cyclopropylmethylcarbinol, 2- and 3-methylcyclobutanol, crotylcarbinol and allylmethylcarbinol.

With 45% fluoroboric acid at room temperature, both cyclopropylcarbinols rapidly rearranged to allylmethylcarbinol and variable amounts of unidentified material. The other alcohols were stable.

With 22% fluoroboric acid, heated under reflux for 30 min., 3-methylcyclobutanol showed approximately 80% starting material and 20% allylmethylcarbinol. Under the same

conditions, 2-methylcyclobutanol was totally rearranged to allylmethylcarbinol and the olefinic alcohols were unaffected.

Allylmethylcarbinol gave only polymer and unrearranged alcohol when heated under reflux for 1 hr. with 25% sulfuric acid. Under the same conditions it is reported[10] that allylmethylethylcarbinol is totally rearranged to 4-methyl-3-hexen-1-ol. This corresponds to rearrangement of allylmethylcarbinol to crotylcarbinol.

Electrophilic Substitution at Saturated Carbon. XIII. Solvent Control of Rate of Acid–Base Reactions that Involve the Carbon–Hydrogen Bond[1,2]

By DONALD J. CRAM, BRUCE RICKBORN, CHARLES A. KINGSBURY AND PAUL HABERFIELD

RECEIVED FEBRUARY 27, 1961

The base-catalyzed hydrogen–deuterium exchange reaction at carbon alpha to the nitrile, amide and ester groups has been found to occur with complete racemization in a number of systems. The kinetics of racemization of these systems has been examined with solvent composition as the main variable, and with methanol, methanol–dimethyl sulfoxide mixtures, ethylene glycol, t-butyl alcohol and n-butyl alcohol as solvents. Rate constants, kinetic order and thermodynamic activation parameters were evaluated. With potassium methoxide as base and (+)-2-methyl-3-phenylpropionitrile as substrate, the rate constant for racemization in dimethyl sulfoxide possessed a value ~10⁹ times that observed in methanol. The reactivity-depressing effect of hydrogen bonds on alkoxides is emphasized.

In our previous studies of electrophilic substitution at saturated carbon,[3] carbon[4] and oxygen[5] were employed as leaving groups, and proton or deuteron donors were used as electrophiles. This and the two succeeding papers report the results of investigations of the stereochemistry and kinetics of base-catalyzed hydrogen–deuterium exchange reactions at saturated carbon. In a formal sense, these acid–base reactions are electrophilic substitutions with hydrogen or deuterium as leaving groups, and deuteron or proton donors as electrophiles.

Two previous studies of the stereochemistry of base-catalyzed hydrogen–deuterium exchange have appeared in the literature. Wilson et al.,[6] observed that the rates of hydrogen–deuterium exchange and of racemization of optically active 1-phenyl-2-methyl-1-butanone in a basic solution of dioxane-deuterium oxide were equal. A similar identity of rates was observed when optically active phenyl-p-tolyldeuterioacetic acid was heated in aqueous base.[7] These results were interpreted as involving proton abstraction by base in the rate-controlling step, followed by deuteration[6] (protonation[7]) of a symmetrical ambient anion on either oxygen[6] or carbon.[7]

Of the many investigations of the kinetics of proton abstraction from carbon, only leading refer-

ences are mentioned here. Among compounds studied are nitroparaffins,[8] tris-p-nitrophenylmethane,[9] acetylene,[10] haloforms,[11] and a number of ketones, nitriles, carboxylic acids, sulfones and amides.[12] In many of these studies, the rates of halogenation were measured, and the rates of proton abstraction and halogenation were presumed to be identical, since in most base-catalyzed halogenations of carbon acids anion formation is rate controlling.[13]

The present study involved use of cyano, amido and ester groups to acidify hydrogen attached to asymmetric carbon. The racemization and exchange reactions of optically active compounds I–V were examined with the possibility in mind that the stereochemistry and mechanism of these electrophilic substitution processes might be solvent dependent as were those that involved carbon leaving groups.[3,5] The main objective was to obtain quantitative data concerning the dependence of the catalytic activity of bases on the character of the solvent.

Results

The preparations of optically active nitriles I[14] and II[4] have been described previously, as have the optically active acids[15,4] from which amides III and

(1) Preliminary communications of some of the results of this paper have appeared previously: (a) D. J. Cram, B. Rickborn and G. R. Knox, J. Am. Chem. Soc., 82, 6412 (1960); (h) D. J. Cram, W. D. Nielsen and B. Rickborn, ibid., 82, 6415 (1960).

(2) This work was supported hy a grant from the National Science Foundation.

(3) D. J. Cram, J. L. Mateos, F. Hauck, A. Langemann, K. R. Kopecky, W. D. Nielsen and J. Allinger, J. Am. Chem. Soc., 81, 5774 (1959), is a summarizing paper.

(4) Previous paper D. J. Cram and P. Haberfield, ibid., 83, 2363 (1961).

(5) D. J. Cram, C. A. Kingshury and A. Langemann, ibid., 81, 5785 (1959).

(6) (a) S. K. Hsu, C. K. Ingold and C. L. Wilson, J. Chem. Soc., 78 (1938); (h) C. L. Wilson, ibid., 1550 (1936).

(7) D. J. G. Ives and G. C. Wilks, ibid., 1455 (1938); see also D. J. G. Ives, ibid., 81 (1938).

(8) O. Reitz, Z. physik. Chem., A176, 363 (1936); (h) R. P. Bell "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959, p. 109.

(9) E. F. Caldin and G. Long, Proc. Roy. Soc. (London), A228, 263 (1955).

(10) L. H. Reyerson, J. Am. Chem. Soc., 57, 779 (1935).

(11) J. Hine, N. W. Burske, M. Hine and P. B. Langford, ibid., 79, 1409 (1957).

(12) (a) R. G. Pearson and R. L. Dillon, ibid., 75, 2441 (1953); (h) K. F. Bonhoeffer, K. H. Geih and O. Reitz, J. Chem. Phys., 7, 664 (1939).

(13) For instance, Hsu and Wilson, J. Chem. Soc., 623 (1936), demonstrated that optically active 1-phenyl-2-methyl-1-butanone was racemized and hrominated at identical rates, hoth processes heing catalyzed hy acetate ion.

(14) D. J. Cram and P. Haberfield, J. Am. Chem. Soc., 83, 2354 (1961).

(15) C. L. Arcus and J. Kenyon, J. Chem. Soc., 916 (1939).

TABLE I

STEREOCHEMISTRY OF BASE-CATALYZED HYDROGEN–DEUTERIUM EXCHANGE REACTIONS OF NITRILE, AMIDE AND ESTER

$$C_6H_5CH_2\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle H}{|}}{\overset{*}{C}}}- = R \qquad\qquad C_6H_5\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle H}{|}}{\overset{*}{C}}}- = R'$$

Run[a]	Substrate			Base		T, °C.	Tm., hr.	% rac,	% exch.[b]
	Nature	Concn., N	Solvent	Nature	Concn., N				
1	RCN[c]	0.140	$(CH_3)_3COD^{b,d}$	$(CH_3)_3COK$	0.0130	25	1.3	20	19
2	RCN[c]	.140	$DOCH_2CH_2OD^{b,e}$	$COCH_2CH_2ONa$	.140	84	19	52	52
3	$R'CON(C_2H_5)_2$[f]	.120	$(CH_3)_3COD^{b,d}$	$(CH_3)_3COK$	.170	70	1.5	54	51
4	$R'CO_2C(CH_3)_3$[g]	.150	$(CH_3)_3COD^{b,d}$	$(CH_3)_3COK$	.0051	25	0.25	25	23
5	$RCON(C_2H_5)_2$[h]	.140	$(CH_3)_3COD^{b,d}$	$(CH_3)_3COK$	.450	75	31	49	47
6	$RCON(C_2H_5)_2$[h]	.140	$DOCH_2CH_2OD^{b,e}$	$DOCH_2CH_2ONa$	.450	155	25	72	71

[a] Runs are numbered consecutively from table to table. [b] Analyzed by combustion and falling drop method by J. Nemeth, Urbana, Ill. Values have been corrected for incompletely deuterated solvent and for solvent protonation by substrate as the reaction proceeds. [c] Almost optically pure, $\alpha^{25}D$ +37.4° (l 1 dm., neat). [d] 97% O–D. [e] 99% (OD). [f] Essentially optically pure, $\alpha^{25}D$ +118.1° (l 1 dm., neat). [g] Essentially optically pure, $\alpha^{25}D$ +35.56° (l 1 dm., neat). [h] Essentially optically pure, $\alpha^{25}D$ +75.04° (l 1 dm., neat).

