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The Deuterium Isotope Effect of the Methanolysis of Some Organometallic Compounds

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RECEIVED MAY 16, 1955

The 1-butyl, phenyl and benzyl Grignard and lithium reagents have been found to react with methanol-d_1 faster or as fast as with ordinary methanol. A similar isotope effect was noted in the reaction of methyl sodiopropionate with methanol. The results are compared with the data available in the literature. The isotope effect of the neutralization of the C-anion of mandelonitrile also was determined, and the rate law for the benzoin condensation has been reconsidered based on this evidence.

Introduction

A knowledge of the magnitude of the deuterium isotope effect which may be found in the neutralization of carbanions is of importance in the study of the mechanisms of some reactions. Since very little work on this subject is available, the products of the methanolysis of several organometallic compounds with mixtures of methanol and methanol-d_1 have been studied. The isotope effect of the neutralization of the C-anion of mandelonitrile has also been determined by measuring the rate of exchange with solvent deuterium using two concentrations of deuterium.

Experimental

Methanol-d_1.—Methanol-d_1 was prepared by mixing ordinary methanol with deuterium oxide[1] followed by distillation through an 18 inch packed column. The product was first analyzed directly using a mass spectrometer. In order to minimize cracking, an apparent ionizing potential of 8 v. was employed. Since the instrument contained a considerable amount of exchangeable hydrogen adsorbed on the walls, repeated samples of methanol were introduced until a constant mass spectrum was obtained in each of three successive determinations. Usually, about ten to twenty samples were employed. The spectrum of ordinary methanol was obtained as well as that of a highly deuterated sample. The spectra of the samples (the latter being corrected for residual ordinary methanol) are given in Table I.

TABLE I

Mass	CH_3OH	CH_3OD
31	46.1	
32	100.0	37.7
33	1.1	100.0
34		1.1

It may be noted that the only cracking peak is due to the loss of a hydrogen from the methyl group rather than from the alcohol group. This is not surprising since the ion would have resonance stabilization because the oxygen can also bear the positive charge. The somewhat smaller cracking peak for the labeled methanol is expected on this basis.

After the spectra of the labeled methanol samples had been obtained, an attempt was made to bring the instrument back to normal abundance of deuterium using ordinary methanol. After a large number of samples had been introduced, the instrument still indicated the presence of about 2% deuterium. This made it appear likely that complete equilibration had not been obtained with the labeled methanol, and so the following procedure was used.

A solution of 0.1 mole of *n*-butylmagnesium bromide was prepared in 80 ml. of di-*n*-butyl ether which had been freshly distilled from sodium hydride. The solution was heated to reflux in a slow stream of nitrogen in order to remove any butane which might have been formed. A solution of 1 ml. of methanol in 20 ml. of di-*n*-butyl ether was then added, and the butane formed was swept into a Dry Ice–acetone cooled trap using a stream of nitrogen. It was necessary to heat the solution in order to liberate the butane. The butane was distilled into a bulb under reduced pressure and then was analyzed using a mass spectrometer (ionizing potential, 70 v.) and the following equation. This equation, which is based on the observed peaks of ordinary butane, is satisfactory since it has been shown[2] that the spectrum of butane-1-d_1 is essentially the same as that of ordinary butane, except displaced by one mass unit. If the small differences noted by them were included, the calculated value would be about 0.1% lower, which is within experimental error. Some typical data are shown in Table II.

$$\frac{I_{33}}{I_{32}} = \frac{100.00x + 4.34(1 - x)}{19.84x + 100.00(1 - x)} \qquad x = \%\ \text{butane-}d_1$$

TABLE II

Mass	Ord. butane	Butane from methanol-2			Butane from methanol-5		
		a	*a*	*b*	*a*	*a*	*a*
60		2.16	2.02	2.12	2.35	2.33	2.25
59	4.34	50.52	49.21	49.94	55.87	55.82	54.20
58	100.00	100.00	100.00	100.00	100.00	100.00	100.00
57	19.84	22.29	23.42	23.44	21.69	21.72	22.31
% D	0.0	33.8	33.2	33.6	36.7	36.7	(35.6)
Av.			33.5 ± 0.2			36.7	

[a] Duplicate runs, methanol added to Grignard reagent. [b] Grignard reagent added to methanol.

