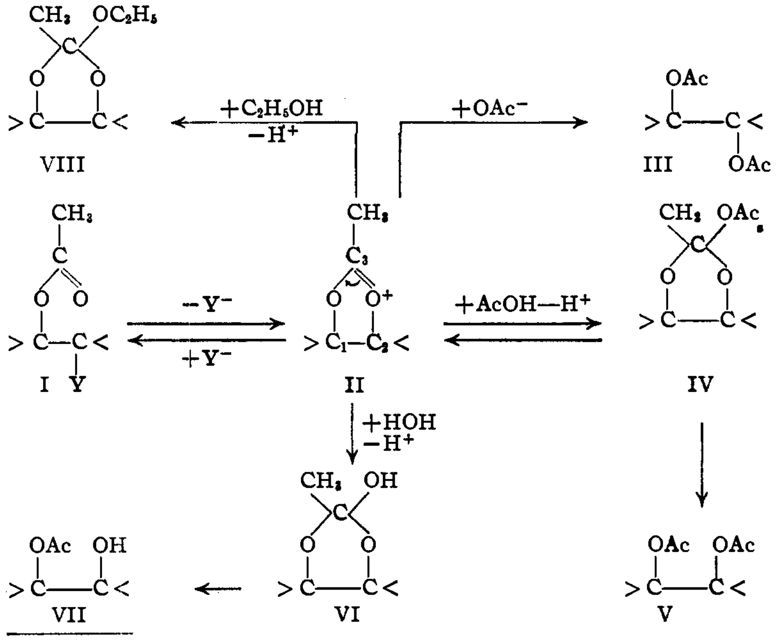
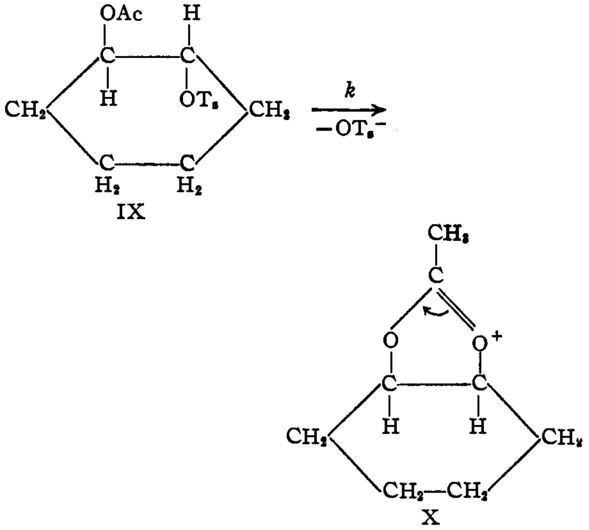
[Contribution from the Chemistry Department of the University of California, Los Angeles]

The Role of Neighboring Groups in Replacement Reactions. X.[1] Kinetics of Solvolysis of trans-2-Acetoxycyclohexyl *p*-Toluenesulfonate[2]

By S. Winstein, Carolyn Hanson and Ernest Grunwald

Of the groups encountered in previous work on the participation of neighboring groups in displacement reactions, the neighboring acetoxy[3–7] group has proved to be, in some respects, the most interesting. Thus, according to our interpretations of the results of previous experiments, the departure or extraction of a group Y such as bromide or toluenesulfonate from a molecule I such as 3-acetoxy-2-bromobutane, *trans*-2-acetoxycyclohexyl bromide or *trans*-2-acetoxycyclohexyl *p*-toluenesulfonate gives rise to the cyclic intermediate II. This intermediate in anhydrous acetic acid containing acetate ion turns up as diacetate III with the familiar over-all steric result of retention of configuration.[3,5,7] In the absence of acetate ion in an acidic solution diacetate V with the inverted configuration is produced probably by way of the orthodiacetate IV. With water, intermediate II is thought to react to give orthomonoacetate VI which isomerizes to monoacetate VII, the over-all steric result being one of inversion.[4,5,7] With alcohol, intermediate II gives the analog of VI, the orthoester[6] VIII.