IV, and ester V were prepared (see Experimental). Compounds I–V were all obtained in either an optically pure or in a state close to optical purity. Preparations of t-butyl alcohol (99% O–D) and deuterated ethylene glycol (99% $(OD)_2$) have been described previously.[16]

$$C_6H_5CH_2\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle H}{|}}{\overset{*}{C}}}CN \qquad C_6H_5\overset{\overset{\displaystyle C_2H_5}{|}}{\underset{\underset{\displaystyle H}{|}}{\overset{*}{C}}}CN \qquad C_6H_5\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle H}{|}}{\overset{*}{C}}}CON(C_2H_5)_2$$
$$\text{I} \qquad\qquad \text{II} \qquad\qquad \text{III}$$

$$C_6H_5CH_2\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle H}{|}}{\overset{*}{C}}}CON(C_2H_5)_2 \qquad C_6H_5\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle H}{|}}{\overset{*}{C}}}CO_2C(CH_3)_3$$
$$\text{IV} \qquad\qquad\qquad \text{V}$$

Table I records the results of experiments in which optically active substrates were submitted to the action of alkoxide bases in deuterated solvents. After racemization was 20–50% completed, the reaction was interrupted, the substrate isolated, and its optical activity and deuterium content determined. Nitrile I was run in deuterated t-butyl alcohol (a typical "retention solvent" when carbon is leaving group)[3] and in deuterated ethylene glycol (a typical "inversion solvent" when carbon is leaving group). Amide IV and ester V were racemized only in deuterated t-butyl alcohol. Within experimental error, the percentages racemized and exchanged were identical. Thus the hydrogen–deuterium exchange reaction occurred with racemization for the three substrates and the two solvent-base systems studied (runs 1–6).

Table II records the results of a kinetic study of the racemization of (+)-2-methyl-3-phenylpropionitrile ((+)-I) in methanol, dimethyl sulfoxide-methanol, ethylene glycol and t-butyl alcohol, with the corresponding potassium, sodium or lithium alkoxides as catalysts. From the observed pseudo-first-order polarimetric rates were calculated the second-order rate constants, k_2, which are listed.

In Table III are listed the second-order rate constants, k_2, for the racemization kinetics of (−)-2-phenylbutyronitrile ((+)-II) at 25° in methanol, ethylene glycol and 1-butanol. In each solvent, potassium or lithium alkoxide or tetramethylammonium hydroxide was used as base.

(16) D. J. Cram and B. Rickborn, *J. Am. Chem. Soc.*, **83**, 2178 (1961).

The second-order rate constants, k_2, for the racemization kinetics of (+)-N,N-diethyl-2-methyl-3-phenylpropionamide ((+)-IV) and (+)-N,N-diethyl-2-phenylpropionamide ((+)-III) were determined in dimethyl sulfoxide with potassium and sodium t-butoxides as catalysts, respectively. Similarly, the rate constants for the latter amide ((+)-III) and for (+)-t-butyl 2-phenylpropionate ((+)-V) were determined with t-butyl alcohol and potassium t-butoxide as base. The results are found in Table IV.

Discussion

Stereochemistry of Hydrogen–Deuterium Exchange Reaction.—The nitrile, amides and ester used here to study the steric course of the hydrogen–deuterium exchange reaction are all weak acids, capable of producing ambident anions under the influence of base. These anions can in principle protonate either on oxygen or nitrogen to give the thermodynamically unstable tautomers, or on carbon to produce the stable tautomeric forms directly. In terms of the kinetic scheme

$$-\overset{|}{\underset{\underset{\displaystyle H}{|}}{C}}-\overset{\|}{\underset{\underset{\displaystyle O}{}}{C}}- \underset{k_{-a}}{\overset{k_a}{\rightleftarrows}} \left\{ \begin{array}{c} \diagdown \\ / \end{array} \overset{}{C}-\overset{\|}{\underset{O}{C}}- \longleftrightarrow \begin{array}{c} \diagdown \\ / \end{array} C=C-\overset{|}{\underset{O}{}} \right\} \underset{k_b}{\overset{k_{-b}}{\rightleftarrows}}$$

$$\begin{array}{c} \diagdown \\ / \end{array} C=C-\overset{|}{\underset{OH}{}}$$

$$-\overset{|}{\underset{\underset{\displaystyle H}{|}}{C}}C\equiv N \underset{k_{-a}}{\overset{k_a}{\rightleftarrows}} \left\{ \begin{array}{c} \diagdown \\ / \end{array} C-C\equiv N \longleftrightarrow \begin{array}{c} \diagdown \\ / \end{array} C=C=N^- \right\} \underset{k_b}{\overset{k_{-b}}{\rightleftarrows}}$$

stable potentially asymmetric tautomers	symmetrical ambident anions	$\begin{array}{c} \diagdown \\ / \end{array} C=C=NH$ unstable symmetric tautomers

formulated, if $k_{-b}/k_{-a} > 1$, then the unstable tautomer predominates in the initial product. However, since $k_b/k_a \gg 1$, then $K = k_a k_{-b}/k_b k_{-a} < 1$, and the stable tautomer would ultimately dominate in the equilibrium mixture. Alternatively, if $k_{-b}/k_{-a} < 1$, then the stable and potentially asymmetric tautomer would be produced without having to pass through the symmetrical unstable tautomer.

Stereospecificity in the hydrogen–deuterium exchange reactions in these systems would be ob-