Butane from Butylmagnesium Bromide.—A Grignard reagent was prepared[3] from 2.1 g. (0.015 mole) of *n*-butyl bromide and 0.28 g. (0.018 g. atom) of magnesium in 15 ml. of di-*n*-butyl ether which had been distilled from sodium hydride immediately before use. The solution was heated to reflux in a slow stream of nitrogen in order to remove any butane which might have been formed. The solution was transferred to a small dropping funnel, and then added slowly to a solution of 5 ml. of methanol (about an eightfold excess) in 15 ml. of di-*n*-butyl ether contained in a three-necked flask which had been carefully dried before use. The solution was stirred vigorously during the addition. The butane was isolated by heating the solution in a slow stream of nitrogen and collecting the gas in a Dry Ice–acetone cooled trap. The butane was separated from the small amount of methanol which came over by bulb-to-bulb distillation at low pressure.

The butane was analyzed as described above giving the data in Table III.

TABLE III

Mass	Butane from C_4H_9MgBr Run 1	Run 2	Run 3	Butane from C_4H_9Li Run 1	Run 2	Ord. butane
60	2.54	2.62	2.28	2.11	2.15	
59	59.90	60.35	55.01	49.84	50.22	4.34
58	100.00	100.00	100.00	100.00	100.00	100.00
57	21.73	24.10	20.08	22.14	22.47	19.84
% D	38.8	38.9	36.3	33.6	33.7	
% D in methanol	34.5	34.5	33.5	33.5	33.5	
k_H/k_D	0.83	0.83	0.87	1.00	0.99	

Butane from Butyllithium.—When the above procedure was employed, substituting an equivalent quantity of lith-

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(1) Obtained from the Stuart Oxygen Co. on allocation from the U. S. Atomic Energy Commission.

(2) D. P. Stevenson and C. D. Wagner, *J. Chem. Phys.*, **19**, 11 (1951).

(3) The apparatus described by L. F. Fieser, "Experiments in Organic Chemistry," 2nd Ed., D. C. Heath and Co., New York, N. Y., 1941, pp. 403–405, was used.

ium for the magnesium, the results were quite erratic and gave low yields of butane. Since this was probably due to ether cleavage by the alkyl lithium reagent, benzene was substituted for the ether in the preparation of the reagent. The benzene solution was then added to the methanol, di-*n*-butyl ether mixture as before. The results are shown in Table III.

Benzene from Phenylmagnesium Bromide.—The Grignard reagent was prepared as described above, using 3.1 g. (0.02 mole) of bromobenzene, 0.50 g. of magnesium and 15 ml. of anhydrous ether which had been distilled from sodium hydride immediately before use. This solution was added to 8 ml. of methanol (a tenfold excess) in 15 ml. of di-*n*-butyl ether with vigorous stirring. After ten minutes, dilute hydrochloric acid was added and the organic layer was separated and dried over anhydrous copper sulfate. Distillation through an 18-inch packed column permitted the isolation of benzene, b.p. 78–82°. This material contained a small amount of diethyl ether and di-*n*-butyl ether as impurities, but these were shown not to interfere with the mass spectrum analysis. It was assumed that the mass spectrum of benzene-d_1 would be essentially the same as that of ordinary benzene, except displaced one mass unit. This is a reasonable assumption since any isotope effect which might be obtained would be reduced by a factor of five because there are five equivalent hydrogens in benzene-d_1, and these hydrogens are equivalent to the deuterium except for mass. The deuterium content was calculated using the equation

$$\frac{I_{79}}{I_{78}} = \frac{100.00x + 6.47(1 - x)}{15.29x + 100.00(1 - x)}$$

where x is the mole fraction of benzene-d_1. The data are shown in Table IV.