Since the participating acetoxy group is apt to be one of the most important ones to organic chemists, it seems desirable to understand its behavior as completely as possible. Toward this end we have studied the kinetics of the homogeneous solvolysis of *trans*-2-acetoxycyclohexyl *p*-toluenesulfonate IX in acetic acid. This rate work, taken in conjunction with the previous work[3–7] on the nature of the product and the steric results, adds considerable precision to our interpretation of the mechanisms involved and shows up some remaining complications.

The solvolysis of the toluenesulfonate IX (ROT_s) was followed by titration of the toluenesulfonic acid which is seen to be generated according to equation 1,

$$ROSO_2C_6H_4CH_3 + AcOH \longrightarrow ROAc + HOSO_2C_6H_4CH_3 \quad (1)$$

The rates were measured in anhydrous acetic acid solvent, and also in solutions containing one or more of the added materials, water, acetic anhydride, potassium acetate, diphenylguanidine (DPG) and diphenylguanidinium *p*-toluenesulfonate ($DPG{\cdot}HOT_s$).

In the presence of added water even in as low a concentration as 0.055 *M*, calculated first-order reaction rate constants were very steady. A typical run is shown in Table I, (ROT_s) representing the molarity of unreacted

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(1) Paper IX, Winstein and Grunwald, This Journal, **68**, 536 (1946).

(2) Most of the material reported in this paper was presented before the Organic Division at the Cleveland meeting of the American Chemical Society, April, 1944.

(3) Winstein and Buckles, This Journal, **64**, 2780 (1942).

(4) Winstein and Buckles, *ibid.*, **64**, 2787 (1942).

(5) Winstein, Hess and Buckles, *ibid.*, **64**, 2796 (1942).

(6) Winstein and Buckles, *ibid.*, **65**, 613 (1943).

(7) Winstein and Seymour, *ibid.*, **68**, 119 (1946).

ROT_s and k the calculated first-order constant.

Without added water, but in the presence of potassium or diphenylguanidinium acetate, integrated first-order rate constants were quite satisfactory but tended to drop some 8 to 10% by the time the reaction was 70 to 80% complete. In the absence of added water or acetate salt, the kinetics were complicated, the rate constant decreasing markedly at first and then increasing again later in the run.

TABLE I

RATE OF SOLVOLYSIS OF 0.1 M *trans*-2-ACETOXYCYCLOHEXYL *p*-TOLUENESULFONATE AT 99.7 ± 0.10° IN AcOH 0.17 M IN H_2O

Time, min.	50(ROT_s)	$10^4 k$ (sec.$^{-1}$)
0.0	4.255	..
15.0	3.550	2.01
40.0	2.610	2.04
85.0	1.510	2.03
125.0	0.925	2.04
210.0	0.325	2.04
	Mean	2.03

TABLE II

SUMMARY OF FIRST-ORDER RATE CONSTANTS FOR ACETOLYSIS OF *trans*-2-ACETOXYCYCLOHEXYL *p*-TOLUENESULFONATE (ROT_s) AT 99.7 ± 0.1°