TABLE II

RATES OF BASE-CATALYZED RACEMIZATION OF (+)-2-METHYL-3-PHENYLPROPIONITRILE (+)-I

Run	Solvent	Nitrile concn., N	Base Nature	Base Concn., N	T, °C.	k_2, l. m.$^{-1}$ sec.$^{-1}$
7	CH_3OH	0.135	CH_3OK	0.2997	80.23	$1.31 \pm 0.02 \times 10^{-4}$
8	CH_3OH	.153	CH_3ONa	.3189	80.20	$1.25 \pm .01 \times 10^{-4}$
9	CH_3OH	.162	CH_3OLi	.1804	80.20	$0.887 \pm 0.025 \times 10^{-4}$
10	CH_3OH	.135	CH_3OK	.2997	54.04	$4.27 \pm 0.04 \times 10^{-6}$
11	CH_3OH	.157	CH_3ONa	.3189	54.00	$3.42 \pm .10 \times 10^{-6}$
12	CH_3OH	.162	CH_3OLi	.1804	54.00	$3.00 \pm .06 \times 10^{-6}$
13	CH_3OH	.128	CH_3OK	.0095	85.30	$1.84 \pm .05 \times 10^{-4}$
14	CH_3OH	.144	CH_3OK	.0735	85.30	$2.20 \pm .07 \times 10^{-4}$
15	CH_3OH	.155	CH_3OK	.5909	85.30	$2.66 \pm .08 \times 10^{-4}$
16[a]	CH_3OH	.122	CH_3OK	.2609	85.30	$2.43 \pm .06 \times 10^{-4}$
17[b]	CH_3OH	.135	CH_3OK	.2602	85.30	$2.41 \pm .03 \times 10^{-4}$
18	CH_3OH	.157	CH_3OLi	.6067	83.88	$1.32 \pm .01 \times 10^{-4}$
19[c]	CH_3OH	.157	CH_3OLi	.6067	83.88	$1.32 \pm .02 \times 10^{-4}$
20	$25\%^d$ $(CH_3)_2SO-75\%^d$ CH_3OH	.180	CH_3ONa	.302	70.00	$9.37 \pm .47 \times 10^{-5}$
21	$25\%^d$ $(CH_3)_2SO-75\%^d$ CH_3OH	.180	CH_3ONa	.302	50.00	$6.13 \pm .31 \times 10^{-6}$
22	$50\%^d$ $(CH_3)_2SO-50\%^d$ CH_3OH	.180	CH_3ONa	.117	70.00	$3.62 \pm .18 \times 10^{-4}$
23	$50\%^d$ $(CH_3)_2SO-50\%^d$ CH_3OH	.180	CH_3ONa	.117	50.00	$2.67 \pm .13 \times 10^{-5}$
24	$76.5\%^d$ $(CH_3)_2SO-23.5\%^d$ CH_3OH	.180	CH_3OLi	.0876	25.00	$1.84 \pm .09 \times 10^{-5}$
25	$76.5\%^d$ $(CH_3)_2SO-23.5\%^d$ CH_3OH	.180	CH_3OLi	.2430	25.00	$1.94 \pm .08 \times 10^{-5}$
26	$90\%^d$ $(CH_3)_2SO-10\%^d$ CH_3OH	.159	CH_3OK	.0049	59.41	$4.53 \pm .08 \times 10^{-2}$
27	$90\%^d$ $(CH_3)_2SO-10\%^d$ CH_3OH	.159	CH_3OK	.0049	31.61	$1.30 \pm .02 \times 10^{-2}$
28	$90\%^d$ $(CH_3)_2SO-10\%^d$ CH_3OH	.182	CH_3OK	.0251	34.62	$8.29 \pm .08 \times 10^{-4}$
29[e]	$90\%^d$ $(CH_3)_2SO-10\%^d$ CH_3OH	.201	CH_3OK	.0252	34.62	$7.02 \pm .20 \times 10^{-4}$
30	$90\%^d$ $(CH_3)_2SO-10\%^d$ CH_3OH	.168	CH_3ONa	.00360	31.61	$1.16 \pm .04 \times 10^{-3}$
31	$90\%^d$ $(CH_3)_2SO-10\%^d$ CH_3OH	.204	CH_3ONa	.0250	31.61	$1.10 \pm .03 \times 10^{-3}$
32	$90\%^d$ $(CH_3)_2SO-10\%^d$ CH_3OH	.154	CH_3ONa	.1207	31.61	$1.53 \pm .04 \times 10^{-3}$
33	$90\%^d$ $(CH_3)_2SO-10\%^d$ CH_3OH	.154	CH_3ONa	.0036	54.35	$2.16 \pm .02 \times 10^{-2}$
34	$90\%^d$ $(CH_3)_2SO-10\%^d$ CH_3OH	.168	CH_3OLi	.0112	54.35	$2.22 \pm .04 \times 10^{-2}$
35	$90\%^d$ $(CH_3)_2SO-10\%^d$ CH_3OH	.168	CH_3OLi	.0112	31.61	$1.29 \pm .03 \times 10^{-3}$
36	$97\%^d$ $(CH_3)_2SO-3\%^d$ CH_3OH	.180	CH_3OK	.0023	25.00	$1.60 \pm .04 \times 10^{-2}$
37	$97\%^d$ $(CH_3)_2SO-3\%^d$ CH_3OH	.180	CH_3OK	.0094	25.00	$1.59 \pm .03 \times 10^{-2}$
38	$97\%^d$ $(CH_3)_2SO-3\%^d$ CH_3OH	.180	CH_3OK	.0201	25.00	$1.95 \pm .04 \times 10^{-2}$
39	$97\%^d$ $(CH_3)_2SO-3\%^d$ CH_3OH	.180	CH_3OK	.0469	25.00	$2.47 \pm .05 \times 10^{-2}$
40	$97\%^d$ $(CH_3)_2SO-3\%^d$ CH_3OH	.180	CH_3OK	.0943	25.00	$3.91 \pm .08 \times 10^{-2}$
41[f]	$97\%^d$ $(CH_3)_2SO-3\%^d$ CH_3OH	.180	CH_3OK	.0463	25.00	$2.25 \pm .04 \times 10^{-2}$
42	$97\%^d$ $(CH_3)_2SO-3\%^d$ CH_3OH	.180	CH_3ONa	.0075	25.00	$1.67 \pm .03 \times 10^{-2}$
43	$97\%^d$ $(CH_3)_2SO-3\%^d$ CH_3OH	.180	CH_3ONa	.0210	25.00	$1.98 \pm .04 \times 10^{-2}$
44	$97\%^d$ $(CH_3)_2SO-3\%^d$ CH_3OH	.180	CH_3ONa	.0722	25.00	$2.89 \pm .06 \times 10^{-2}$
45	$97\%^d$ $(CH_3)_2SO-3\%^d$ CH_3OH	.180	CH_3ONa	.145	25.00	$4.74 \pm .20 \times 10^{-2}$
46[g]	$97\%^d$ $(CH_3)_2SO-3\%^d$ CH_3OH	.180	CH_3ONa	.0210	25.00	$1.31 \pm .03 \times 10^{-2}$
47	$97\%^d$ $(CH_3)_2SO-3\%^d$ CH_3OH	.180	CH_3OLi	.0027[h]	25.00	$1.62 \pm .04 \times 10^{-2}$
48	$98.5\%^d$ $(CH_3)_2SO-1.5\%^d$ CH_3OH	.180	CH_3OK	.0498	25.00	$1.92 \pm .20 \times 10^{-1}$
49	$98\%^d$ $(CH_2)_4SO_2-2\%^d$ CH_3OH	.180	CH_3OK	.0720	25.00	$2.96 \pm .09 \times 10^{-4}$
50	$HOCH_2CH_2OH$	.170	$HOCH_2CH_2OK$	.00583	83.85	$6.02 \pm .61 \times 10^{-5}$
51	$HOCH_2CH_2OH$	.158	$HOCH_2CH_2OK$	.0742	83.82	$5.70 \pm .23 \times 10^{-5}$
52	$HOCH_2CH_2OH$	.170	$HOCH_2CH_2OK$	.231	83.85	$6.02 \pm .09 \times 10^{-5}$
53	$HOCH_2CH_2OH$	.170	$HOCH_2CH_2ONa$	.0103	83.85	$6.45 \pm .27 \times 10^{-5}$
54	$HOCH_2CH_2OH$	.153	$HOCH_2CH_2ONa$	.1037	83.84	$5.68 \pm .07 \times 10^{-5}$
55	$HOCH_2CH_2OH$	.170	$HOCH_2CH_2ONa$	.256	83.85	$5.55 \pm .08 \times 10^{-5}$
56	$HOCH_2CH_2OH$	.170	$HOCH_2CH_2OLi$	.00954	83.85	$6.08 \pm .34 \times 10^{-5}$
57	$HOCH_2CH_2OH$	.170	$HOCH_2CH_2OLi$	.0751	83.85	$5.99 \pm .17 \times 10^{-5}$
58	$HOCH_2CH_2OH$	.162	$HOCH_2CH_2OLi$	.1481	83.82	$4.58 \pm .09 \times 10^{-5}$
59	$HOCH_2CH_2OH$	.150	$HOCH_2CH_2OLi$	.305	83.88	$4.07 \pm .07 \times 10^{-5}$
60	$HOCH_2CH_2OH$	.187	$HOCH_2CH_2OLi$	.6642	83.88	$3.46 \pm .12 \times 10^{-5}$
61[i]	$HOCH_2CH_2OH$	.170	$HOCH_2CH_2OLi$	.0751	83.85	$4.70 \pm .17 \times 10^{-5}$
62	$HOCH_2CH_2OH$	.153	$HOCH_2CH_2ONa$	.1037	60.28	$2.28 \pm .05 \times 10^{-6}$
63	$HOCH_2CH_2OH$	.162	$HOCH_2CH_2OLi$	.1481	60.28	$2.48 \pm .12 \times 10^{-6}$
64	$(CH_3)_3COH^j$	.180	$(CH_3)_3COK$	.0016	25.00	$1.57 \pm .03 \times 10^{-2}$
65	$(CH_3)_3COH^j$	.180	$(CH_3)_3COK$	.0161	25.00	$7.83 \pm .16 \times 10^{-3}$
66	$(CH_3)_3COH^k$	.180	$(CH_3)_3COK$	.0099	25.00	$5.20 \pm .07 \times 10^{-3}$
67	$(CH_3)_3COH^k$	.180	$(CH_3)_3COK$	.0207	25.00	$5.06 \pm .10 \times 10^{-3}$
68	$(CH_3)_3COH^k$	.180	$(CH_3)_3COK$	.0828	25.00	$7.01 \pm .13 \times 10^{-3}$

69	$(CH_3)_3COH^k$	.180	$(CH_3)_3COK$	.229	25.00	$1.04 \pm .02 \times 10^{-2}$
70	$(CH_3)_3COH^k$	.180	$(CH_4)_3COK$	.439	25.00	$1.35 \pm .07 \times 10^{-2}$
71	$(CH_3)_3COH^l$	.180	$(CH_3)_3COK$	.033	25.00	$1.2 \pm .1 \times 10^{-4}$

[a] Solution was 0.170 M in potassium iodide. [b] Solution was 0.353 M in potassium iodide. [c] Solution was 0.180 M in lithium bromide. [d] Percentage by weight. [e] Solution was 0.229 M in potassium iodide. [f] Solution was 0.2 M in H_2O. [g] Solution was 0.15 M in sodium iodide. [h] Upper limit of solubility of lithium methoxide. [i] Solution 0.192 M in lithium perchlorate. [j] Less than 0.003 M in water. [k] Water 0.01 M. [l] Water 0.22 M.

TABLE III

RATES OF BASE-CATALYZED RACEMIZATION OF 0.100 M CONCENTRATIONS OF ($-$)-2-PHENYLBUTYRONITRILE AT 25.00°

Run[a]	Solvent	Base Nature	Base Concn., N	k_2, 1. m.$^{-1}$ sec.$^{-1}$
72	CH_3OH	CH_3OK	0.00548	$10.5 \pm 0.3 \times 10^{-2}$
73	CH_3OH	CH_3OK	.0376	$11.0 \pm .2 \times 10^{-2}$
74	CH_3OH	$N(CH_3)_4OH^b$	.00895	$11.1 \pm .2 \times 10^{-2}$
75	CH_3OH	CH_3OLi	.00824	$9.75 \pm .22 \times 10^{-2}$
76	CH_3OH	CH_3OLi	.0170	$9.70 \pm .16 \times 10^{-2}$
77	CH_3OH^c	CH_3OLi	.0202	$10.5 \pm .2 \times 10^{-2}$
78	$HOCH_2CH_2OH$	$HOCH_2CH_2OK$	.00715	$3.57 \pm .08 \times 10^{-2}$
79	$HOCH_2CH_2OH$	$HOCH_2CH_2OK$	.0448	$3.67 \pm .05 \times 10^{-2}$
80	$HOCH_2CH_2OH$	$N(CH_3)_4OH^b$	.0267	$3.72 \pm .04 \times 10^{-2}$
81	$HOCH_2CH_2OH$	$HOCH_2CH_2OLi$	.00442	$3.34 \pm .10 \times 10^{-2}$
82	$HOCH_2CH_2OH$	$HOCH_2CH_2OLi$	.0370	$3.29 \pm .04 \times 10^{-2}$
83[d]	$HOCH_2CH_2OH$	$HOCH_2CH_2OLi$	.0340	$2.71 \pm .04 \times 10^{-2}$
84[e]	$CH_3(CH_2)_3OH$	KOH	.00123	$3.75 \pm .08$
85[e]	$CH_3(CH_2)_3OH$	KOH	.00348	$3.95 \pm .20$
86[e]	$CH_3(CH_2)_3OH$	$N(CH_3)_4OH^b$	.000706	$4.55 \pm .63$
87[e]	$CH_3(CH_2)_3OH$	$N(CH_3)_4OH^b$	.00165	$7.13 \pm .62$
88[e]	$CH_3(CH_2)_3OH$	$LiOH$	.000706	$1.85 \pm .26$
89[e]	$CH_3(CH_2)_3OH$	$LiOH$	.00794	$1.55 \pm .05$

[a] Runs are numbered consecutively from table to table. [b] Actually $N(CH_3)_4OH \cdot 2H_2O \cdot 0.27$ $N(CH_3)_3$. [c] Solution was 0.100 M in water. [d] Solution was 0.200 M in lithium perchlorate. [e] Solution was 0.100 M in water.

