Cleavage Reactions.—All of the runs were conducted in solvent which was first saturated with nitrogen. Runs 108–129, 141–144 and 151–155 were conducted in closed systems under nitrogen, either in sealed tubes or pressure bottles. The other runs were carried out in flasks with reflux condensers under nitrogen. All runs were homogeneous. In those runs involving lithium, the metal was dissolved directly in the alcohol for preparation of the base. The same was true for potassium and lithium when *t*-butoxide or diethylene glycoxide was the base. Potassium or sodium metal could not be dissolved directly in ethylene glycol without danger of explosion and therefore potassium and sodium ethylene glycoxide was prepared from the corresponding *t*-butoxide as described earlier.[2b,2c] The reactions were run in a Wood metal-bath heated electrically. The products were isolated as described in previous investigations.[2b,2c] In representative runs the 1-methoxy-1-phenylethane or 2-phenylbutane products were demonstrated to have infrared spectra identical with those of authentic samples of these compounds.

Cleavage of (–)-V in (+)-2-octanol provides a typical procedure (other examples are found in papers II[2b] and III[2c] of this series). A solution of 0.96 *M* potassium alkoxide was prepared by dissolving 0.188 g. of potassium metal in a nitrogen-saturated solution of 5 ml. of optically pure (+)-2-octanol,[16] $[\alpha]^{25}\text{D}$ +48.1° (*c* 5, ethanol). To the resulting solution was added 1.0 g. of racemic V, and the solution was heated in a sealed tube at 150° for 16 hours. The reaction mixture was then chromatographed on 200 g. of alumina in pure pentane, and the 2-phenylbutane was eluted with pentane. Pentane was evaporated through a Vigreux column, and the residual 2-phenylbutane was twice distilled through a micro still at 25 mm. to give 0.43 g. of product, $n^{25}\text{D}$ 1.4878, $\alpha^{25}\text{D}$ 0.00 ± 0.02°.

In the other runs, solvent was washed from the reaction mixture in the isolation procedure by shaking the reaction mixture with pentane and water before chromatography.

Control Runs.—The products (I and XVI) of electrophilic substitution in these experiments were demonstrated to be optically stable under the conditions of their formation by control experiments reported in papers II and III of this series.[2b,2c] In runs 109, 120, 121, 135, 137 and 139, optically pure starting materials were recovered.

Protonation of 2-Phenyl-2-butylpotassium with (–)-2 Octanol.—A solution (30 ml.) of 2-phenyl-2-butylpotassium in ether was prepared by the action of sodium-potassium alloy on 3 g. of racemic 2-methoxy-2-phenylbutane.[2c] This material was protonated by addition of 1.0 g. of optically pure (–)-2-octanol, $[\alpha]^{24}\text{D}$ –48.3° (*c* 5, ethanol).[6] The resulting mixture was shaken with water, dried, and evaporated to an oil. This material was dissolved in pure pentane, passed through 50 g. of alumina, and the 2-phenylbutane was isolated in the usual way to give 1.9 g. of material, $n^{25}\text{D}$ 1.4878, $\alpha^{25}\text{D}$ 0.00 ± 0.02°.

LOS ANGELES 24, CALIF.

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[16] A. W. Ingersoll in "Organic Reactions," John Wiley and Sons, Inc., New York, 1944, p. 402.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

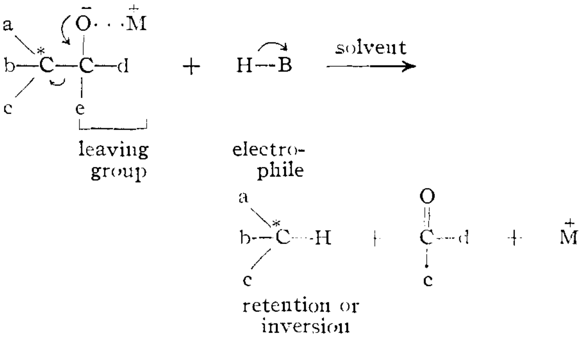
Electrophilic Substitution at Saturated Carbon. VI. Stereochemical Capabilities of Carbanions[1]

BY DONALD J. CRAM, JOSÉ LUIS MATEOS,[2] FRED HAUCK, ALBERT LANGEMANN, KARL R. KOPECKY, W. DAVID NIELSEN AND J. ALLINGER

RECEIVED JANUARY 2, 1959

Evidence is presented that in base-catalyzed reverse condensation reactions, carbanions or ion pairs involving carbanions intervene which capture protons from neighboring molecules, either before or after their solvent envelope becomes symmetric. Depending chiefly on the character of the medium, this electrophilic substitution at saturated carbon can occur with either predominating retention, predominating inversion or complete racemization. In solvents of low dissociating power (*e.g.*, *t*-butyl alcohol) and with metal alkoxides as bases, high retention of configuration is observed. This result is attributed to a favorable orientation of proton donors, which coördinate with the metal cation of an intimate ion-pair which undergoes cleavage. This species reacts to give a very reactive, carbanion–metal–cation intimate ion pair which is favorably solvated from the side of the leaving group by proton donors. Retention of configuration is observed because of the proximity of a very strong base and acidic hydroxyl or amino groups. In similar solvents with quaternary ammonium hydroxides as bases, complete racemization is observed since the carbanion survives long enough to pass into a symmetrical environment. In solvents of high dissociating power which are not proton donors (*e.g.*, dimethyl sulfoxide), the carbanion is long enough lived to become symmetrically solvated, and electrophilic substitution gives racemic product. In solvents of high dissociating power which are good proton donors (*e.g.*, diethylene glycol), a solvent-separated ion pair undergoes cleavage. The carbanion produced is protonated more rapidly from the side remote from the leaving group because of the shielding effect of that group. In diethylene glycol, metal and quaternary ammonium salts give the same result. The behavior of carbanions and carbonium ions is compared.

In the five previous papers of this series,[3] the steric course of electrophilic substitution at saturated carbon has been examined in a number of systems which are generally represented below. The substituents of both the asymmetric carbon (a, b and c) and of the leaving group (d and e) have been varied, as well as the characters of the metal cation, the electrophile, and the solvent. With various combinations of the above factors, the reactions were found to give product that ranged from 99% retention to 60% inversion of configuration.



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[1] This work was supported by a grant from the Petroleum Research Fund administered by the American Chemical Society. Grateful acknowledgment is hereby made to the donors of this fund.

[2] Rockefeller Postdoctoral Fellow at U.C.L.A., 1957–1958.

[3] (a) D. J. Cram, A. Langemann, J. Allinger and K. R. Kopecky, THIS JOURNAL, **81**, 5740 (1959); (b) D. J. Cram, A. Langemann and F. Hauck, *ibid.*, **81**, 5750 (1959); (c) D. J. Cram, K. R. Kopecky, F. Hauck and A. Langemann, *ibid.*, **81**, 5754 (1959); (d) D. J. Cram, A. Langemann, W. Lwowski and K. R. Kopecky, *ibid.*, **81**, 5760 (1959); (e) D. J. Cram, F. Hauck, K. R. Kopecky and W. D. Nielsen, *ibid.*, **81**, 5767 (1959). Tables, compounds and runs are numbered consecutively throughout the first six papers of this series.

TABLE XVI

DIMETHYL SULFOXIDE AND BENZYLTRIMETHYLAMMONIUM HYDROXIDE AS SOLVENTS IN CLEAVAGE AND RACEMIZATION REACTIONS

	Starting material			Base				Product					Predom.
Run	Compound	Concn., *M*	Solvent	Nature	Concn., *M*	T, °C.	Time, hr.	Nature	Yld., %	$n^{25}\mathrm{D}$[a]	$\alpha^{25}\mathrm{D}$[b]	% opt. purity	steric course
156	(+)-VIII	0.14	DMS[d]	$KOC(CH_3)_3$	0.11	25	12	(±)-I	68	1.4874	0.00°	0	Racem.
157	(+)-VIII	.08	DMS[d]–1 *M* KCl	$KOC(CH_3)_3$	.08	25	28	(±)-I	84	1.4878	0.00	0	Racem.
158	(+)-VIII	.2	DMS[d]	$NaOC(CH_3)_3$	.20	75	24	(±)-I	28	1.4876	0.00	0	Racem.
159	(+)-VIII	.2	DMS[d]	$LiOC(CH_3)_3$	.20	170	24	(−)-I	25	1.4877	−0.26	1	Ret.
160	(+)-VIII	.2	50 mol % $(CH_3)_3COH$ 50 mol % DMS[d]	$KOC(CH_3)_3$	.40	150	24	(−)-I	37	1.4880	−1.26	5	Ret.
161	(+)-VIII	.2	66 mol % CH_3OH 34 mol % DMS[d]	$KOCH_3$	.20	180	72	(+)-I	48	1.4878	+2.26	9	Inv.
162	(+)-VIII	.2	89 mol % CH_3OH 11 mol % DMS[d]	$KOCH_3$	.20	150	72	(+)-I	45	1.4875	+5.82	24	Inv.
163	(−)-X	.11	DMS[d]	$KOC(CH_3)_3$	.11	25	28	(±)-I	90	1.4880	0.00	0	Racem.
164	(+)-XIV	.09	DMS[d]	$KOC(CH_3)_3$	.10	25	24	(−)-XVI	38	1.4897	−0.42	0.3	Ret.
165	(−)-X	.10	BTA^+OH^-[e]	BTA^+OH^-[e]	..	110	20	(−)-I	74	1.4854	−0.20	1	Inv.
166	(−)-X	.10	BTA^+OH^-[e]	KOH	1.80	110	24	(+)-I	33	1.4876	+0.23	1	Ret.