TABLE IV

	Benzene from C_6H_5MgBr		Benzene from C_6H_5Li		Ord. benzene
Mass	Run 1	Run 2	Run 1	Run 2	
80	3.36	3.69	3.60	3.47	0.21
79	55.90	60.89	60.02	56.86	6.47
78	100.00	100.00	100.00	100.00	100.00
77	16.89	17.08	17.05	16.91	15.29
% D	34.4	37.5	37.1	35.7	
% D in methanol	33.5	36.7	34.5	33.5	
k_H/k_D	0.96	0.97	0.89	0.91	

Benzene from Phenyllithium.—The procedure described above was used except that an equivalent amount of lithium was substituted for the magnesium. The results are given in Table IV.

Toluene from Benzylmagnesium Chloride.—The Grignard reagent was prepared as described above using 2.5 g. (0.02 mole) of benzyl chloride and 0.50 g. of magnesium. After the addition of the Grignard reagent solution to the methanol, the mixture was worked up as before, and the material, b.p. 108–112°, was collected. This sample of toluene contained small amounts of diethyl and di-*n*-butyl ethers as impurities, but these were shown not to interfere with the analysis. Since it is known that the hydrolysis of a benzyl Grignard reagent with deuterium oxide does not lead to introduction of deuterium into the ring,[4] analysis for excess deuterium should indicate only that which is in the methyl group. The mass spectrum was determined at an apparent ionizing potential of 8 v. in order to prevent cracking, and thus simplifying the calculation of the deuterium content. The results obtained in two experiments are summarized in Table V.

TABLE V

	Toluene from $C_6H_5CH_2MgBr$		Ord. toluene
Mass	Run 1	Run 2	
94	4.11	4.40	
93	61.05	65.71	7.20
92	100.00	100.00	100.00
% D	35.0	36.9	
% D in methanol	33.5	36.7	
k_H/k_D	0.93	0.99	

Neutralization of Methyl Sodiopropionate.—To 100 ml. of a 0.45 *N* solution of triphenylmethylsodium[5] was added 3 ml. (0.021 mole) of methyl propionate with shaking. The ether solution was added with stirring to 15 ml. of methanol-d_1 mixed with 20 ml. of di-*n*-butyl ether. After one-half minute, 55 ml. (20% excess) of 1 *N* hydrochloric acid was rapidly added with stirring. The solution was transferred to a separatory funnel and the aqueous layer was discarded. The ether solution was washed with water and dried over anhydrous copper sulfate. Distillation gave 1.5 ml. of methyl propionate, b.p. 77–79°. The mass spectrum is shown in Table VI, and indicated the absence of species with two deuteriums.

TABLE VI

	Methyl propionate	
Mass	Product	Reactant
90	15.68	0.48
89	223.7	4.50
88	100.00	100.00
87	9.55	8.14
% D	72.8	
% D in methanol	75.7	
k_H/k_D	1.16	

Deuterium Exchange during Benzoin Condensation.—The procedure described previously[6] was employed, except that ethanol-d_1 (~90%) was used instead of ordinary ethanol in preparing the solvent. The deuterium content of the solvent was determined by conversion to butane as described above.[7] The data are given in Table VII.

TABLE VII

	% D in solvent = 52.0		% D in solvent = 93.7	
Time, min.	Exchange, %	k_e	Exchange, %	k_e
75	10	1.4×10^{-3}	23	3.5×10^{-3}
120	16	1.5×10^{-3}	32	3.2×10^{-3}
	Av.	$1.5 \pm 0.1 \times 10^{-3}$	Av.	$3.4 \pm 0.2 \times 10^{-3}$

Under the same conditions, benzaldehyde was found not to undergo exchange in the absence of potassium cyanide, even when a base such as potassium carbonate was added.