No.	[ROT_s]	[H_2O]	[OAc]	Remarks	$10^4 k$ (sec.$^{-1}$)
1	0.100	0.055	....		1.95 ± 0.03
2	.100	.11	....		2.07 ± .03
3	.199	.11	....		2.05 ± .02
4	.100	.17	....		2.03 ± .02
5	.025	.35	....		2.00 ± .02
6	.100	.33	....		2.07 ± .03
7	.100	.33	....	*cis*-diacetate[a]	2.12 ± .03
8	.100	.55	....		2.25 ± .03
9	.028	..	0.0249 KOAc	Ac_2O—0.0459 M	1.97 ± .02
10	.030	..	.0293 DPG		2.00 ± .11
11	.050	..	.0488 DPG		2.04 ± .13
12	.100	..	.0671 KOAc	Ac_2O[b]	1.91 ± .07
13	.101	..	.0883 KOAc	Ac_2O[b]	1.92 ± .05
14	.100	..	.0995 KOAc		2.03 ± .06
15	.100	..	.100 DPG		2.09 ± .07
16	.100	.07	.1072 KOAc		2.14 ± .03
17	.100	.11	.0994 DPG		2.25 ± .03
18	.100	.33	.1007 DPG		2.30 ± .05
19	.100	.55	.0996 DPG		2.40 ± .03
20	.101	..	.1425 KOAc	Ac_2O[b]	2.09 ± .03
21	.200	..	.1981 DPG		2.25 ± .06
22	.100	..	.0997 DPG	0.0997 M DPG·HOT_s	2.16 ± .11
23	.100	.33		74.90°	0.148 ± .003
24	.100	.33		74.90°	0.152 ± .002
25[c]	.040	..	.0847 KOAc	75.04°	0.0995 ± .0019

[a] 0.10 M in *cis*-1,2-diacetoxycyclohexane. [b] Excess acetic anhydride. M. p. of solvent 16.32°. [c] Anhydrous ethanol as solvent.

In Table II are collected the data from the runs which yielded satisfactory first-order reaction rate constants. A number of comparisons are possible from this table which show the insensitivity of the rate constant to initial concentration of toluenesulfonate IX. The addition of water or acetate is seen to produce small increases in rate. A linear catalysis by water has been sometimes observed[8] in situations of this kind. In the present case, the catalysis may be linear, but the effect is so small that rigid linearity is obscured by normal experimental variations. The extrapolated rate constant for no added water or salt appears to be approximately 1.90 × 10^{-4} sec.$^{-1}$, 0.55 M water giving an increase in rate of 18%. At a concentration of 0.1 M diphenylguanidinium acetate, 0.55 M water increases the rate by 15%. For the acetolysis of α-phenylethyl chloride, Steigman and Hammett[8a] found the effect of water to be considerably larger.

The increase in rate due to addition of 0.1 M diphenylguanidine to the normal anhydrous solvent amounts to about 10%. The rates with potassium acetate in the presence of a slight excess of acetic anhydride in the solvent are in general a few per cent. lower, in part, at least, due to the removal of the residual trace of water from the glacial acetic acid.

Following the previous interpretations,[3-7] the first order reaction rate constants in Table II represent the rate constant k of formation of the cyclic intermediate X (or II) and toluenesulfonate

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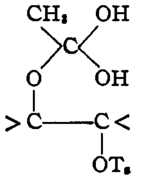
[8] (a) Steigman and Hammett, THIS JOURNAL, **59**, 2536 (1937); (b) Farinacci and Hammett, *ibid.*, **59**, 2542 (1937).

ion from toluenesulfonate IX. The effects of water and acetate salt are then solvent and salt effects.

The small magnitude of the effect of water on the rate constant for solvolysis of the acetate-tosylate IX makes it very clear that water, which in the presence of acetate ion diverts the product to monoacetate VII and the steric result to inversion of configuration, does not accomplish these results in the rate-determining stage of the solvolysis. Were its action in the rate-determining step, then, judging by its efficiency, the reaction involving water when appreciable water concentrations are used would be much faster than the residual one. Thus, the presence of water would give rise to a large rate increase, unless, by some chance, toluenesulfonate IX and water combine quite completely to give a compound which is only moderately reactive. Conceivable examples of such compounds are a hydrogen-bond complex or the addition compound[4,5] XI (which may be criticized on other grounds).



XI

Actually, such compound formation would be reflected in abnormally small depressions of the freezing point of acetic acid by mixtures of toluenesulfonate IX and water. Pertinent freezing point measurements, summarized in Table III, speak against compound formation.

