigated by Long *et al.*<sup>9-11</sup> were studied in a  $\Delta pK$  interval between 5 and 15, and if  $pK_{SH}^{\circ} = 30$  for 2-methyl-3-phenylpropionitrile, the corresponding interval for the study of the latter compound has been between 9 and 15. Thus the observations refer to systems with comparable  $\Delta pK$ . In conclusion, the experimental results of the present investigation and the treatment of the rate data of Cram *et al.* indicate that the rather weak



carbon acid 2-methyl-3-phenylpropionitrile behaves like the considerably more acidic substrates investigated in aqueous solution by Long *et al.*

It is interesting to proceed one step further. A decrease in the acidity of ten more  $pK$  units corresponds to reaching the region of saturated hydrocarbons. There seems to be no reason why their behavior should be different in principle, and consequently, the reaction between a saturated carbanion without any resonance stabilization and water or an alcohol could be expected to be diffusion controlled. Using equilibrium data, Hibbert and Long<sup>10</sup> could also compute the primary isotope effect in the reverse of their reactions, and they found that it was extremely weak, which depends on the unsymmetric conformation of the transition state in the same way as for the forward reaction and the fact that the transition state is now reactant-like. A very weak effect is then also to be expected for the protonation/deuteration of very simple carbanions. This has already been pointed out by Pocker and Exner,<sup>13</sup> and their experimental results and earlier ones<sup>14,15</sup> are easily understood in such terms, although a two-step reaction may seem more likely. The weak primary tritium isotope effects, observed for instance in Assarssons investigations (1955–63)<sup>15</sup> on the decomposition of simple Grignard compounds with water and methanol, are certainly not astonishing. Although these compounds have undoubtedly a very complex structure, and the free carbanion seems to be an oversimplified model, much stronger effects were hardly to be expected even if they were primary in nature, owing to the high proton affinity of the carbanion moiety. The possibility of an explanation in terms of the simple unsymmetric three-center transition state was mentioned briefly by Assarsson, but this possibility seemed much more remote at that time.

*Acknowledgements.* Our thanks are due to Professor William H. Saunders, Jr., for interesting discussions and for reading the manuscript. We also wish to thank Docent Arne Brändström for valuable discussions concerning the preparative problems. Financial support from the *Swedish Natural Science Research Council* is gratefully acknowledged.

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Received November 20, 1970.

*Acta Chem. Scand.* **25** (1971) No. 6