TABLE IV

RATES OF BASE-CATALYZED RACEMIZATION OF AMIDES AND ESTER AT 25.00°

$$C_6H_5CH_2\overset{*}{\underset{H}{\overset{CH_3}{C}}}- = R \qquad\qquad C_6H_5\overset{*}{\underset{H}{\overset{CH_3}{C}}}- = R'$$

Run[a]	Substrate Nature	Substrate Concn., N	Solvent	Base Nature	Base Concn., N	k_2, 1. m.$^{-1}$ sec.$^{-1}$
90	$RCON(C_2H_5)_2$	0.150	$(CH_3)_2SO$, 0.004 M $(CH_3)_3COH$	$(CH_3)_3COK$	0.0870	$3.96 \pm 0.19 \times 10^{-2}$
91	$R'CON(C_2H_5)_2$	.150	$(CH_3)_2SO$, 0.0003 M $(CH_3)_3COH$	$(CH_3)_3CONa$	.0103	$1.04 \pm .03 \times 10^{-1}$
92	$R'CON(C_2H_5)_2$	.150	$(CH_3)_3COH$	$(CH_3)_3COK$	.124	$4.59 \pm .15 \times 10$
93	$R'CO_2C(CH_3)_3$	.150	$(CH_3)_3COH$	$(CH_3)_3COK$	.0099	$3.05 \pm .09 \times 10^{-2}$
94	$R'CO_2C(CH_3)_3$	.150	$(CH_3)_3COH$	$(CH_3)_3COK$	.127	$3.82 \pm .23 \times 10^{-2}$

[a] Runs are numbered consecutively from table to table.

served only if two conditions were fulfilled. First, k_{-h}/k_{-a} would have to be less than unity. Second, the symmetrical anionic intermediate would have to be asymmetrically solvated and consumed before it passed into a symmetrical solvent shell. Some hope that these conditions would be at least partially fulfilled was found in the fact that optically pure 2-cyano-2-phenylbutanoic acid was found in a previous investigation to undergo base-catalyzed decarboxylations to give 2-phenylbutyronitrile with from 16% net retention to 11% net inversion of configuration, depending on the solvent.[14] The 2-phenylbutyronitrile anion produced during this decarboxylation was even more stable than the 2-methyl-3-phenylpropionitrile anion which was produced as intermediate in runs 1 and 2 of Table I.

The results indicate that within experimental error, the exchange and racemization rates for the 6 runs of Table I are equal to one another, and that the exchange reaction is non-stereospecific.[17] The

preferred interpretation of these results resembles that used by Ingold, et al.,[6] to explain the equality of rates of racemization and exchange of optically active 1-phenyl-2-methyl-1-butanone, namely, that protonation or deuteration occurs more rapidly on the more electronegative center of the ambident anion $(k_{-h}/k_{-a} > 1)$. Thus the present results do not test the possibility that symmetrical carbanions might provide optically active products by virtue of asymmetric solvation.

The lack of stereospecificity in the racemization reactions of systems I, III, IV and V in two solvents as different as ethylene glycol and t-butyl alcohol strongly suggests that the reaction would be non-stereospecific in any solvent, and that racemization and exchange rates can be presumed almost identical. This assumption greatly simplifies interpretation of the kinetic data in the next section.

(17) Stereospecificity of less than 15% net inversion and less than 7% net retention could not have been detected by the methods used.
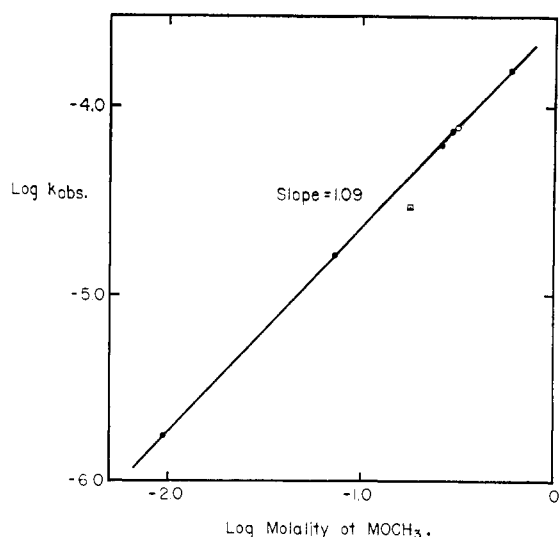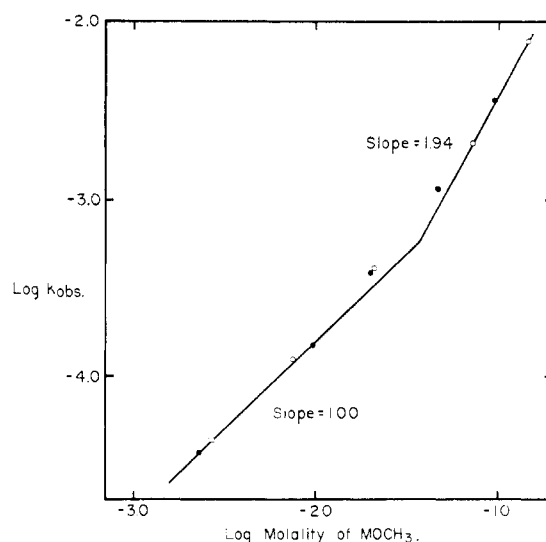
Fig. 1.—Order plot of logarithm of base concentration against logarithm k_{obs} for racemization of (+)-2-methyl-3-phenylpropionitrile in methanol at 85.3°: ●, KOCH₃ as base; O, NaOCH₃ as base; □, LiOCH₃ as base.

Kinetic Order in Base for Racemization Processes.

—A large number of kinetic runs described in Tables II and III were made to establish the kinetic order in base for the racemization process, and to identify as far as possible the structure of the kinetically active catalytic species. At low base concentrations (0.00548 to 0.0376 M) and at 25°, the rate of racemization of (−)-2-phenylbutyronitrile in methanol was first order in base, as shown by the similarity in values of the over-all second-order rate constants for runs 72–76 of Table III. Two of these runs involved potassium methoxide, two lithium methoxide, and one tetramethylammonium hydroxide as base. In run 77, the methanol solution was made 0.10 M in water with only a slight increase in the second-order rate constant. The reaction order coupled with the lack of dependence of rate on the nature of the anion of the base suggest that with the potassium and quaternary ammonium bases, the base is completely dissociated at these concentrations, and methoxide anion is the active catalytic species. With lithium methoxide, the slightly lower values for k_2 are attributed to incomplete dissociation of the base.[18]

Figure 1 is an order plot of logarithm of the base concentration against the logarithm of the pseudo-first-order rate constant for the rate of racemization of (+)-2-methyl-3-phenylpropionitrile in methanol at 85.3°. With base concentrations ranging from about 0.01 to 0.60 M, 5 points that involve potassium methoxide and one sodium methoxide fall on a straight line with a slope of about 1.09. The single point for lithium methoxide falls somewhat below the line. Thus an order somewhat above unity is observed for the base in the racemization process at

(18) J. D. Reinheimer, W. F. Kieffer, S. W. Frey, J. C. Cochran and E. W. Barr [J. Am. Chem. Soc., 80, 164 (1958)] studied the kinetics of the reaction of lithium, sodium and potassium methoxides with 2,4-dinitrochlorobenzene in methanol at 25°. These authors from a study of the effect of added common ion and non-common ion salts preferred an explanation of their results that methoxide ion was the active nucleophile, and that ion-pairing became important particularly with lithium methoxide.

Fig. 2.—Order plot of logarithm of base concentration against logarithm of k_{obs} for racemization of (+)-2-methyl-3-phenylpropionitrile in 97% (CH₃)₂SO-3% CH₃OH (by weight) at 25.00°: ●, KOCH₃ as base; O, NaOCH₃ as base; □, LiOCH₃ as base.

this temperature and for these base concentrations. The lack of a common ion effect or even a marked salt effect is demonstrated by the following comparisons. A value of 2.38×10^{-4} l. m.⁻¹ sec.⁻¹ can be calculated for k_2 (from Fig. 1) for racemization in methanol at 85.3° with potassium methoxide at 0.260 M concentration. Runs 16 and 17 were conducted at this base concentration and temperature, but enough potassium iodide was added to each reaction medium to give concentrations of 0.170 and 0.353 M of the salt, respectively. The rate constants, k_2, were not altered by the presence of the salt, and were found to be 2.43×10^{-4} and 2.41×10^{-4} l. m.⁻¹ sec.⁻¹, respectively. Less striking is the fact that addition of lithium bromide to give a concentration of 0.180 M of the salt in run 19 gave the same k_2 as that of run 18 conducted with the same concentration of lithium methoxide (0.6067 M), but in the absence of added salt.