Results and Discussion

The reactions of 1-butylmagnesium bromide, 1-butyllithium, phenylmagnesium bromide, phenyllithium and benzylmagnesium chloride with mixtures of methanol and methanol-*d* have been studied. An eightfold excess of alcohol was used in order to maintain an essentially constant deuterium content in this reactant. The hydrocarbons formed were analyzed using a mass spectrometer and the observed deuterium content was compared with that of the methanol. This was determined by the analysis of butane prepared by the addition of the alcohol to an excess of butylmagnesium bromide. The isotope effects were calculated using equation 1, and the data are summarized in Table VIII.

$$k_H/k_D = \frac{\%\ \text{D in solvent}}{\%\ \text{H in solvent}} \times \frac{\%\ \text{H in product}}{\%\ \text{D in product}} \quad (1)$$

In most cases, a small inverse isotope effect was noted. Since this reaction probably involves the cleavage of the methanol oxygen–hydrogen bond

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(4) A. I. Brodskii, L. L. Chervyatsora and G. P. Miklukhin, *Doklady Akad. Nauk S. S. S. R.*, **76**, 843 (1951) (*C. A.*, **45**, 1951 (1951)).

(5) C. R. Hauser and B. E. Hudson, Jr., "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 609.

(6) K. B. Wiberg, THIS JOURNAL, **76**, 5371 (1954).

(7) The solvent used previously, ref. 6, was incorrectly reported to be 58%. The calculated value is 54%. The slightly lower observed value probably arose from a small amount of water in the ethanol.

TABLE VIII

ISOTOPE EFFECTS IN THE METHANOLYSIS OF SOME ORGANOMETALLIC COMPOUNDS

Compound	k_{CH_3OH}/k_{CH_3OD}
1-Butylmagnesium bromide	0.84
1-Butyllithium	1.00
Phenylmagnesium bromide	0.97
Phenyllithium	.90
Benzylmagnesium chloride	.96

in the rate-determining step, this observation is contrary to the usual observation that the hydrogen compound reacts more rapidly than the corresponding deuterium compound. It is interesting to note that the reaction of methylmagnesium iodide with deuterium-containing water, which uses only one of the two available hydrogens, has been reported to give methane with the same proportion of methane and methane-d_1 as the water contained hydrogen and deuterium,[8] indicating a negligible isotope effect. The reaction of diethylzinc with water has also been studied, and in this case an isotope effect, k_H/k_D, of about 2.5 was observed.[9]

If only the bond undergoing reaction is considered, the magnitude of the isotope effect is given by[10]

$$\frac{k_H}{k_D} = \left(\frac{m_D^*}{m_H^*}\right)^{1/2} \frac{f}{f^{\ddagger}} \qquad (2)$$

where m^* is the reduced mass in the direction of reaction in the activated complex, and f is a free energy term which is given by

$$f = \frac{\nu_D}{\nu_H} e^{h\Delta\nu/2RT} \frac{1 - e^{h\nu_H/RT}}{1 - e^{h\nu_D/RT}} \qquad (3)$$

Here, ν is the vibrational stretching frequency for the bond which is broken. A corresponding equation may be written for $f^{\ddagger}$. At room temperature, the last term is essentially unity, and the exponential term represents the effect of the difference in zero-point energy on the ratio of rates.

If the bonding to hydrogen or deuterium in the activated complex is weak, $f^{\ddagger}$ becomes equal to unity and, in most cases, $(m_D^*/m_H^*)^{1/2}$ is approximately equal to (ν_H/ν_D). The isotope effect is then given by

$$\frac{k_H}{k_D} = e^{h\Delta\nu/2RT} \qquad (4)$$

For the oxygen–hydrogen bond in methanol, the ratio of rates should equal approximately 10.6 at room temperature. If the bonding in the activated complex is as strong as that in the reactants, f will become equal to $f^{\ddagger}$ and only the mass factor will remain. Under these conditions, the isotope effect should be 1.4.

In the methanolysis of the Grignard and lithium reagents, the observation of a small isotope effect is not surprising. Since the activation energy appears to be only a small fraction of the dissociation energy for an oxygen–hydrogen bond going to the ions, the new bond must be formed to a large extent as the old bond is cleaved. Thus, the net bonding of the hydrogen or deuterium in the activated complex may be as large as that in the reactants. If the bonding were equal in the reactants and activated complex, one would expect an isotope effect of 1.4 because of the mass factor. The lower observed value suggests that the bonding in the activated complex may have been stronger than that in the reactants.