TABLE III

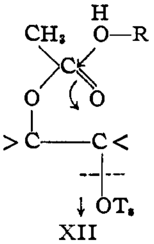
FREEZING POINTS OF ACETIC ACID SOLUTIONS OF WATER AND *trans*-2-ACETOXYCYCLOHEXYL *p*-TOLUENESULFONATE

(ROT_s), M	0.00	0.00	0.00	0.20	0.50	0.20
(H_2O), M	.00	.30	0.50	0.00	0.00	0.30
F. p. lowering, °C.	.00	.97	1.69	0.57	1.32	1.72

It can be seen that the depression of the freezing-point for the solution containing both the acetate-tosylate and water is even greater than the sum of the depressions for the appropriate concentrations of each solute alone, although this difference is not much greater than the experimental error. Thus no compound formation is indicated at the freezing point and is expected to be even less probable at the higher temperatures used in the rate experiments.

In the case of alcoholysis of the toluenesulfonate IX (which gives rise to orthoacetate VIII) again it is clear that no unique role is to be ascribed to the alcohol in the rate-determining step. The first-order rate constant for alcoholysis at 75° was steady and amounted to about two-thirds (Table II) of the value in glacial acetic acid. This is in line with the near equality of acetic acid and ethanol as solvents for solvolysis of halides.[9]

It becomes possible therefore to rule out for the present case such mechanisms as the one symbolized by XII which postulate a concerted attack by a water or alcohol molecule and simultaneous departure of the toluenesulfonate ion. This latter type of mechanism has been envisioned by Isbell[10] for orthoester formation from acetohalogen sugars. Similar mechanisms involving acetate ion instead of water are ruled out also by the data.



XII

The data for several runs with no added water or acetate salt (which gave the decreasing and then increasing first-order reaction rate constants) are summarized in Table IV. The first column lists *a*, the initial concentration of toluenesulfonate IX, and the second column indicates the concentration of added diphenylguanidinium *p*-toluenesulfonate (DPG·HOT$_s$) when it was used. From a plot of ln $(a - x)$ against time, t, x being the concentration of generated toluenesulfonic acid, fairly accurate values of the slope, d ln $(a - x)/dt$,

TABLE IV

SUMMARY OF DATA ON ACETOLYSIS OF *trans*-2-ACETOXYCYCLOHEXYL *p*-TOLUENESULFONATE IN ACETIC ACID CONTAINING 0.0459 *M* ACETIC ANHYDRIDE AT 99.7°

a	Solute	x at min.	Min. $10^4 k$ (sec.$^{-1}$)	10^4 k_0 (sec.$^{-1}$)
0.028		0.008	0.98	
.05		.008	.87	1.91 ± 0.29
.10		.012	.61	
.032	0.027 *M* DPG·HOT$_s$	.009	.84	2.3

TABLE V

INSTANTANEOUS FIRST-ORDER RATE CONSTANTS FOR ACETOLYSIS OF 0.02766 *M* *trans*-2-ACETOXYCYCLOHEXYL *p*-TOLUENESULFONATE AT 99.7° IN ACETIC ACID 0.0459 *M* IN ACETIC ANHYDRIDE

Time, min.	$10^3 x$	$10^4 k$ (sec.$^{-1}$)
0.00	0.00	2.02
2.15	0.67	1.81
14.15	3.15	1.14
22.15	4.45	1.10
30.15	5.64	1.08
51.57	8.32	0.95
77.90	11.18	1.03

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[9] *E. g.*, for methylvinylcarbinyl chloride see Roberts, Young and Winstein, *ibid.*, **64**, 2157 (1942), and Young and Andrews, *ibid.*, **66**, 421 (1944).

[10] Isbell, "Annual Review of Biochemistry," Annual Reviews, Inc., Stanford Univ. Press, Stanford Univ. P. O., Calif., 1940, p. 65.

called k, could be measured at various points with the aid of a tangent meter. In Table V are shown the k values thus determined for one run. In the third and fourth columns of Table IV are listed the values of x and k at the minima. The last column gives the extrapolated initial value of k, k_0. It is seen that, within the accuracy of this kind of a procedure, the initial rate constants, k_0, were roughly those expected. The minimum rate constant, one-third to one-half the initial value, occurred at a value of x of about 0.01 M.