In runs 20–48 of Table II with (+)-2-methyl-3-phenylpropionitrile as substrate, the solvent composition was varied between 25% and 98.5% (by weight) of dimethyl sulfoxide with methanol as the second component. At 76.5% dimethyl sulfoxide, the value of the second-order rate constant did not change when lithium methoxide concentration was changed from 0.0876 to 0.243 M (runs 24 + 25 conducted at 25°). In 90% dimethyl sulfoxide at 31.61°, at concentrations ranging from 0.0049 to 0.0250 M, lithium, sodium and potassium methoxides exhibited values for k_2 which are essentially constant (runs 27, 30, 31 and 35). In runs 28 and 29 conducted in the same solvent mixture at 34.62° with 0.0251 M potassium methoxide as catalyst, only a 16% reduction in rate was observed when the reaction mixture was made 0.229 M in potassium iodide.

Figure 2 is an order plot for base in 97% dimethyl sulfoxide at 25°. At concentrations below 0.01 M (runs 36, 37, 42 and 47), lithium, sodium

and potassium methoxides gave the same values for k_2. Above this concentration[19] values increase until above 0.06 M concentration of base the reaction becomes about second order in base. In runs 43 and 46, with 0.0210 M sodium methoxide as base, the effect of added sodium iodide on the rate was evaluated. A rate depression of about 35% was observed. Comparison of the results of runs 39 and 41 indicates that the presence of 0.02 M water had only a small effect on the rate.

With respect to the effect of base concentration and character on the order in base for the racemization reaction, methanol and dimethyl sulfoxide exhibit surprisingly similar behavior. At base concentrations below 0.01–0.02 M, the reactions are first order in base and almost independent of the nature of the cation. At higher concentrations, the order in base for potassium and sodium methoxides increases, and decreases for lithium methoxide. Addition of common ion salts or small amounts of water to the media have if anything only a small depressing effect on k_2. These generalizations support the explanation that at low concentrations, the bases are fully dissociated, and methoxide anion is the catalytic species. At higher concentrations, ion pairs are present and are also catalysts, with lithium methoxide less and potassium methoxide more active than free methoxide ion. Superimposed on this general picture is a small salt effect, negative for free methoxide anion and negligible for associated base.[20]

In ethylene glycol at 25.0°, the racemization of (−)-2-phenylbutyronitrile follows good over-all second-order kinetics for base concentrations ranging from about 0.007 to 0.045 M, with either potassium ethylene glycoxide or tetramethylammonium hydroxide as base (runs 78–80). As in methanol, the lithium alkoxide over the same concentration range gave rate constants about 10% lower (see runs 81 and 82 of Table III). Run 83, conducted in the presence of 0.200 M lithium perchlorate (solution was 0.034 M in lithium ethylene glycoxide) gave about a 20% reduction in second-order rate constant as compared to the run 82 made without added common ion salt.

In ethylene glycol at 83.5°, the racemization of (+)-2-methyl-3-phenylpropionitrile exhibits good over-all second-order kinetics with concentrations of sodium or potassium ethylene glycoxide that range from 0.00583 to 0.256 M, and with lithium ethylene glycoxide up to 0.0751 M (runs 50 through 57, Table II). Higher values of this base gave lower values for k_2. Figure 3 is an order plot of the data, and all but the points for lithium alkoxide at higher concentration fall on a line with a slope of unity. These data indicate that ethylene glycol as a solvent provides a simpler kinetic picture than methanol, and this fact is attributed to the greater dissociating power of the glycol. Except for those runs made at higher lithium alkoxide concentrations where both
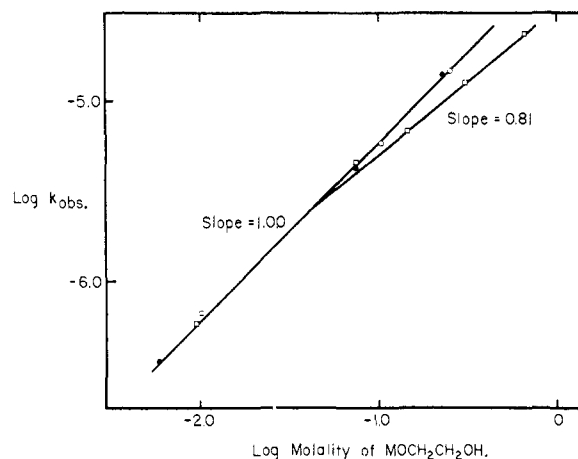
(19) The solubility of lithium methoxide in 97% dimethyl sulfoxide is only 0.0027 m. 1. $^{-1}$ (see Experimental).

(20) A. Brandström [Arkiv. Kemi, 13, 51 (1959), and earlier articles] following the early work of S. F. Acree [e.g., J. Am. Chem. Soc., 37, 1909 (1915)] devised a method for measuring the relative importance of associated and dissociated salts (bases) in a given reaction through use of dissociation constants obtained from conductivity data.

Fig. 3.—Order plot of logarithm of base concentration against logarithm of k_{obs} for racemization of (+)-2-methyl-3-phenylpropionitrile in ethylene glycol at 83.8°: ●, $KOCH_2CH_2OH$ as base; O, $NaOCH_2CH_2OH$ as base; □, $LiOCH_2CH_2OH$ as base.

associated and dissociated anions are probably catalytically active, the data strongly suggest that free glycoxide ions are the catalytic species, and that essentially all the base is dissociated.

As might be expected in n- and t-butyl alcohols as solvents, the dependence of k_2 on base concentration and character is more marked. In the racemization at 25.0° of (−)-2-phenylbutyronitrile in n-butyl alcohol which was 0.100 M in water (base concentrations less than 0.008 M) the values of k_2 for the bases decreased in the order $(CH_3)_4NOH >$ $KOH > LiOH$ (runs 84–89). Except for the quaternary ammonium base, only small changes in the value for k_2 are visible with changes in base concentration. With both variables operating, the maximum spread in values for k_2 is less than a factor of 5.

Runs 64–71 were conducted at 25.0° with (+)-2-methyl-3-phenylpropionitrile as substrate, t-butyl alcohol as solvent and potassium t-butoxide as base. Over a range of base concentrations from 0.0016 to 0.439 M and water concentrations from less than 0.003 to 0.01 M, k_2 varied by only a factor of about 3. In the two runs in which water was excluded as much as possible (runs 64 and 65), a tenfold increase in base concentration decreased the value of k_2 by only a factor of 2. At about 0.01 M base concentration, an increase in water concentration from less than 0.003 M to 0.01 M decreased the value of k_2 by only about 35% (run 65 slightly adjusted and run 66). This small decrease points to potassium alkoxide as being the active species in both runs, rather than potassium alkoxide in one and potassium hydroxide in the other. However, when water concentration was increased to 0.22 M (base concentration was 0.033 M), the rate dropped by a factor of almost 50 (run 67 slightly adjusted and run 71). In this case it seems probable that most of the base is in the form of potassium hydroxide, whose catalytic activity is much less than that of the alkoxide. In the presence of 0.01 M water, the value of k_2 increased by a factor of about 2.5 as base concentration was increased from about

TABLE V

ACTIVATION PARAMETERS IN BASE-CATALYZED RACEMIZATION OF (+)-2-METHYL-3-PHENYLPROPIONITRILE

| Nos. runs used[a] | Solvent | Bases | | ΔH^*, kcal./mole | ΔS^*, e.u. |
		Nature	Concn., N		
7 + 10	CH₃OH	CH₃OK	0.2997	29.3 ± 0.3	6.3 ± 0.7
8 + 11	CH₃OH	CH₃ONa	.3189	30.9 ± .3	10.6 ± 0.9
9 + 12	CH₃OH	CH₃OLi	.1804	29.0 ± .4	4.6 ± 1.4
20 + 21	75% CH₃OH–25% (CH₃)₂SO	CH₃ONa	.302	29.4 ± .3	8.4 ± 0.9
22 + 23	50% CH₃OH–50% (CH₃)₂SO	CH₃ONa	.117	28.1 ± .3	7.4 ± 1.0
26 + 27	10% CH₃OH–90% (CH₃)₂SO	CH₃OK	.00490	24.7 ± .3	9.4 ± 0.9
30 + 33	10% CH₃OH–90% (CH₃)₂SO	CH₃ONa	.00360	24.4 ± .3	6.0 ± 1.0
34 + 35	10% CH₃OH–90% (CH₃)₂SO	CH₃OLi	.0112	24.3 ± .3	7.8 ± 1.0
54 + 62	HOCH₂CH₂OH	HOCH₂CH₂ONa	.104	29.0 ± .3	1.6 ± 1.0
58 + 63	HOCH₂CH₂OH	HOCH₂CH₂OLi	.148	28.6 ± .3	3.1 ± 1.0

[a] Table II.