[a] Pure XVI has $n^{25}\mathrm{D}$ 1.4882 and pure I, $n^{25}\mathrm{D}$ 1.4878. [b] *l* 1 dm., neat. [c] Optically pure XVI has $\alpha^{25}\mathrm{D}$ ±120.2° (*l* 1 dm., neat), and I has $\alpha^{25}\mathrm{D}$ ±24.3° (*l* 1 dm., neat). [d] DMS = dimethyl sulfoxide. [e] BTA^+OH^- = benzyltrimethylammonium hydroxide.

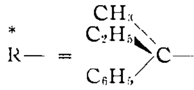
Evidence has been presented that the carbon–carbon bond is broken and the carbon–hydrogen bond is made in two different transition states in both the retention and inversion mechanisms.[3e] Intimate ion-pairs cleave to give predominating retention, whereas solvent-separated ion pairs give predominating inversion as the steric result.[3e]

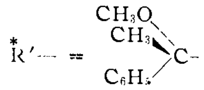
This paper, in the section on results, reports further data which have a direct bearing on the mechanism of the reaction. In the discussion section, these results are interpreted in terms of the limited mechanistic scheme which has been developed in earlier papers of this series. In the next section, a general mechanism is presented in terms of which the results of this and previous papers of this series are collated and interpreted. Finally, a section is devoted to a comparison of the behavior of carbanions and carbonium ions.

Results

The configurations of starting materials and products have been established in previous investigations.[3b,3c] In all experiments, optically pure starting materials were employed. All of the reactions reported in this paper except that of run 159 (Table XVI) were carried out under conditions which preserved the optical integrity of the products (see Experimental for control runs). Under the conditions of run 159, the product was found to undergo 17% racemization.

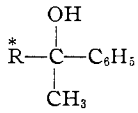
The results of cleavages of VIII, IX and XIV in dimethylsulfoxide and benzyltrimethylammonium hydroxide as solvents are recorded in Table XVI. In Table XVII are found the results of parallel runs in which the behavior of potassium and quaternary ammonium salts are compared. Unfortunately the reactions of all systems studied except VIII and XI occur only at temperatures above that at which quaternary ammonium bases decompose. Quaternary ammonium salts of both VIII and XI cleaved in *t*-butyl alcohol, but in diethylene glycol, only the salt of XI could be induced to undergo reaction at a temperature which preserved the quaternary ammonium cations. This latter system suffers from competition between radical and anionic cleavage. The former reaction both racemizes the starting material and produces racemic product.[3d] To at least partially overcome this disadvantage, the optical purity of the product was studied as a function of time, and the results obtained after very short reaction times provide a good indication of the steric course of the electrophilic substitution reaction.


$\overset{*}{\mathrm{R}}\text{—} = (\mathrm{CH_3})(\mathrm{C_2H_5})(\mathrm{C_6H_5})\mathrm{C}\text{—}$

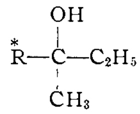

$\overset{*}{\mathrm{R}}'\text{—} = (\mathrm{CH_3O})(\mathrm{CH_3})(\mathrm{C_6H_5})\mathrm{C}\text{—}$

$\overset{*}{\mathrm{R}}\text{—H}$

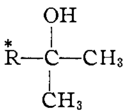
(+)-I


$\overset{*}{\mathrm{R}}\text{—}\mathrm{C(OH)(CH_3)}\text{—}\mathrm{C_6H_5}$

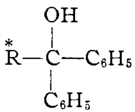
(+)-VIII


$\overset{*}{\mathrm{R}}\text{—}\mathrm{C(OH)(CH_3)}\text{—}\mathrm{C_2H_5}$

(−)-IX


$\overset{*}{\mathrm{R}}\text{—}\mathrm{C(OH)(CH_3)}\text{—}\mathrm{CH_3}$

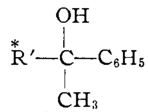
(−)-X


$\overset{*}{\mathrm{R}}\text{—}\mathrm{C(OH)(C_6H_5)}\text{—}\mathrm{C_6H_5}$

(+)-XI

$\overset{*}{\mathrm{R}}'\text{—H}$

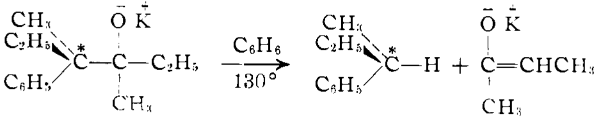
(−)-XVI


$\overset{*}{\mathrm{R}}'\text{—}\mathrm{C(OH)(CH_3)}\text{—}\mathrm{C_6H_5}$

(+)-XIV

In Table XVIII, the results of experiments are reported in which X was cleaved in dimethyl tetraethylene glycol both in the presence and absence of carbon dioxide.

An experiment was conducted in which system IX was cleaved in benzene in the complete absence of external proton sources. This alcohol was titrated with phenylpotassium at a low temperature, and the resulting solution was heated to 133° for 24 hours. From this reaction mixture was isolated a 54% yield of 2-phenylbutane which was 73% optically pure. It was demonstrated earlier[3a] that 2-phenyl-2-butylpotassium reacts with 2-butanone to give 2-phenylbutane.


$$(\mathrm{CH_3})(\mathrm{C_2H_5})(\mathrm{C_6H_5})\overset{*}{\mathrm{C}}\text{—}\mathrm{C}(\bar{\mathrm{O}}\overset{+}{\mathrm{K}})(\mathrm{CH_3})\text{—}\mathrm{C_2H_5} \xrightarrow[130°]{\mathrm{C_6H_6}} (\mathrm{CH_3})(\mathrm{C_2H_5})(\mathrm{C_6H_5})\overset{*}{\mathrm{C}}\text{—H} + \mathrm{C}(\bar{\mathrm{O}}\overset{+}{\mathrm{K}})(\mathrm{CH_3})\text{=}\mathrm{CHCH_3}$$

(−)-IX
optically pure

(+)-I
73% optically pure

Discussion

Solvents that Provide Racemic Products.— Unlike any other solvents, dimethyl sulfoxide and

TABLE XVII

VARIATION OF STERIC COURSE OF ELECTROPHILIC SUBSTITUTION WITH EXCHANGE OF QUATERNARY AMMONIUM FOR METAL CATIONS

	Starting mater.			Base				2-Phenylbutane						Recovered start. mat.	
Run	Nature	Concn., M	Solvent	Nature	Concn., M	T, °C.	Tm., hr.	Yld., %	$n^{25}D^a$	$\alpha^{25}D^b$	% opt. purity[c]	Predom. steric course	% yld. dimer[d]	Recov., %	% opt pur
167	(+)-XI	0.13	$(CH_3)_3COH$	$KOC(CH_3)_3$	0.57	59	0.67	19	1.4884	+12.40°	52	Ret.	..	23	5
168	(+)-XI	.13	$(CH_3)_3COH$	$KOC(CH_3)_3$	.57	50	4	27	1.4890	+8.90	37	Ret.	..	15	5
169	(+)-XI	.13	$(CH_3)_3COH$	$KOC(CH_3)_3$	.57	50	7	35	1.4885	+7.00	29	Ret.	18	12	1
170	(+)-XI	.15	$(CH_3)_3COH$	$KOC(CH_3)_3$	.57	50	10	33	1.4888	+6.76	28	Ret.	27	6	0
171	(+)-XI	.09	$(CH_3)_3COH$	$(CH_3)_4\overset{+}{N}\overset{-}{O}H$	.60	50	0.33	8	1.4880	+0.18	1	Ret.	..	42	86
172	(+)-XI	.10	$(CH_3)_3COH$	$(CH_3)_4\overset{+}{N}\overset{-}{O}H$	.57	50	0.5	29	1.4880	+ .34	1	Ret.	4	..	..
173	(+)-XI	.10	$(CH_3)_3COH$	$(CH_3)_4\overset{+}{N}\overset{-}{O}H$	.57	50	2	28	1.4890	+ .16	1	Ret.	54	..	..
174	(+)-XI	.10	$(CH_3)_3COH$	$(CH_3)_4\overset{+}{N}\overset{-}{O}H$	.60	35	1	5	....	0.00	0	Rac.	..	81	99
175	(+)-XI	.10	$(CH_3)_3COH$	$KOC(CH_3)_3$	.60	81	8	8	1.4888	+7.76	32	Ret.	39	..	..
176	(+)-XI	.07	$(CH_3)_3COH$	$(CH_3)_4\overset{+}{N}\overset{-}{O}H$	.60	81	8	59	1.4877	+0.1	0.4	Ret.	20	..	..
177	(+)-XI	.07	$O(CH_2CH_2OH)_2$	$KO(CH_2CH_2O)_2H$	1.56	110	25	47	1.4879	−3.26	13	Inv.	39	..	..
178	(+)-XI	.05	$O(CH_2CH_2OH)_2$	$(CH_3)_4\overset{+}{N}\overset{-}{O}H$	2.13[e]	110	25	23	1.4878	−2.40	10	Inv.	48	..	..
179	(+)-XI	.11	$O(CH_2CH_2OH)_2$	$(CH_3)_4\overset{+}{N}\overset{-}{O}H$	1.57	70	1	6	1.4888	−4.82	20	Inv.	..	74	96
180	(+)-XI	.11	$O(CH_2CH_2OH)_2$	$(CH_3)_4\overset{+}{N}\overset{-}{O}H$	1.56	70	2	43	1.4878	−2.20	9	Inv.	..	25	46
181	(+)-XI	.11	$O(CH_2CH_2OH)_2$	$KO(CH_2CH_2O)_2H$	1.56	70	3	40	1.4866	−1.00	16	Inv.	..	..	..
182	(+)-XI	.11	$O(CH_2CH_2OH)_2$	BTA^+OH^-[f]	0.42	110	24	41	1.4880	−2.17	9	Inv.	..	..	..
183	(+)-VIII	.10	$(CH_3)_3COH$	BTA^+OH^-[f]	.10	110	66	4	1.4877	−0.19	1	Inv.	..	..	..
184	(+)-VIII	.10	$(CH_3)_3COH$	$KOC(CH_3)_3$	.10	110	48	64	1.4878	+20.4	84	Ret.	..	..	..