It is very clear that the complex behavior of the rate constant is due to generated toluenesulfonic acid. Toluenesulfonate ion by itself did not give a lowered rate by virtue of any ability to compete successfully with solvent or acetate ion for the intermediate X (or II). Thus the initial rate constant with added diphenylguanidinium *p*-toluenesulfonate (Table IV) was normal. Also, the substitution of DPG·HOTs for half of the diphenylguanidine in runs 21 and 22, Table II, gave essentially no rate lowering. On the other hand, runs with two moles of ester per mole of diphenylguanidine gave a quite normal rate constant initially which held up fairly well until the solution became acidic when it decreased very markedly and then increased again.

This phase of the subject has not been more completely investigated and requires more knowledge of the chemistry of orthoester intermediates. The indications from the rate work and the earlier work are that toluenesulfonate ion in acid acetic acid solution in the absence of water is able to divert some intermediate back to *trans*-2-acetoxycyclohexyl *p*-toluenesulfonate IX (or I). The back reaction may involve orthodiacetate IV (which may not proceed to *cis*-diacetate V rapidly enough and thus accumulate), a proton and toluenesulfonate ion, perhaps by way of the cation X (or II) in equilibrium with orthodiacetate IV. In the presence of water no such complication is possible because of the very successful competition of water with acetic acid for coördination to carbon atom C_3 of the intermediate II, producing orthomonoacetate VI and subsequently monoacetate VII.

Experimental

Anhydrous Acetic Acid.—The water content of General Chemical Company reagent grade glacial acetic acid, m. p. 16.2° or higher, was estimated from its m. p., assuming water to be the impurity. Enough pure acetic anhydride was added to react with the water and the mixture was held under reflux for four hours. Distillation yielded, as a main fraction, acid, m. p. 16.55°. Virtually the same m. p. was obtained when the acid was dried with triacetyl borate.[11]

Solvent with excess acetic anhydride was prepared by refluxing 250 ml. of dry acid with 2.0 ml. pure acetic anhydride for three hours (m. p. 16.32°). For some of the runs, another solvent, 0.0459 M in acetic anhydride, was used.[12]

Diphenylguanidinium *p*-Toluenesulfonate.—To 150 ml. of dry ether was added 4.3 g. (0.0226 mole) of *p*-toluenesulfonic acid monohydrate. A small aqueous phase appeared which was separated and extracted with 50 ml. of ether. The combined ether solutions were slowly added with shaking to a solution of 4.9 g. (0.0232 mole) of diphenylguanidine in 150 ml. of dry ether. The mixture was kept in a refrigerator several hours. Then the crystals were filtered off, washed with cold ether and dried to yield 7.8 g. (0.0204 mole), 91% of material; m. p., after recrystallization from chloroform–benzene, 171.9–172.4°.

Anal.[13] Calcd. for $C_{20}H_{21}O_3N_3S$: C, 62.64; H, 5.52. Found: C, 62.61; H, 5.75.

***trans*-2-Acetoxycyclohexyl *p*-Toluenesulfonate.**—This material, m. p. 78°, was prepared as described previously.[5]

Titrations in Glacial Acetic Acid.—Approximately 0.05 N or 0.10 N perchloric acid in glacial acetic acid, prepared from 60% aqueous acid of known titer against aqueous standard sodium hydroxide, was used as standard acid. As standard base was employed either Eastman Kodak Co. diphenylguanidine, m. p. 147–148°, or standard sodium acetate prepared from pure sodium carbonate. As indicator was used either crystal violet[8a,14] or, in the later stage of the work, a brom phenol blue indicator solution.[12]