0.01 to 0.44 M. In this solvent, the base undoubtedly exists in the form of ion pairs, and this form must be the catalytic species.[21]

Effect of Solvent on Rates of Racemization Reactions.—Table V records the activation parameters for the base-catalyzed racemization of (+)-2-methyl-3-phenylpropionitrile which were calculated from the rate data of Table II. The values of ΔH^* were used to compute second-order rate constants at 25.0° for the racemization in the various media, and in Table V are found the factors by which the rates in various media differ from that in pure methanol. In Fig. 4 is plotted the mole per cent. dimethyl sulfoxide in methanol against the logarithm of the rate of racemization at 25.0°.
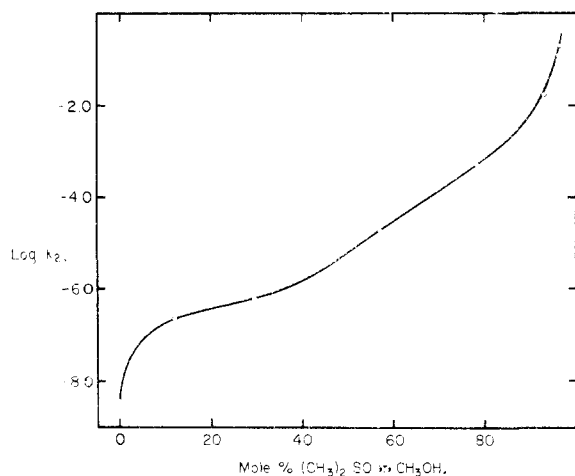

Fig. 4.—Plot of mole % (CH₃)₂CO in CH₃OH against logarithm of k_2 (l. m.⁻¹ sec.⁻¹) for CH₃OM catalyzed racemization of 2-methyl-3-phenylpropionitrile at 25.0°.

The data of Table VI offer striking evidence for the importance of medium in the activity of methoxide anion as a base. In passing from methanol to 98.5% dimethyl sulfoxide, the rate of racemization by methoxide anion increased by a factor of 5 × 10⁷. Extrapolation of the curve of Fig. 4 to 100% dimethyl sulfoxide gives a rate increase over that in methanol of an estimated *nine powers of ten*.

(21) Although kinetic runs were conducted in *t*-butyl alcohol as solvent with lithium *t*-butoxide as base, the solutions were always cloudy due to the extreme insolubility of traces of lithium carbonate that always formed. However, the rate data obtained left little doubt that lithium *t*-butoxide was less active than potassium *t*-butoxide by about a power of ten.

TABLE VI

RELATIVE RATES OF RACEMIZATION OF (+)-2-METHYL-3-PHENYLPROPIONITRILE WITH ALKOXIDE BASES AT 25.0°

Rates calcd. from runs[a]	Solvent, % by weight	Relative rates[b]
7–11	100% CH₃OH	1
20, 21	75% CH₃OH–25% (CH₃)₂SO	3.2 × 10¹
22, 23	50% CH₃OH–50% (CH₃)₂SO	1.6 × 10²
24, 25	23.5% CH₃OH–76.5% (CH₃)₂SO	4.9 × 10³
26, 27, 30, 33–35	10% CH₃OH–90% (CH₃)₂SO	1.3 × 10⁵
37, 42, 47	3% CH₃OH–97% (CH₃)₂SO	1.4 × 10⁶
48	1.5% CH₃OH–98.5% (CH₃)₂SO	5.0 × 10⁷
49	2% CH₃OH–98% (CH₂)₄SO₂	7.8 × 10⁴
66	(CH₃)₃COH, 0.01 M in H₂O	1.4 × 10⁶
64	(CH₃)₃COH, <0.003 M in H₂O	4.2 × 10⁸

[a] Where data were available (Table II), averages of rates involving different cations were averaged. [b] Rates corrected to 25° through use of data of Table V.
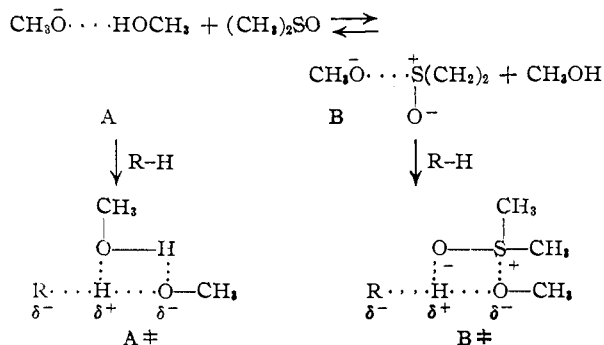
These two solvents have dielectric constants that do not differ widely from one another (34 for methanol and 49 for dimethyl sulfoxide[22]), and the bulk of the evidence in the last section supports the hypothesis that at low base concentrations the metal alkoxides are dissociated. The big difference in activity for the methoxide anion in the two solvents is attributed to the presence of solvent–anion hydrogen bonds in methanol (CH₃OH· · ·OCH₃) that are absent in dimethyl sulfoxide. Thus methoxide ions are in a sense "buffered" by solvent in methanol, but are less solvated in dimethyl sulfoxide. In methanol the driving force for dissociation of a metal methoxide derives from solvation of methoxide anion by the hydrogen, and of the metal cation by the oxygen of the hydroxyl group. In dimethyl sulfoxide, positive sulfur solvates the methoxide anion and negative oxygen the metal cation. Since the charge on sulfur is shielded by three shells of electrons, and is also sterically hindered, the main impetus for dissociation probably derives from solvation of the metal cation,[22] which leaves the methoxide anion relatively poorly solvated and highly reactive.

The shape of the curve of Fig. 4 is informative. The first 10 mole % of dimethyl sulfoxide increased the rate by a factor of 18, whereas the second 10 mole % increment only by an additional factor of about 2.5, after which the additional factor increased steadily with each additional 10 mole % of dimethyl sulfoxide. Finally in passing from 93 to 96.5% mole % dimethyl sulfoxide, the rate increased by a factor of about 35. Thus two effects

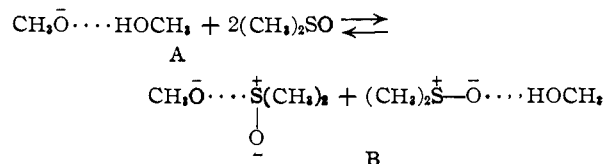(22) H. L. Schläfer and W. Schaffernicht, *Angew. Chem.*, **72**, 618 (1960).

seem to be operative, one of which becomes more important at high concentrations of dimethyl sulfoxide.[23]

The effect visible at low concentrations of dimethyl sulfoxide is attributed to specific solvation by dimethyl sulfoxide of the transition state for proton abstraction. Thus transition state $B^{\ddagger}$ should be more stable than $A^{\ddagger}$ since in

$$CH_3\bar{O}\cdots\cdot HOCH_3 + (CH_3)_2SO \rightleftharpoons$$

$$CH_3\bar{O}\cdots\cdot\overset{+}{\underset{O^-}{S}}(CH_2)_2 + CH_3OH$$

B[ddagger] a strong hydrogen bond between a methanol and a dimethyl sulfoxide molecule is being made, whereas in $A^{\ddagger}$, a strong hydrogen bond between a methanol molecule and a methoxide anion is being exchanged for two weak hydrogen bonds between two methanol molecules. Although at low concentrations of dimethyl sulfoxide the equilibrium between A and B probably is unfavorable to B, the lower energy of $B^{\ddagger}$ would more than compensate for the unfavorable ground state concentrations.[24]

The effect visible at high concentrations of dimethyl sulfoxide is attributed to raising the energy of the ground state methoxide anion by a shift in equilibrium from A → B. Accentuation of this shift would occur at high dimethyl sulfoxide concentrations by virtue of this solvent's well known ability to hydrogen bond with hydroxyl groups. Thus dimethyl sulfoxide competes with methoxide anions for the remaining methanol molecules, and in effect decreases the concentration of methanol available to methoxide ion. Thus the equilibrium between A and B would involve two moles of dimethyl sulfoxide.

$$CH_3\bar{O}\cdots\cdot HOCH_3 + 2(CH_3)_2SO \rightleftharpoons$$
$$\text{A}$$

$$CH_3\bar{O}\cdots\cdot\overset{+}{\underset{O}{S}}(CH_3)_2 + (CH_3)_2\overset{+}{S}-\bar{O}\cdots\cdot HOCH_3$$
$$\text{B}$$

In connection with this hypothesis, it is interesting that sulfolane (tetramethylene sulfone) is substantially inferior to dimethyl sulfoxide at promot-

ing the activity of methoxide ion. In run 49 of Table II is reported k_2 for racemization of (+)-2-methyl-3-phenylpropionitrile in 93 mole % sulfolane, 7 mole % methanol at 25.0°. Although a rate enhancement of 7.8×10^4 (methanol = 1) is observed for the solvent mixture, the rate factor is over two powers of ten short of the enhancement found for dimethyl sulfoxide at the same mole % concentration. This difference in activating ability between the two solvents is attributed to the widely different abilities of the two solvents to form hydrogen bonds with methanol. Sulfones are inferior in this respect.[25]

A number of other interesting rate relationships are found in Table VI. Although k_2 for potassium t-butoxide in t-butyl alcohol is 4×10^6 as great as that of potassium methoxide in methanol, k_2 for potassium methoxide in pure dimethyl sulfoxide is several powers of ten greater than that for potassium t-butoxide in t-butyl alcohol.