[a] Pure 2-phenylbutane has $n^{25}D$ 1.4878. [b] l 1 dm., neat. [c] Optically pure 2-phenylbutane has $\alpha^{25}D$ ±24.3°, l = 1 dm., neat. [d] Dimer is 3,4-dimethyl-3,4-diphenylhexane, the product of homolytic cleavage reaction (ref. 3c). [e] At the end of the reaction, the concentration of tetramethylammonium hydroxide was 1.26 N; some decomposition of this base occurs at this temperature. [f] BTA^+OH^- = benzyltrimethylammonium hydroxide.

TABLE XVIII

EFFECT OF ADDED CARBON DIOXIDE ON STERIC COURSE OF CLEAVAGE OF 0.10 M SOLUTION OF OPTICALLY PURE (−)-2,3-DIMETHYL-3-PHENYL-2-PENTANOL [(−)-X] IN DIMETHYL TETRAETHYLENE GLYCOL AT 210° FOR 36 HOURS

	Base		2-Phenylbutane					
Run	Nature	Concn., M	Yld., %	$n^{25}D^a$	$\alpha^{25}D^b$	% opt. purity[c]	Predom. steric course	Remarks
185	$KO(CH_2CH_2O)_2CH_3$	0.12	79	1.4875	+12.2°	50	Ret.	....
186	$KOC(CH_3)_3 + CO_2$	.45	75	1.4875	+ 2.67	11	Ret.	CO_2 added at 180°
187	$KOC(CH_3)_3 + CO_2$	.45	70	1.4872	+ 3.02	12	Ret.	CO_2 added at 25°
188	K_2CO_3	.50	90	1.4878	+11.19	46	Ret.	Base not sol. at start

[a] $n^{25}D$ 1.4878 for pure 2-phenylbutane. [b] l 1 dm., neat. [c] Optically pure 2-phenylbutane has $\alpha^{25}D$ ±24.3° (l 1 dm., neat)

benzyltrimethylammonium hydroxide provide reaction media in which electrophilic substitution occurs with essentially complete racemization. The effect seems to be general, since all three systems, VIII, X and XIV, gave the same result in dimethyl sulfoxide (only VIII was run in benzyltrimethylammonium hydroxide),

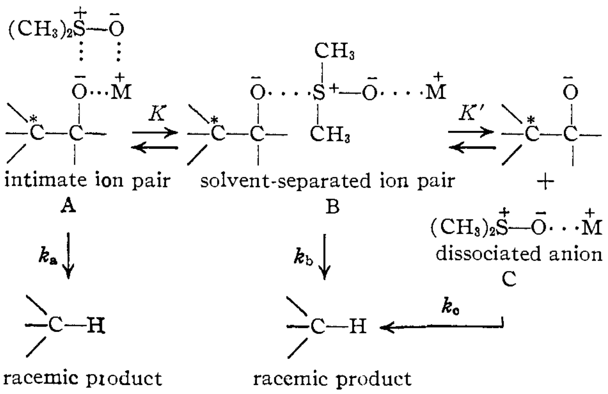
Another unique feature of these solvents, particularly of dimethyl sulfoxide, is the low temperature at which cleavage occurs. For example, XIV gives a 38% yield of product (XVI) at 25° in a 0.1 *M* potassium *t*-butoxide solution after 24 hours (run 164). A smaller yield (27%) was obtained for the same system at the same base and base concentration, the same reaction time, but with dioxane as solvent and 125° as the temperature (run 69, ref. 3c).

Runs 156, 158 and 159 were carried out at the lowest temperatures which provided reasonable yields of products. *Clearly the potassium salt cleaves orders of magnitude faster than the sodium salt, which in turn cleaves orders of magnitude faster than the lithium salt.* Although differences in rates of cleavage of the three kinds of salts have been observed in solvents such as *t*-butyl alcohol and diethylene glycol,[3e] the differences in dimethyl sulfoxide are much more dramatic.

Salt	Temp., °C.	Time, hr.	Yield, %	Run
K salt of VIII	25	12	68	156
Na salt of VIII	75	24	28	158
Li salt of VIII	170	24	25	159

Comparison of the yields and times of runs 156 and 157 (Table XVI) indicates that the rates of cleavage in 0.1 molar solutions of potassium *t*-butoxide are not materially altered by the presence of enough potassium chloride to make the solution 1 molar in this salt. No large common ion rate depression[3e] is visible in these results.

Three effects require explanation. (1) Cleavages of *potassium alkoxides* in dimethyl sulfoxide occur orders of magnitude faster than in any of the other solvents yet tried. (2) Rates of cleavage of metal alkoxides in dimethyl sulfoxide follow the order ROK $\gg$ RONa $\gg$ ROLi. (3) Dimethyl sulfoxide and benzyltrimethylammonium hydroxide are solvents that give essentially racemic product. The first two effects can be accounted for by the partial mechanistic scheme developed earlier,[3e] and the last will be discussed in the next section.



In this scheme, $k_c \gtrsim k_b \gg k_a$. Although the values of k_a vary with the changes in the character of M^+, the values of k_b and k_c are relatively insensitive to the nature of the metal. The values of k_b and k_c are probably much higher in dimethyl sulfoxide than in alcohols or amines, because anions in dimethyl sulfoxide are not hydrogen bonded (the hindered, positive sulfur of dimethyl sulfoxide should provide less solvation for anions than hydroxyl groups). As a result, the cleavage reaction in dimethyl sulfoxide is channeled through either B or C, which have low activation energies for the cleavage reaction.

In dimethyl sulfoxide, the values of K and K' are probably much more dependent on the character of the metal cation than in hydroxylic solvents, since in the former solvent, the main driving force for dissociation is solvation of M^+. The values of K and K' decrease with changes in M^+ in the order of decreased shielding of positive charge by electrons, with $K^+ \gg Na^+ \gg Li^+$. Thus the enhanced rates of cleavage of potassium alkoxides in dimethyl sulfoxides are associated with relatively high values of K or K', and of k_b or k_c. The wide difference in rates for alkoxides of different metals is associated with the widely different values of K and K' for different metals in dimethyl sulfoxide.

Effect of Quaternary Ammonium Cations on Steric Course of Electrophilic Substitution.—The results of Table XIX indicate that the substitution of quaternary ammonium for metal cations in *t*-butyl alcohol (extreme retention solvent) changes the steric result from high retention to essentially total racemization. System VIII as the potassium salt gives 84% net retention, and as the benzyltrimethylammonium salt, the system gives 1% inversion (runs 183 and 184). In the same solvent, XI underwent electrophilic substitution as the potassium salt to give higher than 90% net retention,[4]

TABLE XIX

COMPARISON OF POTASSIUM AND QUATERNARY AMMONIUM IONS

Salt	Solvent	Steric course	Run
K salt of VIII	$(CH_3)_3COH$	84% R[a]	184
BTA[b] salt of VIII	$(CH_3)_3COH$	1% I[c]	183
K salt of XI	$(CH_3)_3COH$	>90% R[a,d]	167
$(CH_3)_4\overset{+}{N}$ salt of XI	$(CH_3)_3COH$	Racem.	174
K salt of XI	$HO(CH_2CH_2O)_2H$	16% I[c]	181
$(CH_3)_4\overset{+}{N}$ salt of XI	$HO(CH_2CH_2O)_2H$	20% I[c]	179

[a] Net retention. [b] BTA = benzyltrimethylammonium cation. [c] Net inversion. [d] Extrapolated to zero time when starting material had not racemized by reversible homolytic cleavage (see ref. 3d and footnote 4).