Procedure for Rate Measurements.—The reagents were weighed out and made up to volume in the proper acetic acid solvent at 20–23°, water being added from a graduated pipet in some cases. Concentrations are all given at room temperature. Approximately 6–7-ml. portions were sealed in tubes and immersed either in the vapor over boiling water in a 100° thermostat or an ordinary thermostat at 74.90 ± 0.05°. The exact temperature in the 100° thermostat was obtained from the barometric reading, but was always 99.70 ± 0.10. Time was counted from immersion of the tube to its removal and quenching in ice-water. After being cooled a tube was allowed to come to room temperature, then it was opened and a 5-ml. aliquot was pipetted out for titration with standard acid or base from a 5-ml. microburet. Time was called zero for the first tube after attainment of temperature, initial concentrations being adjusted from the titration data on this tube. In the experiments with added acetate ion titration of an unheated tube was used to check on the initial acetate ion concentration.

In the dry acetic acid solvent in the absence of acetate ion, the tubes tended to darken toward the end of a run. This made it impossible to obtain an infinity titre. With acetate ion present, titration after seventeen hours at 100° showed 99.9% of the theoretical consumption of base. Another series of experiments showed 99.6% after ten hours at 110°.

Titration of toluenesulfonic acid and diphenylguanidine solutions in glacial acetic acid showed that the former maintained its titre within 0.5% after two and one-half hours at 100°, and the latter within 0.4% after four hours at 100°.

Diphenylguanidinium *p*-toluenesulfonate, which was added in some of the rate runs, was shown not to liberate any detectable acid on heating two hours in acetic acid containing 0.0459 M acetic anhydride either in neutral solution or in solution 0.016 M in perchloric acid.

For the alcoholysis of the toluenesulfonate in absolute ethanol, the reaction was followed by titration of 5 ml. aliquot portions with 0.05 N standard aqueous base to the brom thymol blue end-point.

The potassium acetate used as a solute in some of the runs was carefully dried reagent-grade material.

Summary

The kinetics of acetolysis of *trans*-2-acetoxycycylohexyl *p*-toluenesulfonate are closely first-order in the presence of small concentrations of water or acetate ion. The evidence is that the

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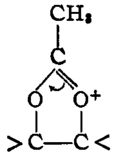
(11) Eichelberger and La Mer, THIS JOURNAL, **55**, 3633 (1933).

(12) Winstein, Grunwald and Ingraham, *ibid.*, **70**, 821 (1948).

(13) Analysis by Mr. Jack Ralls.

(14) Nadeau and Branchen, THIS JOURNAL, **57**, 1363 (1935).

rate-determining step in the solvolysis is the formation of the ion II.



II

Water and acetate ion, which control the nature of the product and the steric result, do not exercise this control in the rate-determining step.

Similarly, for alcoholysis of *trans*-2-acetoxycyclohexyl *p*-toluenesulfonate, II appears to be the intermediate, orthoester formation being accomplished at a later step than the rate-determining one.

The rate constants for acetolysis of the toluenesulfonate in acetic acid not containing water or acetate ion decrease seriously as acid develops and then increase again. The best interpretation of the downward drift is that *trans*-2-acetoxycyclohexyl *p*-toluenesulfonate is regenerated by the action of acid and toluenesulfonate ion on an intermediate such as orthodiacetate.

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

The Role of Neighboring Groups in Replacement Reactions. XI. Some Reactivities Involving Neighboring Groups[1]

BY S. WINSTEIN, E. GRUNWALD, R. E. BUCKLES AND C. HANSON

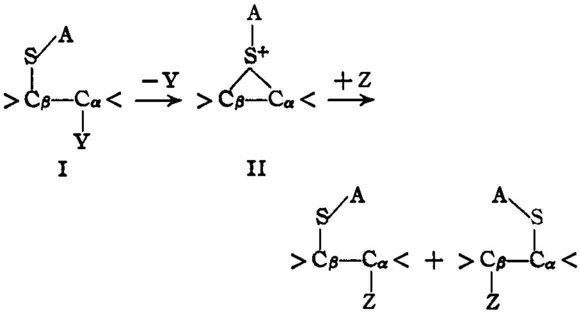
Participation of neighboring groups in displacement reactions has long been known with such groups as O^- (from OH) and NH_2, prior ring closure[2] to isolatable oxide or imine occurring on attempted displacement of halide in a halohydrin or aminohalide. In these cases the groups are those which also take part in known bimolecular displacements[3] symbolized in equations 1 and 2.