The catalytic activity of metal t-butoxides is also subject to the activating influence of dimethyl sulfoxide, as is shown by the data of Table IV. At 25.0°, k_2 for racemization of (+)-N,N-diethyl-2-phenylpropionamide in dimethyl sulfoxide with potassium t-butoxide as base was too fast to measure, but k_2 was clearly greater than 2 l. m.$^{-1}$ sec.$^{-1}$. With sodium t-butoxide in the same solvent, k_2 amounted to 0.1 l. m.$^{-1}$ sec.$^{-1}$ (run 91), whereas with potassium t-butoxide in t-butyl alcohol k_2 was 4.6×10^{-6} l. m.$^{-1}$ sec.$^{-1}$ (run 92). Thus substitution of potassium for sodium t-butoxide in dimethyl sulfoxide increases the rate by a factor of > 20, and substitution of dimethyl sulfoxide for t-butyl alcohol increases the rate by a factor of > 4×10^5.

Activation Parameters.—The values of ΔH^* of Table V for the racemization of (+)-2-methyl-3-phenylpropionitrile with sodium methoxide as base decrease as the solution is enriched in dimethyl sulfoxide in the order 30.9, 29.4, 28.1 and 24.4 kcal. per mole, while the entropy decreases in the order 10.6, 8.4, 7.4 and 6.0 e.u. Thus the rate increase is due entirely to the decreased enthalpy of activation, since the entropy changes oppose the rate increase. However, with lithium and potassium methoxides as base, the limited data indicate that the entropy changes contribute in a minor way to the rate increases. The major role played by ΔH^* in the rate enhancement is not inconsistent with the interpretation that the accentuation of rate is associated with the changes in hydrogen bonding of methoxide anions in the two solvents.

Effect of Substrate Structure on Rates of Racemization.—Comparison of the rates of racemization of the two nitriles in ethylene glycol and in methanol indicates that a certain amount of specificity of base for substrate is possible. Thus at 25.0°, (−)-2-phenylbutyronitrile racemizes faster by a factor of about 3 in methanol with potassium

(23) H. E. Zaugg, B. W. Horrom and S. Borgwardt [*J. Am. Chem. Soc.*, **82**, 2895, 2903 (1960)] observed that additions of small amounts of solvents such as dimethylformamide or dimethyl sulfoxide to benzene as solvent enhanced the rates of alkylations of sodiomalonic esters by factors of about one power of ten. They attribute this effect to specific solvation of the metal cation by the additive, which depolymerizes the ion-pair aggregates and thus activates the nucleophile.

(24) In this formulation, O—H···O bond angles of 90% are envisioned. Although this bond angle may not be ideal [G. C. Pimentel and A. L. McClellan, "The Hydrogen Bond," W. H. Freeman & Co., San Francisco, Calif., 1960, p. 264] the strain energy involved in deformation of a bond angle containing a hydrogen bond should be far less than that involved in deformation of bond angles involving only covalent bonds.

(25) C. H. Langford and R. L. Burwell, Jr. [*J. Am. Chem. Soc.*, **82**, 1503 (1960)] observed that the activity coefficient of hydroxide ion in sulfolane (5 mole % in water) is largely responsible for the increase of 10^4 in basicity of this solvent as compared with that in water. We are currently investigating the relationship between the thermodynamic and kinetic basicities of methoxide anion in dimethyl sulfoxide–methanol mixtures.

methoxide (run 72) than in ethylene glycol with potassium ethylene glycoxide (run 78). Extrapolation to 25.0° of the values of k_2 for (+)-2-methyl-3-phenylpropionitrile (runs 54, 62, 58 and 63) indicates that the rate in ethylene glycol with potassium ethylene glycoxide is faster by a factor of 4.3 than the rate in methanol with potassium methoxide. Comparison of the k_2's for the two systems at 25° in the two solvent–base systems indicates that (−)-2-phenylbutyronitrile racemized faster than (+)-2-methyl-3-phenylpropionitrile by a factor of 2.7 × 10⁷ in methanol and 2.2 × 10⁶ in ethylene glycol. These data suggest that the carbon–hydrogen bond is more broken in the rate-determining transition state in methanol than in ethylene glycol. Thus the ability of phenyl in the benzyl nitrile to delocalize negative charge is more utilized in the transition state in methanol than in ethylene glycol.

Comparison of k_2's of runs 92 and 94 (Table IV) indicates that the t-butyl ester group of t-butyl 2-phenylpropionate acidifies the proton on α-carbon more than the diethylamido groups of N,N-diethyl-2-phenylpropionamide. The two compounds differ in rate by a factor of about 10⁴ in t-butyl alcohol–potassium t-butoxide at 25°. The rate of the corresponding nitrile was too fast to measure in this solvent–base system.

Relevance of This Investigation to Other Organic Reactions.—A large number of organic reactions involve the breaking of carbon–hydrogen bonds as the rate-determining step, and in some cases this reaction involves very strong bases or otherwise brutal reaction conditions. It is probable that the rates of many such reactions could be dramatically increased by the substitution of dimethyl sulfoxide for the usual hydroxylic solvents. Base-catalyzed elimination reactions (e.g., carbene, aryn, olefin and acetylene formation), certain condensation reactions, prototropic and other rearrangements (e.g., Wittig), and even some nucleophilic substitution reactions might be subject to rate and possibly yield enhancement. The Cope pyrolytic elimination reaction of amine oxides should also be subject to rate increase. Of the two reactions tried thus far, both have responded in the expected manner. Thus the potassium t-butoxide-catalyzed cleavage of systems such as VI has been found to proceed with improved yields at 120° lower temperature when dimethyl sulfoxide was substituted for t-butyl alcohol. The reaction of

bromobenzene with potassium t-butoxide to give phenyl t-butyl ether proceeds at 25° in dimethyl sulfoxide, but requires 175° in t-butyl alcohol.[1a]

Experimental

Starting Materials.—The (+)-2-methyl-3-phenylpropionitrile[14] used in this investigation had α^{25}D + 37.4° (l 1 dm., neat), n^{25}D 1.5091, and (−)-2-phenylbutyronitrile had α^{24}D −23.0° (l 1 dm., neat), n^{25}D 1.5061. The other three substrates were prepared as follows.

Optically pure (+)-2-methyl-3-phenylpropionic acid,[14] α^{25}D + 20.68° (l 1 dm., neat), 6.5 g., was dissolved in 15 ml. of purified thionyl chloride, and after 2 hr. the excess reagent

was evaporated under reduced pressure at room temperature, the last traces being removed by codistillation with dry benzene. A solution of 6 g. of redistilled diethylamine, b.p. 54–55° (free of ethylamine), in 50 ml. of dry ether was cooled to 0°, and treated dropwise with the acid chloride. The ethereal solution was washed repeatedly with water, dilute acid, dilute base, dried and evaporated. The residue was distilled to yield 6.3 g. of the desired amide as a clear colorless liquid, b.p. 108–109° (0.9 min.), α^{26}D + 75.04°, α^{28}_{546} + 89.44°, α^{28}_{436} + 158.04° (l 1 dm., neat).

Anal. Calcd. for $C_{14}H_{21}NO$: C, 76.67; H, 9.65. Found: C, 76.56; H, 9.69.

The compound, (+)-2-phenylpropanoic acid,[15] α^{25}D + 98.06° (l 1 dm., neat) (98% optically pure), was converted in 86% yield to (+)-N,N-diethyl-2-phenylpropionamide by the above procedure, b.p. 111–113° (1.5 mm.), α^{25}D + 118.12° (l 1 dm., neat).

Anal. Calcd. for $C_{13}H_{19}NO$: C, 76.06; H, 9.33. Found: C, 75.97; H, 9.37.

The ester (+)-t-butyl 2-phenylpropionate was prepared as follows. The above (+)-2-phenylpropanoic acid was converted by the above procedure to the corresponding acid chloride, 5 g. of which was added to 25 ml. of dry pyridine at 0°. The resulting suspension was stirred for 10 min. at 0°, mixed with 10 ml. of t-butyl alcohol, and stirred for 8 hr. The mixture was shaken with a mixture of ether and dilute acid. The ether layer was washed with water, dilute acid, dilute base, water, dried and evaporated. Distillation of the residue gave the desired ester (78% yield), b.p. 70–72° (1.1 mm.), α^{25}D + 35.6° (l 1 dm., neat).

Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.68; H, 8.80. Found: C, 75.72; H, 8.90.

Solvents.—J. T. Baker analyzed grade methanol was allowed to react with magnesium turnings and distilled through a 105-plate tantalum helices column into a dried receiver. Sodium metal was allowed to react with Eastman Kodak Co. white label ethylene glycol, the glycol was distilled, passed through a column containing Linde Molecular Sieves, and redistilled under reduced pressure. Potassium metal was allowed to react with Eastman Kodak Co. white label t-butyl alcohol, and the alcohol was then fractionally distilled through a 4-ft. column packed with stainless steel helices, and a center cut collected. Titration of this alcohol with Karl Fischer reagent indicated it to be 0.010 M in water. The material was dried over Molecular Sieves, then passed through a column of Molecular Sieves into a dried flask from which it was distilled into a dried flask. This material did not give a test for water with Karl Fischer reagent (estimated less than 0.003 M in water). Eastman Kodak Co. white label 1-butanol was refluxed over solid sodium hydroxide, distilled, dried over Molecular Sieves and distilled, the fraction b.p. 115–116° being collected. Dimethyl sulfoxide was dried by passing it through a column of Molecular Sieves.