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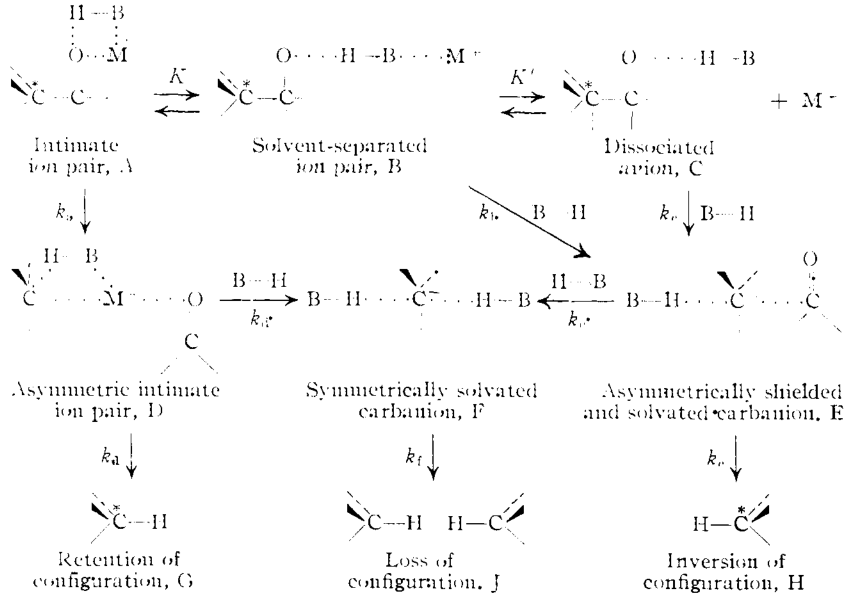
(4) In paper IV (ref. 3d), reversible homolytic cleavage of XI was demonstrated to compete with non-reversible heterolytic cleavage. In run 167 (Table XVII), almost equal amounts of 2-phenylbutane (52% optical purity, retention) and starting material (5% optically pure) were obtained. Clearly, starting material was racemizing about four times as fast as electrophilic substitution occurred. The electrophilic substitution itself must have been well over 90% stereospecific (retention) with potassium salt in *t*-butyl alcohol. In run 174, 81% of essentially optically pure starting material was recovered, and a 5% yield of racemic 2-phenylbutane was obtained. Thus the electrophilic substitution itself must have occurred with racemization with tetramethylammonium salt in *t*-butyl alcohol.

CHART I



and as the quaternary ammonium salt total racemization (runs 167 and 174). *These results conclusively demonstrate that the presence of metal cations is a requirement for the operation of the retention mechanism.*

In the extreme inversion solvent, diethylene glycol, approximately the same results were obtained from cleavage of the potassium and tetramethylammonium salts of XI. The metal salt of XI gave 16% net inversion and the quaternary ammonium salt gave 20% (runs 181 and 179, respectively). These values undoubtedly would have been much higher if homolytic cleavage and substitution had not competed with the heterolytic process.[3d] *Clearly, the presence of metal cations is not a requirement for the operation of either the inversion or racemization mechanisms.*

Effect of Added Carbon Dioxide on the Steric Course of Electrophilic Substitution.—The data of Table XVIII indicate that the presence of carbon dioxide in dimethyl tetraethylene glycol reduces the stereospecificity of the cleavage of the potassium salt of X from about 50% net retention (run 185) to about 12% net retention (runs 186 and 187). The presence of potassium carbonate in the medium had little effect on the stereospecificity of the reaction carried out in the absence of carbon dioxide (run 188).

Stereospecificity in Electrophilic Substitution at Saturated Carbon

A number of independent kinds of evidence have now been obtained that either ion pairs which contain carbanions, or carbanions themselves, intervene as discrete intermediates in the substitution reactions that occur with all three kinds of steric results, retention, racemization and inversion. This evidence is summarized as: (1) In retention solvents, the steric result varies only to a minor extent with gross changes in either the concentration or acidity of the electrophile.[3b,3c,3e] (2) In both retention and inversion solvents, the steric result is independent of the configuration of the leaving group.[3e] (3) In racemization solvents, the steric result is completely independent of the nature of the leaving group. In extreme retention solvents, the results differ in degree but not in kind as the leaving group is changed. In extreme inversion solvents, the results differ only slightly with changes in the leaving group. These results are incompatible with reaction mechanisms in which the carbon–carbon bond is broken and the carbon–hydrogen bond is made in the same transition state. Thus an SE1 mechanism would appear to apply to the reactions studied in these papers. The purpose of this section is to explain the observed stereochemical fate of the carbanion intermediates under various sets of conditions.

In Chart I is sketched an over-all mechanistic scheme in which A, B, C · · · etc. stand for discrete intermediates which are considered to be involved in electrophilic substitution at saturated carbon. Rate constants which control the formation of intermediates and products are written over the arrows. A given mechanism will be denoted by notations such as A → D → G, and the various mechanistic sequences will be correlated with specific experimental results.

Species A is a generalized alkoxide in which the strength of the oxygen–metal bond varies considerably with the nature of the metal and of solvent. At least one solvating molecule (H–B) is bound in A through coördination of the metal with unshared pairs of electrons on B (oxygen or nitrogen), and by hydrogen bonding of H–B with negative oxygen. This species is an *intimate ion pair*, since no solvent molecules intervene between positive metal and negative oxygen.

In equilibrium with A is a *solvent-separated ion pair* (B) in which the two ions are much farther apart. These ions each have their own solvent shells, and are held together by electrostatic forces. This ion-pair is in turn in equilibrium with the dissociated anion C, and the cation, M^+.[3e]

In this mechanistic scheme,[3e] A, B and C are all capable of undergoing cleavage, and $k_c \gtrless k_b \gg k_a$. However, in extreme retention solvents, only A undergoes cleavage because essentially only this species is present in these solvents. In extreme inversion solvents, only B undergoes cleavage. Although A, B and C vary in concentration, the values of the rate and equilibrium constants combine in such a way as to make cleavage of C negligible, except possibly in dimethyl sulfoxide. In intermediate solvents, various amounts of A and B cleave, depending on the character of the metal, leaving group, and substituents on the carbon atom that undergoes substitution. Equation 1 describes the relative amounts of A and B that cleave as a function of K, k_a and k_b.[3e]

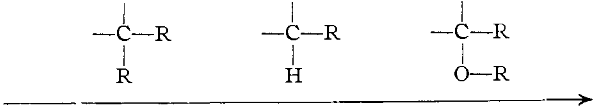
$$\frac{D}{E} = \frac{k_a}{k_b K} \qquad (1)$$

Retention and Racemization in Non-dissociating Solvents.—In solvents such as benzene, dioxane, N-methylaniline or *t*-butyl alcohol (extreme retention solvents), A cleaves to give D, which is a new intimate ion pair which involves a carbanion and a metal cation. The proton donor, H–B, solvates this new intimate ion-pair in much the same way it solvated A, through coördination of the unshared pair of electrons of H–B with the metal cation, and hydrogen bonding of the hydrogen of H–B with the carbanion. The carbanion is probably flat due to delocalization of negative charge into the benzene ring.[5] The stereochemical fate of the carbanion is largely determined by the symmetry properties of its environment rather than by its configuration. Since in D, a hydrogen atom is favorably oriented on the side originally occupied by the leaving group, collapse to give product of retained configuration (G) is its main reaction. In a competing process, D gives F, which is a symmetrically solvated carbanion. Collapse of F gives racemic product. In solvents in which only A cleaves, the stereospecificity of the reaction depends only on the value of $k_d/k_{d'}$. This scheme explains the various effects noted earlier.

(1) *High retention is observed with electrophiles that range from N-methylaniline to ethylene glycol in acidity.*[3a,3b,3c] Because of the high reactivity of the carbanion of D, the activation energy for proton abstraction is very low. In the transition state, the carbon–hydrogen bond is very little made, and the oxygen–hydrogen or nitrogen–hydrogen bond is very little broken.[6] Thus the acidity of the electrophile plays little role in controlling the value of $k_d/k_{d'}$.

(2) *High retention is observed in non-dissociating solvents such as dioxane or t-butyl alcohol, irrespective of the concentration of electrophiles.* The structures of A and D are not affected by electrophile concentration, and therefore the rate constants k_a and k_d are not subject to concentration effects. In non-dissociating solvents, $k_d >> k_{d'}$, irrespective of electrophile concentration. On the other hand, as the solvent medium becomes more dissociating, $k_{d'}$ and k_d could approach one another if the electrophile concentration was high enough. Possible examples of such a situation are found in the loss of stereospecificity as the concentrations of glycol in dioxane are increased in the cleavages of VIII, IX and XIV (see Fig. 1, paper III of this series).[3c] This effect accounts for the loss of stereospecificity only for those solvent compositions in which A is the main reacting species.