$$RO^- + R'X \longrightarrow ROR' + X^- \qquad (1)$$

$$RNH_2 + R'X \longrightarrow (RNH_2R')^+ + X^- \qquad (2)$$

While the so-called classical groups, O^-, NR_2 and SR have been mentioned in preceding articles of this series,[4] the main stress[5] has been on participation in nucleophilic displacement reactions by such neighboring groups as OAc, Br and OCH_3, which are not known to participate in external displacements. Actually there is no sharp division between the latter groups and the more classical ones.

Participation by a neighboring group S-A is symbolized[4a] below, Y and Z indicating the leaving and entering groups, respectively.



We have previously indicated there are questions of intimate mechanism with respect to both the closing and opening of the ring in II.[4a] Rate measurements are helpful in this connection, and in the present article and subsequent ones are reported reactivity measurements in some unimolecular-type[6] nucleophilic displacement reactions.

As is brought out in this paper and articles XII and XIII in the series, the rate measurements yield important formation concerning the nature of the rate-determining ionization step. Using a common set of symbols for all three papers, the ionization step may be[4a] either **A**, a one-stage ring closure to the cyclic intermediate II with Walden inversion (W.I.) at C_α or **B**, an ionization to the substituted carbonium ion III.[3,4a,7]

Two different criteria for distinguishing between the two rate-determining steps A and B have been employed in the work described in this paper. First, the effect on the rate of the disposition of the neighboring group *cis* or *trans* to the departing

(1) Most of the material contained in this paper was reported before the Organic Division of the American Chemical Society at the Cleveland and Atlantic City meetings, April, 1944, and April, 1946.

(2) (a) Smith and Nilsson, *J. prakt. Chem.*, **162**, 63 (1943); (b) Braun and Weissbach, *Ber.*, **63**, 3052 (1930); (c) Freundlich and Salomon, *Z. physik. Chem.*, **A166**, 161 (1933).

(3) Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, Chapters V and VI.

(4) (a) Winstein and Buckles, THIS JOURNAL, **64**, 2780 (1942); (b) Winstein and Buckles, *ibid.*, **64**, 2787 (1942); (c) Winstein, *ibid.*, **64**, 2791 (1942); (d) Winstein, *ibid.*, **64**, 2792 (1942); (e) Winstein, Hess and Buckles, *ibid.*, **64**, 2796 (1942); (f) Winstein and Buckles, *ibid.*, **65**, 613 (1943); (g) Winstein and Henderson, *ibid.*, **65**, 2196 (1943); (h) Winstein and Seymour, *ibid.*, **68**, 119 (1946); (i) Winstein, Hanson and Grunwald, *ibid.*, **70**, 812 (1948).

(5) Very recently a number of cases of participation by NR_2 and SR have been noted, *e. g.*: (a) Schultz, Robb and Sprague, THIS JOURNAL, **69**, 188 (1947); (b) Gilman and Philips, *Science*, **103**, 409 (1946); (c) Golumbic, Stahmann and Bergmann, *J. Org. Chem.* **11**, 550 (1946); (d) Fuson, Price and Burness, *ibid.*, **11**, 475 (1946).

(6) This term is used to indicate nucleophilic displacement reactions which do not involve in the rate-determining step a nucleophilic attack on carbon by an external reagent. The term *SN1* type was used previously[4] but this expression is best reserved for step **B**.

(7) (a) Bateman, Church, Hughes, Ingold and Taher, *J. Chem. Soc.*, 979 (1940); (b) Hughes, *Trans. Faraday Soc.*, **37**, 603 (1941).