Another possibility is that the rate-determining step involves coördination of the organometallic compound with the oxygen of the alcohol followed by a rapid intramolecular proton transfer. This would not be unreasonable with the Grignard reagents, but would be less likely with the lithium reagents and with methyl sodiopropionate which will be mentioned later. Since the activation energy for the reaction is probably quite low, it is also possible that the reactions might be diffusion controlled, and this type of process would be expected to give essentially no isotope effect. The fact that methylmagnesium iodide does not discriminate between the hydrogen and deuterium of partially labeled water[8] makes it unlikely that this could be the entire explanation of the small observed isotope effect.

It may be predicted that the normal isotope effect would be observed with less basic anions. Hsu, Ingold and Wilson[11] in studying the racemization and deuterium exchange of (−)2-butyl phenyl ketone in 99% deuterium oxide found that the rate of racemization was slightly higher than the rate of deuterium exchange. They attributed this difference to an isotope effect, and concluded that a value of k_H/k_D of 12 would accommodate the difference in rate. This value would of course be subject to a large uncertainty.

Walters and Bonhoeffer[12] studied the rate of deuterium exchange of acetone in basic solution as a function of the deuterium content of the solvent. An extrapolation of their results give $k = 1.55$ at 50% D, and $k = 13.8$ at 100% D. Since in the absence of an isotope effect, one would expect the rate in 50% D_2O to be one-half that in 100% D_2O, the isotope effect for the neutralization of the acetone anion may be calculated to be 4.5. This value should be corrected for the increased rate of enolization in D_2O (about 30%).[13]

Maron and LaMer[14] have studied the rate of the acid catalyzed conversion of *aci*-nitroethane to the normal form in water and in deuterium oxide, and found the rates to be identical. The exact nature of this reaction is not known, and therefore this result cannot be compared with the other cases.

In order to obtain directly the isotope effect for the neutralization of an anion less basic than the butyl, phenyl and benzyl ions, methyl sodiopropionate was studied. This compound was chosen since esters are the most acidic compounds which will not readily exchange deuterium with the solvent. This ester was chosen since it is one of the

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[8] M. Orchin, I. Wender and R. A. Friedel, *Anal. Chem.*, **21**, 1072 (1949).

[9] L. Friedman and A. P. Irsa, *ibid.*, **24**, 876 (1952).

[10] J. Bigeleisen, *J. Chem. Phys.*, **17**, 675 (1949).

[11] S. K. Hsu, C. K. Ingold and C. L. Wilson, *J. Chem. Soc.*, **78**, (1938).

[12] W. D. Walters and K. F. Bonhoeffer, *Z. physik. Chem.*, **A182**, 265 (1938).

[13] S. H. Maron and V. K. LaMer, THIS JOURNAL, **60**, 2588 (1938).

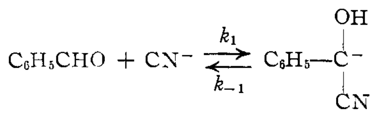
[14] S. H. Maron and V. K. LaMer, *ibid.*, **61**, 692 (1939).

few volatile esters which give strong parent peaks in the mass spectrum.

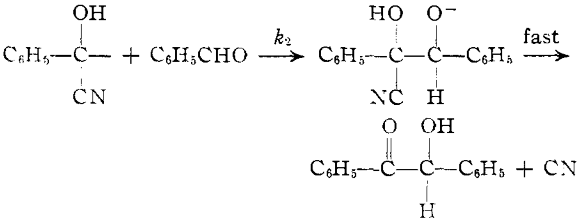
Methyl propionate was converted to the sodium salt with triphenylmethylsodium, and the solution was added to an excess of a mixture of methanol and methanol-*d*. The product methyl propionate had only slightly less deuterium than the methanol, and since no dideutero compound was observed, the deuterium could not have been introduced by exchange. The isotope effect was calculated to be $k_H/k_D = 1.16$. This result is essentially the same as that obtained with the organometallic compounds derived from the more basic anions, and is quite different from the results reported with the ketones. It is apparent that there still is insufficient data for a comprehensive discussion of the problem.