(3) *The highest retention is observed with systems in which the alkoxide anion, the metal cation and the electrophile of A are the most tightly bound together.* Examples of this effect are: In the cleavage of VIII in dioxane, a 1 mole % concentration of *t*-butyl alcohol gave 95% net retention whereas a 0.5 mole % concentration of diethylene glycol gave 91% retention (see table of ref. 3c). This result correlates with the fact that *t*-butyl alcohol is a stronger base than diethylene glycol. In extreme retention solvents, lithium alkoxides give higher retention than sodium or potassium alkoxides.[3e] This result reflects the strong tendency of the relatively unshielded lithium ion to become bound to negative centers. In extreme retention solvents, stereospecificity decreases as the oxygen of the leaving group becomes less basic. The more basic oxygen tends to bind the metal and therefore the electrophiles more tightly.

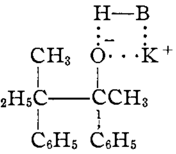


Decreasing basicity and decreasing retention in non-dissociating solvents.

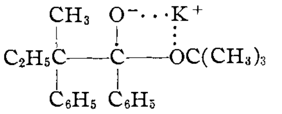
The same effects that apply to A must equally well apply to D, since both are intimate ion pairs. The more intimately bound together are the parts of A, the slower becomes the rate at which A → B relative to the rate at which A → D. Similarly, the stronger the forces that bind the parts of D together, the higher the value of $k_d/k_{d'}$, which controls the stereospecificity.

(4) *In extreme retention solvents, systems that contain two oxygen atoms capable of coördinating with metal cations give a less stereospecific result than those with only one oxygen atom.* Examples of this effect are formulated. Due to intramolecular coördination of the metal cation in the two latter systems, electrophile is less tightly bound by the metal in A. As a result, electrophile is less well oriented for front side attack in D, and $k_d/k_{d'}$ and the stereospecificity are lowered.

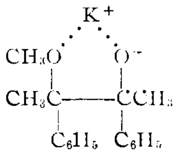
Solvent, dioxane; electrophile, 1 mole % *t*-butyl alcohol



At 150°, 95% optically pure 2-phenylbutane of retained configuration, run 67[3c]



At 150°, 74% optically pure 2-phenylbutane of retained configuration, run 70[3c]



At 125°, 84% optically pure 1-methoxy-1-phenylethane of retained configuration, run 69[3c]

(5) *Diastereomers give the same steric results in extreme retention solvents.* Since D contains only one

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[5] The deep red color associated with 2-phenyl-2-butylpotassium prepared in dry ether [D. J. Cram and J. D. Knight, THIS JOURNAL, **74**, 5835 (1952)] leaves little doubt that this species is better regarded as an ion pair rather than as a covalently bound species. Further evidence in favor of an ion pair formulation derives from Wittig's observation [G. Wittig and E. Stahnecker, *Ann.*, **605**, 69 (1957)] that the ultraviolet absorption spectra of diphenylphenoxymethylpotassium, sodium and lithium were essentially identical (λmax 450 mμ).

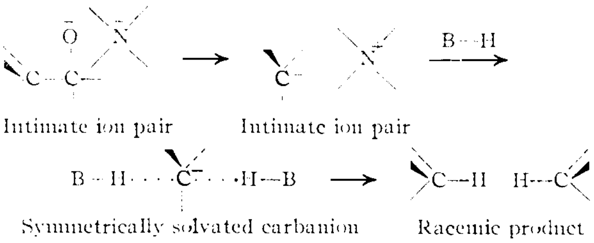
[6] See G. S. Hammond, THIS JOURNAL, **77**, 334 (1955). In this connection, K. B. Wiberg, *ibid.*, **78**, 5987 (1956), observed very little isotopic discrimination when organometallic reagents were decomposed in mixtures of ordinary and deuterated methanol or water.

asymmetric center, its structure and therefore its fate is independent of the configuration of the leaving group.[3e]

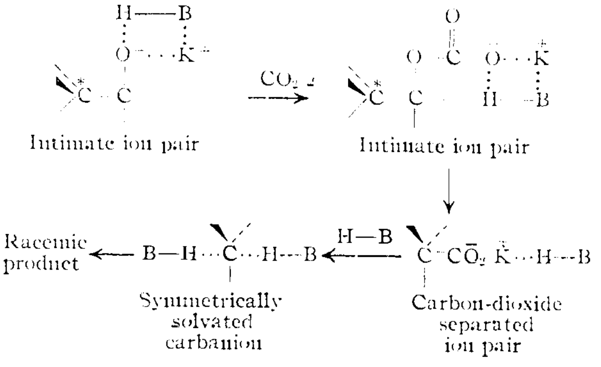
(6) *In extreme retention solvents, the higher the temperature,* the lower the stereospecificity.[3c] The process, D $\xrightarrow{k_d}$ G, is monomolecular, and D $\xrightarrow{k_{d'}}$ F, polymolecular. Therefore, higher temperatures should provide lower values of $k_d/k_{d'}$, and therefore a less stereospecific result.

(7) *Cleavage of the potassium salt of VIII in a mixture 50 mole % in t-butyl alcohol and 50 mole % dimethyl sulfoxide gives product with only 5% net retention of configuration (run 160).* In this medium, both A and B probably underwent cleavage. To some extent, a molecule of dimethyl sulfoxide could have replaced *t*-butyl alcohol in both A and D. Since dimethyl sulfoxide does not contain a proton donor, the reaction D → G would be eliminated, and the reaction D → F favored.

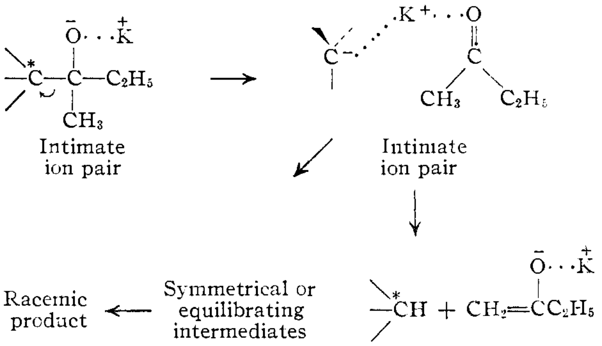
(8) *In t-butyl alcohol as solvent, substitution of quaternary ammonium for potassium cations in cleavage of VIII and XI results in a change in steric result from high retention to essentially complete racemization (see Table XVII).* Since quaternary ammonium ions are incapable of coördinating with and binding electrophiles in A and D, these species do not contain electrophiles, and the reaction path A → D → G is eliminated. As a result, the intimate ion pair produced on cleavage lives long enough to produce the symmetrically solvated carbanion (F) which can only give racemic product.



(9) *Addition of carbon dioxide to the reaction medium in cleavage of X in dimethyl tetraethylene glycol reduces the stereospecificity from about 49% net retention to about 12% net retention.* To a large extent, the species that cleaved was probably the tertiary alkyl potassium carbonate in which the metal cation and its coördinating electrophile were separated from the carbon that undergoes substitution by two extra atoms. As a result, a carbon dioxide-separated ion pair was produced in which the electrophile was too remote from the carbanion to provide a favorable rate for front side attack of H–B on the carbanion. As a result, the carbanion lived long enough to become symmetrically solvated, and almost racemic material was produced.[6a]

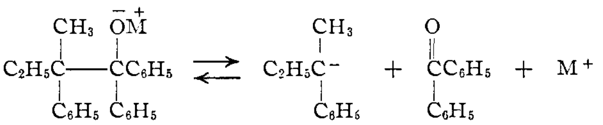


(10) *In the cleavage of the potassium salt of IX in benzene in the absence of any external proton source, 2-phenylbutane was produced which was 73% optically pure.* In this reaction, the protons must have been supplied by the α-carbons of the leaving group in a mechanism similar to that formulated. This reaction was less stereospecific than one carried out in benzene which was 0.80 *M* in *t*-butyl alcohol (run 16)[3b] with the same starting material. Retained product of 93% optical purity was obtained in the latter run. Thus higher stereospecificity is observed with an external proton source, and a mechanism such as A → D → G.



Benzophenone as a leaving group contains no acidic protons, and yet cleavage of XI in dioxane with diethylene glycol as electrophile gave 2-phenylbutane of 99% stereospecificity (extrapolation of the curve of Fig. 1 of ref. 3d to zero time gives this value). Thus high stereospecificity does not depend on the presence in the leaving group of acidic hydrogens. Had internal electrophiles been utilized to any extent in cleavage reactions carried out in hydroxylic solvents, the retention mechanism would not have been dependent on a metal cation with coördinated solvent as part of the leaving group. Thus internal proton sources would seem to be involved only in the absence of external proton donors.

The interesting question arises as to what happens when a system such as XI cleaves in the absence of proton donors in the solvent. Unfortunately, with this system radical cleavage competes with anionic cleavage,[3d] and in the absence of proton donors in the solvent, only evidence of radical cleavage can be obtained.[7] It is possible, however, that in the absence of either internal or external



$$C_2H_5\underset{C_6H_5}{\overset{CH_3}{C}}-\underset{C_6H_5}{\overset{\bar{O}\overset{+}{M}}{C}}C_6H_5 \rightleftarrows C_2H_5\underset{C_6H_5}{\overset{CH_3}{C}}{}^- + \underset{C_6H_5}{\overset{O}{\overset{\|}{C}}}C_6H_5 + M^+$$

XI

[6a] Although the odor of the reaction product of runs 186 and 187 suggested that some 2-methyl-2-phenylbutanoic acid was produced in this reaction, the amount was too small to be isolated and characterized. As might be expected, carbon dioxide is a much poorer electrophile than the primary alcohol present in the medium, and in spite of the favorable orientation of the carbon dioxide, the carbanion reacted with the proton donors.