The material was then distilled through a 3-ft. column packed with stainless steel helices at 90°, 20 mm. pressure, and the first and last fractions were rejected. The solvent was then passed through a column of Molecular Sieves directly into a distilling flask and distilled through a Vigreux column into a dried receiver at reduced pressure. The purified solvent was virtually odorless. Sulfolane was purified by a procedure identical with that used for dimethyl sulfoxide. Dry, carbon dioxide- and oxygen-free nitrogen gas was passed through all solvents for an hour before use.

Bases.—Potassium metal was allowed to react with purified t-butyl alcohol. The solvent was distilled at reduced pressure, and the remaining colorless solid was heated at 90° at 2 mm. for 12 hr. The potassium t-butoxide retained 38% t-butyl alcohol by weight. Similar preparations of sodium and lithium t-butoxides retained 20% and 3% solvent by weight (titration experiments), respectively. Tetramethylammonium hydroxide was prepared by evaporation (after a norite treatment) under reduced pressure of a commercial solution of the reagent (Eastman Kodak Co.). The composition $N(CH_3)_4OH·0.27$ $(N(CH_3)_4·2.0$ H_2O was determined by titrating a weighed sample of the crystalline material. The strong base was titrated with aqueous hydrochloric acid with phenolphthalein as indicator. The weak base was then determined by continuing the titration with brom cresol green as indicator.

Kinetic Solutions.—The basic solutions of ethylene glycol. methanol, 1-butanol and t-butyl alcohol were prepared by

adding weighed amounts of clean metal directly to the solvent in an atmosphere of purified nitrogen. The violence of the reaction of potassium metal with ethylene glycol and methanol was moderated by cooling the solvent, adding small pieces of metal, and stirring very vigorously to disperse the heat. Solutions involving the quaternary ammonium base were made by weighing out the required amount of base directly. Solutions of potassium and sodium *t*-butoxide in dimethyl sulfoxide were prepared by rapidly weighing out the solid bases under dry conditions.

Solutions of the metal methoxides in methanol–dimethyl sulfoxide mixtures were prepared as follows. Concentrated (3–4 M) stock solutions of potassium, sodium and lithium methoxides were prepared by adding a carefully weighed amount of clean metal to methanol in a clean, dry, pre-weighed flask under an atmosphere of pure nitrogen. After reaction was complete, the flask was weighed, and the weights of the metal alkoxide and solvent determined. The stock solutions were placed in clean, dry automatic burets, which were kept sealed and protected from the atmosphere. The solvents methanol and dimethyl sulfoxide were also placed in automatic burets and similarly protected. The desired amount of each solution or solvent was added to a pre-weighed flask, with a weighing between each addition, and the weight $\%$ of each solvent was calculated.

The only solubility difficulty was encountered with lithium methoxide in solutions rich in dimethyl sulfoxide. The solubility of this base was determined in mixtures of dimethyl sulfoxide–methanol at 25°. Mixtures were prepared by the above procedure from which the precipitated base was removed by centrifugation, and an aliquot of the clear supernatant liquid was titrated with standard acid. The results were

Wt. $\%$ dimethyl sulfoxide	97	90	86	77
Solubility (M)	0.0027	0.051	0.087	0.238

Hydrogen–Deuterium Exchange Experiments (Runs 1–6).

—The deuterated ethylene glycol and *t*-butyl alcohol were prepared as previously reported.[16] The desired solutions were prepared as in the kinetic runs (see below), a weighed amount of substrate added (0.25 g.) and the solutions placed in a constant temperature bath for the desired time (kinetic experiments made before these runs allowed the times to be calculated). Runs 1 and 4 were carried out in stoppered flasks at 25° and runs 2, 3, 5 and 6 were conducted in sealed ampoules. At the end of the run, the solutions were shaken with a mixture of pure pentane and water. The pentane layer was washed thoroughly with water, dried, evaporated, and the residue was distilled under reduced pressure in a micro-still. Rotations (neat) then were taken on the material, and deuterium analysis was carried out by combustion and the falling drop method (J. Nemeth, Urbana, Ill.). The deuterium analyses were corrected to values that would have been obtained had the solvent been originally 100% deuterated, and not diluted with protium as the exchange proceeded. This correction involves the assumption of no isotope effect in proton or deuteron capture by the carbanion. The correction was never more than 2%.

Kinetic Runs.

—All runs made at 34.6° or below were carried out in jacketed polarimeter tubes attached to a thermostat. The tube and reaction medium were pre-equilibrated, the substrate added to the volumetric flask, and readings were started less than a minute after mixing. It was possible to take as many as five readings a minute, and rates with half-lives of less than a minute could be studied. The length of the polarimeter tube was chosen to give initially observed rotation between 1.0 and 1.5°, although in some cases the values were much greater. The polarimeter could be read with ease to ±0.01°, and temperature was controlled to ±0.01°. When possible, for each point three observations of the optical rotation were made in quick succession. The time before the first and after the last of these three observations (usually an interval of 30 sec.) was recorded. The average of the three optical observations and the average of the two observations of time were then taken to constitute one point. All of the rates examined gave clear straight line plots of time *vs*. logarithm of rotation. Reactions with half-lives of less than 15 min. were followed to completion. All reactions were examined for at least one half-life, except for those with half-lives greater than 50 hr. In all cases not less than eighteen points, and usually many

more were taken. No trends were observed in the data. The sodium D line was used.

The rates were calculated by a simple graphic method, and the rate calculated from the line. A number of runs with apparent average deviation in points from the line were subjected to point by point calculation, and gave an average deviation of ±1.5%. Very fast and slow rates with greater inherent errors did not exceed ±5% average deviation.

The base concentration was determined by withdrawing either 1 or 2 ml. of solution from the polarimeter tube at the end of the run, adding it to water and titrating the base with standard 0.05 N or 0.01 N acid to the phenolphthalein endpoint.

Data obtained in a typical run (run 77) are recorded in Table VII.

TABLE VII

RACEMIZATION AT 25.00° OF (−)-2-PHENYLBUTYRONITRILE IN METHANOL, 0.01 M IN WATER, 0.100 M IN SUBSTRATE, 0.0170 M IN LITHIUM METHOXIDE

Time, min.	αD	Time, min.	αD
1.6	1.530°	8.0	0.786°
2.3	1.417	9.0	.692
3.0	1.339	10.0	.626
3.6	1.244	11.0	.560
4.3	1.159	12.0	.502
5.0	1.053	13.0	.452
5.8	0.990	14.0	.410
6.4	.919	15.0	.379
7.0	.860	28.5	.068
		80	.000

$k_{obs} = 1.78 \pm 0.02 \times 10^{-3}$ sec.$^{-1}$,

$$k_2 = 10.5 \pm 0.2 \times 10^{-2} \text{ l. m.}^{-1} \text{ sec.}^{-1}$$

TABLE VIII

RACEMIZATION AT 54.00° OF (+)-2-METHYL-3-PHENYL-PROPIONITRILE IN METHANOL, 0.157 M IN SUBSTRATE AND 0.3189 M IN BASE

Time, min.	$n^{25}D$	αD	k, sec.$^{-1}$ $\times 10^6$
0	1.5090	8.33°	...
2,638	1.5098	7.16	1.023
4,180	1.5086	6.35	1.087
5,623	1.5090	5.71	1.105
8,033	1.5090	4.67	1.085
10,092	1.5094	4.12	1.074
11,278	1.5094	3.65	1.135
12,730	1.5092	3.26	1.150

k_{obs} 1.09 ± 0.03

$$k_2 = 3.42 \pm 0.10 \times 10^{-6} \text{ l. m.}^{-1} \text{ sec.}^{-1}$$

Those runs conducted at temperatures higher than 34.6° were carried out utilizing the ampoule technique. Rate tubes were cleaned with cleaning solution, washed with ammonium hydroxide, detergent solution, rinsed 10 times with distilled water, and dried for at least 24 hr. at 100°. The tubes were allowed to cool in a desiccator and flushed with purified nitrogen prior to use. A weighed sample of substrate was added to the basic solution in a volumetric flask under a purified nitrogen atmosphere, the solution was brought to the mark, mixed, and a sample was withdrawn for titration of the base. The rate tubes were filled by a fast-draining pipet with 3.8 ml. of the reaction mixture. A stream of nitrogen was passed over the stock solution during this time. The tubes were sealed and placed in a constant temperature bath (±0.03°). The tubes were cooled, opened, quenched with water, and the product was extracted with pure pentane. The pentane layer was washed with water, dried, evaporated through a small packed column, and the product was flash distilled. Rotations were taken neat on the distillate in a 0.25-dm. tube. In representative cases infrared spectra were taken of these samples, and the spectra were identical in detail with that of the starting material. Seven or more points spread over a minimum of one-half life were taken. Data for a typical run (run 11) are given in Table VIII.