In the study of the benzoin condensation, the isotope effect associated with the neutralization of the C-anion of mandelonitrile is of importance. The preceding results suggest that it may be small, but to obtain an experimental value, the rate of exchange of benzaldehyde with solvent deuterium in the presence of potassium cyanide was measured for a higher concentration of deuterium than previously reported.[6] With a solvent containing 52.0% D, a first-order rate constant, $1.5 \pm 0.1 \times 10^{-3}$ min.$^{-1}$ was obtained, and in 93.7% deuterium, the constant $3.4 \pm 0.2 \times 10^{-3}$ was obtained. The isotope effect was calculated by extrapolating to 50 and 100% deuterium content in the solvent, and a comparison of these values indicated an isotope effect of $k_H/k_D = 1.3 \pm 0.2$. Since base-catalyzed reactions usually proceed about 30% faster in D_2O than in H_2O,[12] it is apparent that there was essentially no isotope effect in this reaction.

One may derive the rate law for the benzoin condensation based on the Lapworth formulation[15] using the steady-state approximation.



$$\mathrm{C_6H_5CHO} + \mathrm{CN}^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{C_6H_5{-}C(OH)(CN)^-}$$



$$\mathrm{C_6H_5{-}C(OH)(CN){-}} + \mathrm{C_6H_5CHO} \xrightarrow{k_2} \mathrm{C_6H_5{-}C(HO)(NC){-}C(O^-)(H){-}C_6H_5} \xrightarrow{\text{fast}} \mathrm{C_6H_5{-}C({=}O){-}C(OH)(H){-}C_6H_5} + \mathrm{CN}^-$$

Let the anion be designated as x

$$-\frac{d[\mathrm{RCHO}]}{dt} = k_2[\mathrm{x}][\mathrm{RCHO}]$$

$$0 = \frac{d[\mathrm{x}]}{dt} = k_1[\mathrm{RCHO}][\mathrm{CN}^-] - k_{-1}[\mathrm{x}] - k_2[\mathrm{x}][\mathrm{RCHO}]$$

$$[\mathrm{x}](k_{-1} + k_2[\mathrm{RCHO}]) = k_1[\mathrm{RCHO}][\mathrm{CN}^-]$$

$$-\frac{d[\mathrm{RCHO}]}{dt} = \frac{k_1k_2[\mathrm{RCHO}]^2[\mathrm{CN}^-]}{(k_{-1} + k_2[\mathrm{RCHO}])}$$

This reduces to the observed third-order rate law when $k_{-1} >> k_2[\mathrm{RCHO}]$. The ratio of rates, k_{-1}/k_2, may be determined from the above data since it is known that the rate of the benzoin condensation is the same as the rate of exchange in a solvent containing 52% deuterium.[6] This indicates that the actual rate of conversion of x back to benzaldehyde was twice the rate of condensation, and thus, $k_{-1}/k_2[\mathrm{RCHO}]$ was equal to two at an 0.8 *M* benzaldehyde concentration. The ratio, k_{-1}/k_2 was then equal to 1.6. This allows the rate law to be written

$$-\frac{d[\mathrm{RCHO}]}{dt} = \frac{k_1[\mathrm{RCHO})^2[\mathrm{CN}^-]}{1.6 + [\mathrm{RCHO}]}$$

Thus, third-order kinetics would be expected only with relatively low benzaldehyde concentrations. Although a given experiment might show approximate third-order dependence, the observed rate constants should depend noticeably on the benzaldehyde concentration when it is over about 0.2 *M*. It is interesting to note that Stern[16] found that the observed third-order rate constants were not dependent on the benzaldehyde concentration between 0.3 and 0.8 *M*. These data suggest that the above mechanism may not be correct.

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[15] A. Lapworth, *J. Chem. Soc.*, **83**, 995 (1903); **85**, 1206 (1904).

[16] E. Stern, *Z. physik. Chem.*, **50**, 513 (1905).