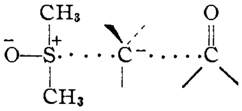
[7] D. J. Cram and A. Langemann, unpublished results.

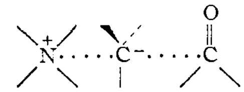
electrophiles, the system cleaves anionically but recombines without loss of optical activity. Evidence for or against such a process would be very difficult to obtain. That such a reversible reaction occurs with loss of optical activity has not been observed in any of the systems studied thus far. In many runs which were not carried to completion, optically pure starting material was recovered.

Inversion and Racemization in Dissociating Solvents.—In dissociating solvents such as ethylene or diethylene glycol, the solvent-separated ion pair (B of Chart I) is presumed to be the species that cleaves.[3e] A carbanion is produced which is solvated from the side remote from the leaving group by electrophiles, and which is shielded at the front by the leaving group (E of Chart I). This species partitions to give product of inverted configuration (H), or symmetrically solvated carbanion (F), which collapses to give racemic product (J). The stereospecificity of the reaction depends on the value of the ratio $k_e/k_{e'}$. Although charge is partially delocalized in the phenyl group of carbanion E, the benzyl carbon atom probably possesses more negative charge than the *ortho* or *para* carbon atoms of the benzene ring, and reaction is presumed to occur mainly at the benzyl carbon atom.[8] Electrophilic attack on this highly reactive carbanion from the side remote from the leaving group is favored because this side is more sterically available. This mechanistic scheme provides an explanation for the effects observed in dissociating solvents.

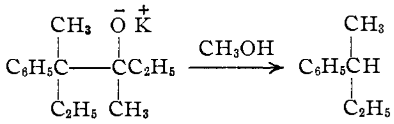
(1) *Highest inversion is found in solvents which provide the highest concentration of electrophiles.*[3b] Although the reaction B → E involves a mole of electrophile, very little driving force for the reaction is provided by specific solvation of the carbanion for two reasons. First, the negative charge in the carbanion is spread over the benzyl carbon and three positions of the benzene ring. Second, in the starting material, the benzyl carbon atom is highly hindered. The distance between any proton donor at the side remote from the leaving group and the electrons of the bond being broken is large. Thus solvation of carbanion E is of a general rather than a specific type, and the inversion mechanism depends on having a medium in which a high probability exists that random orientation of *unhindered hydroxyl groups* will place the electrophile in the proper position for solvation of the benzyl carbon. At best, the highest net inversion observed (run 78)[3b] was 60%, a fact which suggests that stereospecificity depends more on probability than on a highly specific configurational requirement for the cleavage reaction to occur.

The results in dimethyl sulfoxide and benzyltetramethylammonium hydroxide as solvents strongly support this view. In these solvents, either B or C cleave, but solvation of the carbanion is provided not by proton donors, but by positive sulfur in dimethyl sulfoxide and positive nitrogen in the quaternary ammonium hydroxide. In these solvents the reaction path E → H is unavailable, and the carbanion lives long enough to become enveloped in a symmetrical solvent shell. Thus a totally racemic product is obtained.


Solvated carbanion produced in dimethyl sulfoxide as solvent


Solvated carbanion produced in benzyltetramethylammonium hydroxide

In the cleavage of VIII in mixtures of methanol and dimethyl sulfoxide, the stereospecificity dropped rapidly with increasing concentration of dimethyl sulfoxide.


$$C_6H_5\underset{C_2H_5}{\overset{CH_3}{C}}-\underset{CH_3}{\overset{\bar{O}\overset{+}{K}}{C}}C_2H_5 \xrightarrow{CH_3OH} C_6H_5\underset{C_2H_5}{\overset{CH_3}{C}}H$$

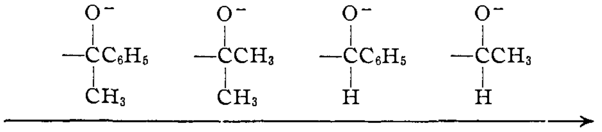
Mole % CH_3OH	Mole % $(CH_3)_2SO$	Steric course	Run
100	0	45% net inversion	152[3e]
89	11	24% net inversion	162
66	34	9% net inversion	161
0	100	Racemization	163

No specific requirement that H–B solvate the back side of the incipient carbanion can be seen in these results.

(2) *In extreme inversion solvents, with VIII and IX, the steric course of the reaction is independent of the nature of the cation* (Table XIV).[3e] When B is the only species which undergoes cleavage, lithium and potassium alkoxides cleave to give the same net inversion in several systems. Substitution of quaternary ammonium for potassium ion did not alter the amount of net inversion (runs 179–181) observed in the cleavage of XI in glycol. The reaction paths B → E → H and B → E → F → G (Chart I) in no way involve cations. The stereospecificity of the reaction is controlled by the value of $k_e/k_{e'}$, and this ratio is independent of the character of M^+.

(3) *In extreme inversion solvents, the steric course of the reaction is independent of the configuration of the leaving group.*[3e] Since the same species, E, is produced from two diastereomeric B's, the fate of E is independent of its source.

(4) *In extreme inversion solvents, the larger the leaving groups the more stereospecific the reaction.*[3b,3e]


Order of decreasing size and order of decreasing stereospecificity in extreme inversion solvents

Since the rate ratio ($k_e/k_{e'}$) which controls the stereospecificity of the reaction depends on the ability of the leaving group to shield the front side of the carbanion from electrophiles, the larger leaving groups are more effective at reducing the value of $k_{e'}$ than the smaller leaving groups.

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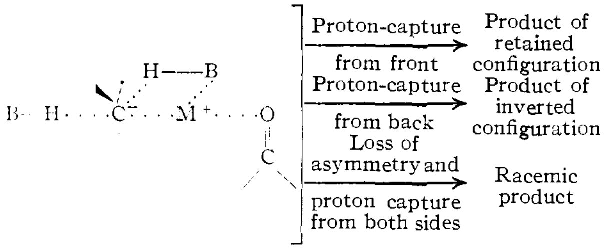
[8] Support for this contention is found in the results of G. A. Russell, THIS JOURNAL, **81**, 2017 (1959), who treated 2-phenyl-2-propylpotassium in ether with deuteron-donors. Deuteration of the 2-propyl-position dominated over the *p*-position of the phenyl group by the following factors: with D_2O, factor of 7500; DOAc, factor of 65; DCl, factor of 4.5. In $CH_3OCH_2CH_2OCH_3$, DCl gave a factor of 7500.

(5) *In extreme inversion solvents, the higher the temperature, the lower the stereospecificity.* Since the reaction, $E \xrightarrow{k_{e'}} F$ is polymolecular, and the reaction $E \xrightarrow{k_e} H$ monomolecular, higher temperatures provide lower values of $k_e/k_{e'}$, and therefore a less stereospecific result.

Retention, Racemization and Inversion in Intermediate Solvents.—In solvents of intermediate dissociating power, both A and B cleave, and the steric results are intermediate between those found in the extreme retention and inversion solvents. The results represent an interplay of the values of K, k_a, k_b, $k_d/k_{d'}$ and $k_e/k_{e'}$, and can be interpreted in terms of various combinations of the effects discussed in the last two sections.

Other Mechanisms.—Although the mechanism outlined in Chart I provides an explanation for the wide variety of effects which control the steric course of electrophilic substitution at saturated carbon, the question arises as to whether variants of this mechanism might not equally well accommodate the results. Certainly the mechanism of Chart I can be made more elaborate by the introduction of additional intermediates. "Parsimony of explanation" makes such additions not worth consideration unless results require a more complicated picture. The only question is whether a simpler mechanism can apply.

The only modification of the mechanism of Chart I that will be considered here is one in which the character of intermediates D and E are blended into one species of the type formulated. Partition of this intermediate between retention, racemization and inversion reaction paths might explain the results.



The facts which are in conflict with or are unexplained by a mechanism which involves a single intermediate of this type are: (1) In *t*-butyl alcohol when M^+ is potassium, high retention is observed, but when M^+ is quaternary ammonium, total racemization is the result. The above mechanism would predict inversion as the mechanistic result, since quaternary ammonium ions could not orient H–B at the front. (2) In methanol, when M^+ was lithium, higher inversion was observed than when M^+ was potassium.[3e] The above mechanism predicts the opposite effect. (3) In diethylene glycol, the same steric result is obtained whether M^+ is quaternary ammonium, lithium or potassium.[3e] Certainly the above mechanism does not accommodate this observation. (4) Addition of carbon dioxide to the medium in a retention solvent drastically reduces the stereospecificity observed. A single intermediate of the above type provides no explanation of this result. (5) The rates of cleavage of potassium alkoxides in dimethyl sulfoxide are many orders of magnitude faster than cleavages of other alkoxides in the same solvent, or of potassium alkoxides in any other solvents. The above intermediate provides no explanation of this fact. Likewise, many other mechanistic variants inadequately account for the observed results.

Comparison of the Stereochemical Courses of Monomolecular Nucleophilic and Electrophilic Substitutions at Saturated Carbon

In 1935, Hughes and Ingold[9] suggested that both the monomolecular nucleophilic and electrophilic substitutions at saturated carbon (SN1 and SE1 reactions) might occur with retention of configuration. Experiments conducted since that time have made it abundantly clear that the SN1 reaction can occur with inversion,[10] retention[11] or with total racemization.[12] The stereochemical course of the reaction depends on such features as the character of the leaving group, the dissociating power and nucleophilicity of the solvent, and the ability of substituents to stabilize the carbonium ion.

The same spectrum of stereochemical results has now been observed to apply to the SE1 reaction. Not only are all three steric courses now known, but they merge into one another. The patterns of results obtained in the two electronic varieties of substitution reactions are remarkably similar, as is demonstrated in the comparison of Chart II.

The similarity between the nucleophilic and electrophilic substitution reactions stops with the monomolecular variety. The bimolecular nucleophilic substitution reaction at saturated carbon (SN2 reaction) occurs with complete inversion of configuration.[13] In the only electrophilic substitution which might be bimolecular (SE2) and whose stereochemical course has been critically studied,[14] *cis*-2-methoxycyclohexylneophylmercury was found to react with radioactive mercuric chloride to give radioactive *cis*-2-methoxycyclohexylmercuric chloride with better than 99% retention of configuration. In the SN2 reaction, since the entering group is seeking positive charge, it attacks the nucleus along an axis which is as far as possible from any bonds. In the SE2 reaction, since the entering group is seeking electrons, it probably attacks the bond of the leaving group.

Chart II

Comparison of Conditions Required for Different Steric Courses of SN1 and SE1 Reactions

Retention Mechanism.—SN1: Occurs when a complex leaving group carries its own nucleophile, as in the reactions of chlorosulfites in non-dissociating solvents.

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(9) E. D. Hughes and C. K. Ingold, *J. Chem. Soc.*, 244 (1935).

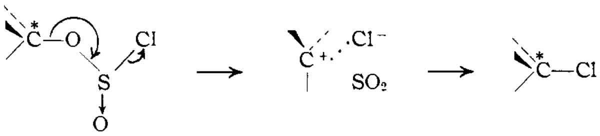
(10) For example, see J. Kenyon, H. Phillips and V. P. Pittman, *ibid.*, 1072 (1935), and H. H. Zeiss, This Journal, **75**, 3154 (1953).

(11) For example, see D. J. Cram, *ibid.*, **75**, 332 (1953) and C. E. Boozer and E. S. Lewis, *ibid.*, **75**, 3182 (1953).

(12) For example, see C. L. Arcus, M. P. Balfe and J. Kenyon, *ibid.*, 485 (1938), and M. P. Balfe, A. A. Evans, J. Kenyon and K. N. Nandi, *ibid.*, 803 (1946).

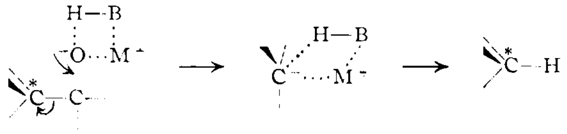
(13) See A. Streitwieser, Jr., *Chem. Revs.*, **56**, 574 (1956), for a summary of references.

(14) S. Winstein, T. G. Traylor and C. S. Garner, This Journal, **77**, 3741 (1955).



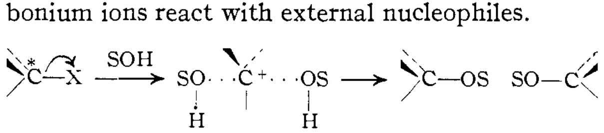
Alkyl sulfite Asymmetric ion pair Retained configuration

SE1: Occurs when complex leaving group carries its own electrophile, as in reactions of alkoxides in non-dissociating solvents.



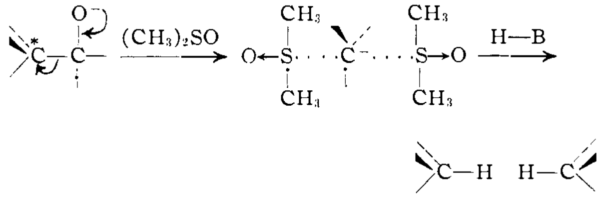
Solvated metal alkoxide Asymmetric ion pair Retainedn configuratio

Racemization Mechanism.—SN1: Occurs in relatively non-nucleophilic but strongly dissociating solvents in which relatively long-lived carbonium ions react with external nucleophiles.



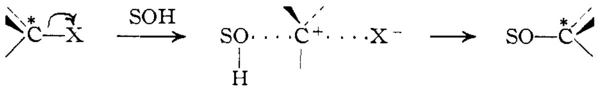
Alkyl halides, tosylates, etc. Symmetrically solvated carbonium ions Racemic product

SE1: Occurs in non-proton donating but strongly dissociating solvents in which relatively long-lived carbanions react with external electrophiles.



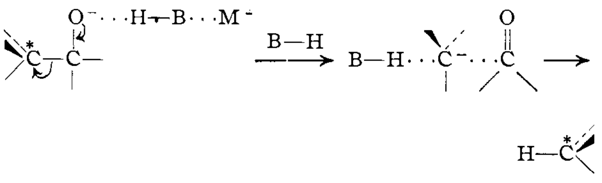
Alkoxide anions or solvent-separated ion pairs Symmetrically solvated carbanions Racemic product

Inversion Mechanism.—SN1: Occurs in strongly-nucleophilic and ionizing solvents in which short-lived carbonium ions react with external nucleophiles.



Alkyl halides, tosylates, etc. Asymmetric ion pair Inverted configuration

SE1: Occurs in strongly-electrophilic and dissociating solvents in which short-lived carbanions react with external electrophiles.



Solvent-separated ion pair Asymmetrically solvated carbanion Inverted configuration

Experimental

Starting Materials.—The preparation of the compounds employed in this investigation have been reported previously. A mixture of optically pure diastereomers of (+)-2,3-diphenyl-3-methoxy-2-butanol [(+)-XIV] which were configurationally homogeneous at C-3 was employed,[3c,15] $[\alpha]^{25}\mathrm{D}$ +4.7° (*c* 5.1, chloroform). The substance, (+)-1-methoxy-1-phenylethane[3c] [(+)-XVI], which was used in control experiments, was not optically pure, $n^{25}\mathrm{D}$ 1.4882, $\alpha^{25}\mathrm{D}$ +17.8° (*l* 1 dm., neat). The compound (−)-2,3-dimethyl-3-phenyl-2-pentanol [(−)-X],[3a] had $\alpha^{27}\mathrm{D}$ −2.03° (*l* 1 dm., neat), $n^{25}\mathrm{D}$ 1.5199. Different samples of (+)-2-phenylbutane [(+)-I] of varying optical purity were used in control experiments. All had $n^{25}\mathrm{D}$ 1.4878, and rotations ranging from $\alpha^{25}\mathrm{D}$ +8° to +14° (*l* 1 dm., neat). A mixture of optically pure diastereomers of (+)-2,3-diphenyl-3-methyl-2-pentanol [(+)-VIII][3a] was used, $[\alpha]^{26}\mathrm{D}$ +17.5° (*c* 71, benzene). The mixture was configurationally homogeneous at C-3. The optically pure (+)-2-methyl-1,1,2-triphenyl-1-butanol [(+)-XI][3a] used had $[\alpha]^{23}\mathrm{D}$ +31.80° (*c* 6.4 in benzene), $n^{25}\mathrm{D}$ 1.6038. A mixture of optically pure diastereomers of (−)-3,4-dimethyl-4-phenyl-3-hexanol [(−)-IX] which was configurationally homogeneous at C-4 was used, $[\alpha]^{23}\mathrm{D}$ −11.20° (*c* 11, benzene).

Solvents.—The solvents used in this investigation were purified as previously described,[3b,c,d] except for those described here. Commercial solutions of 38% aqueous benzyltrimethylammonium hydroxide were decolorized by treatment with charcoal, and were evaporated under reduced pressure to a sirup, and finally dried as thoroughly as possible at 75° at 1 mm. pressure. Dimethyl sulfoxide was distilled at 20 mm. pressure, and a center cut of the distillate collected. This material was dried by passage through a column of molecular sieves, and by a final distillation at 20 mm. pressure. Tetraethylene glycol dimethyl ether was purified by distillation from sodium metal at 20 mm. pressure. Diethylene glycol monomethyl ether was refluxed with dissolved sodium, and then distilled from the mixture. Dissolved oxygen was flushed from these solvents with dry, pure nitrogen before use.

Tetramethylammonium Hydroxide.—To 25 g. of tetramethylammonium chloride (0.23 mole) dissolved in 125 ml. of methanol, a solution of 15.3 g. of potassium hydroxide (0.27 moles) in 125 ml. of methanol was added (the base was first dissolved in a minimum of water). The precipitate of potassium chloride was collected, and the filtrate was evaporated at 4 mm., and finally dried as much as possible at 30° and 1 mm. of pressure.

The stability of tetramethylammonium hydroxide solution in *t*-butyl alcohol was determined by titration procedures. At 81° in a solution that was initially 0.14 *M* in the base, the following results were obtained: after 10 minutes, 7% decomposition; after 75 minutes, 27% decomposition; after 150 minutes, 48% decomposition; after 360 minutes, 66% decomposition.

Cleavage of (−)-3,4-Dimethyl-4-phenyl-3-hexanol [(−)-IX] in Absence of an External Proton Source.—Phenylpotassium was prepared from potassium metal (3.0 g. or 0.077 g. atom), cut into small pieces, and di-*n*-butylmercury (5.0 g.) in dry benzene (50 ml.) under an atmosphere of nitrogen.[16] To the black suspension, 1.00 g. (0.00485 mole) of (−)-IX was added, and the mixture was stirred at room temperature for one hour. The mixture was then filtered through a filter stick under dry nitrogen, was concentrated to approximately 15 ml. by freeze-drying, and was then heated in a sealed tube at 133° for 24 hours. At the end of the reaction, a drop of mercury had collected at the bottom of the tube, which had arisen from decomposition of the excess di-*n*-butylmercury. Desired 2-phenylbutane was isolated in the usual way,[3b,c,d] 0.352 g. (54% yield), $n^{25}\mathrm{D}$ 1.4881, $\alpha^{25}\mathrm{D}$ +17.7° (*l* 1 dm., neat), 73% optical purity.

Cleavage of (−)-2,3-Dimethyl-3-phenyl-2-pentanol [(−)-X] in Benzyltrimethylammonium hydroxide (Run 165).—A solution of 38% aqueous benzyltrimethylammonium hydroxide was evaporated and dried as thoroughly as possible (see section on solvents), and 1.24 g. (0.0060 mole) of (−)-X was added. The resulting solution was heated at 110° for 20 hours. The mixture was then cooled, and shaken with 200

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[15] D. J. Cram and K. R. Kopecky, This Journal, **81**, 2748 (1959).

[16] H. Gilman, H. A. Pacevitz and O. Baine, *ibid.*, **62**, 1514 (1940).

TABLE XX

CONTROL EXPERIMENTS ON OPTICAL STABILITY OF 2-PHENYLBUTANE (I) AND 1-METHOXY-1-PHENYLETHANE (XVI)

Starting material				Base				Product			
Nature	α^{25}D[a]	Concn., *M*	Solvent	Nature	Concn., *M*	T, °C.	Time, hr.	Yld., %	n^{25}D	α^{25}D[a]	% opt. recovery
(+)-XVI	(+17.8°)	0.09	DMS[b]	$KOC(CH_3)_3$	0.12	25	32	82	1.4882	+17.8°	100
(+)-I	(+13.2)	0.11	DMS[b]	$KOC(CH_3)_3$	.11	25	28	82	1.4878	+12.7	96
(+)-I	(+ 8.40)	.11	DMS[b]	$KOC(CH_3)_3$	.12	110	28	80	1.4870	0.00	0
(+)-I	(+ 8.53)	.10	DMS[b]	$NaOCH_3$	.11	68	13	85	1.4878	+ 8.53	100
(+)-I	(+ 8.53)	.10	DMS[b]	$NaOC(CH_3)_3$	.10	68	13	75	1.4880	+ 8.44	99
(+)-I	(+ 8.53)	.10	DMS[b]	$NaOC(CH_3)_3$	.11	110	15	80	1.4879	+ 8.10	95
(+)-I	(+ 8.40)	.12	DMS[b]	KOH	.11	110	28	81	1.4880	+ 8.32	99
(+)-I	(+ 13.2)	.10	BTA^+OH^-	BTA^+OH^-[c]	...	110	24	82	1.4878	+13.1	99
(+)-I	(+15.0)	.10	CH_3ODEG[d]	$KODEGOCH_3$[e]	2.1	210	81	81	1.4878	+12.5	83

[a] *l* 1 dm., neat. [b] DMS = dimethyl sulfoxide. [c] BTA^+OH^- = benzyltrimethylammonium hydroxide. [d] Methyl diethylene glycol. [e] Potassium methyl diethylene glycoxide.

ml. of water and 200 ml. of pure pentane. The pentane layer was washed with water, dried and evaporated through a 2-foot Vigreux column. This material (5.0 g.) was distilled at 20 mm. pressure, and the distillate was chromatographed on 320 g. of activity I neutralized alumina.[17] The column was washed with pentane, and the eluate was evaporated through a Vigreux column, and the residue was distilled twice to give 0.644 g., 74% yield, of 2-phenylbutane, α^{25}D −0.20° (*l* 1 dm., neat). The infrared spectrum of this substance was identical with that of authentic material.

Cleavage of (−)-2,3-Dimethyl-3-phenyl-2-pentanol [(−)-X] in Dimethyl Sulfoxide (Run 163).—Potassium metal (0.23 g.) was allowed to react with *t*-butyl alcohol (5 ml.), and the resulting solution was evaporated to dryness at 1 mm. pressure. A solution of 1.25 g. (0.0060 mole) of (−)-X in 54 ml. of dimethyl sulfoxide was added, and the resulting solution was allowed to stand under nitrogen at 25° for 28 hours. The solution was then shaken with a mixture of 200 ml. of water and 200 ml. of pentane. The pentane layer was washed with water, dried, and evaporated through a Vigreux column. The residual oil was chromatographed on 200 g. of activity I alumina.[17] The pentane eluate was evaporated through a Vigreux column, and the residue was distilled at 20 mm. of pressure to give 0.72 g. of 2-phenylbutane, 90% yield, n^{25}D 1.4880, α^{25}D 0.00° (*l* 1 dm., neat).

Cleavage of (−)-2,3-Dimethyl-3-phenyl-2-pentanol [(−)-X] in Dimethyl Tetraethylene Glycol Saturated with Carbon Dioxide (Run 186).—Potassium, 0.94 g., was allowed to react with 5 ml. of *t*-butyl alcohol, and solvent was evaporated at 1 mm. A solution of 1.013 g. (0.00527 mole) of (−)-X in 55 ml. of dimethyl tetraethylene glycol was added. The resulting solution was heated rapidly to 180°, and the solution was saturated with carbon dioxide with a thin stream of gas which was admitted and which was exhausted through a condenser and then through a Dry Ice trap. Most of the low-boiling components collected in the trap during the period of reaction, which was carried out at 210° for 38 hours. The contents of the trap, condenser and pot were mixed with 100 ml. of water. This solution was distinctly alkaline. This mixture was shaken with a mixture of 200 ml. of water and 200 ml. of pure pentane. The pentane layer was washed with water, dried, evaporated through a Vigreux column, and chromatographed on 100 g. of Activity I alumina.[17] The pentane eluate was evaporated through a Vigreux column, and the residue was distilled at 25 mm. to give 0.528 g. (75% yield) of 2-phenylbutane, n^{25}D 1.4875, α^{25}D +2.66° (*l* 1 dm., neat).

Cleavage of (+)-2-Methyl-1,1,2-triphenyl-1-butanol [(+)-XI] in t-Butyl Alcohol with Tetramethylammonium Hydroxide as Base (Run 171).—A solution of 8.0 g. of tetramethylammonium hydroxide in 100 ml. of *t*-butyl alcohol was prepared, and an aliquot was diluted with water and titrated with standard alkaline solution. Enough *t*-butyl alcohol was added to the original solution to make it 0.60 *M* in base. To 56 ml. of this solution was added 1.58 g. (0.0050 mole) of (+)-XI, and the resulting solution was heated at 50° for 0.33 hour. The mixture was cooled, and shaken with a mixture of 200 ml. of water and 200 ml. of pure pentane. The pentane layer was washed with water, dried and evaporated through a Vigreux column to an oil. This oil was absorbed on 100 g. of activity I neutral alumina.[17] Hydrocarbon was eluted from the column with pure pentane, and the eluate was evaporated through a Vigreux column to an oil. The more volatile component was distilled at 25 mm. pressure to give an oil, which when redistilled gave 0.054 g. (8% yield) of 2-phenylbutane, n^{25}D 1.4880, α^{25}D +0.18°. The residue left after the first distillation weighed less than 10 mg.

The chromatograph column was washed with 2 liters of 10% ether in pentane, and then with 500 ml. of 30% ether in pentane. The latter eluate when evaporated under reduced pressure gave an oil which was dried as a film at 70° and 1 mm., weight 0.66 g. (42% recovery) of starting material, n^{25}D 1.6074, $[\alpha]^{25}$D +27.4° (*c* 6 in benzene). The infrared spectrum of this material was identical with that of the starting material.

Control Runs.—Many of the controls made for runs of earlier papers[3] apply to the runs of this paper. The results of control experiments for those runs conducted in dimethyl sulfoxide and benzyltrimethylammonium hydroxide are reported in Table XX.

LOS ANGELES 24, CALIF.

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(17) H. Brockmann and H. Schodder, *Ber.*, **74B**, 73 (1941).