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## CHAPTER I

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### INTRODUCTION AND HISTORY

A common process in aliphatic chemistry is replacement, of which an example is substitution. Substitutions are of non-solvolytic and solvolytic types. The second is that class in which the solvent is the substituting agent.

A discussion of substitution reactions naturally brings to point those specifically designated as nucleophilic<sup>1</sup> or anionoid.<sup>2</sup> Most discussions of nucleophilic substitution on carbon are based on Hughes and Ingold's  $S_N1-S_N2$  classification,<sup>3</sup> where S stands for substitution, N for nucleophilic, 1 for unimolecular, 2 for bimolecular.

The  $S_N$  class<sup>4</sup> consists in a reaction of the following type:

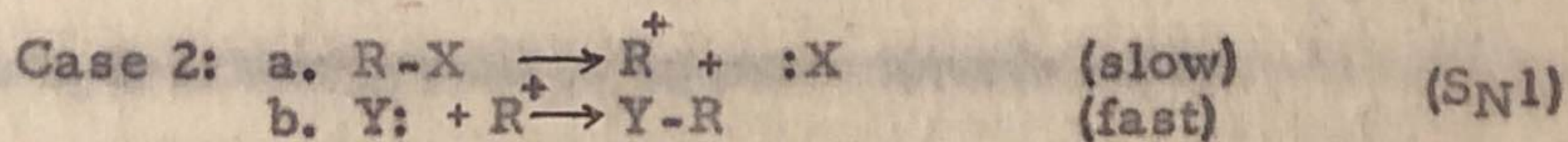
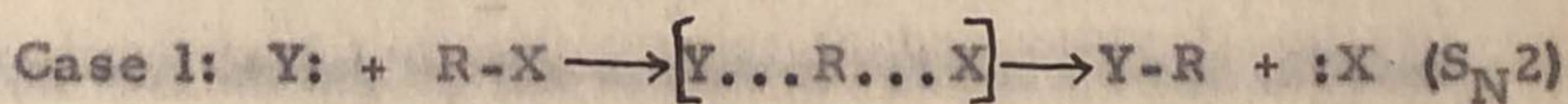
in which X may be neutral or positive, and Y, neutral or negative, initially. The case in which Y is negative and X, neutral, is illustrated by the hydrolysis of alkyl halides (RX) e.g.,

in which the reagent  $OH^- + R-X \longrightarrow R-OH + X^-$ .

For certain compounds (e.g., the methyl and ethyl halides), the rate of hydrolysis in water and aqueous alcohol is dependent on the concentration of  $OH^-$  ions as well as on

that of RX; it is first order in each and second order overall:  $v = k_2(\text{RX})(\text{OH}^-)$ . The hydrolysis of certain other halides, (e.g., the isopropyl and tertiary butyl compounds), in aqueous solutions is found to be first order; the rate is dependent on (RX) but independent of  $(\text{OH}^-)$ :  $v = k_1(\text{RX})$ . The rates for these halides are the same in alkaline, neutral, or acidic solutions.<sup>5</sup>

The dichotomy of these observations has been summarized, in general, as follows:



Observing these formulations, we see that both types of substitutions are heterolytic processes, i.e., dissymmetric ones. Further, we conclude that the  $\text{S}_{\text{N}}2$  type involves synchronous bond-making and bond-breaking, while the  $\text{S}_{\text{N}}1$  type is a two-step process in which the ionization is the first and rate-determining stage. A means of distinction between the two mechanisms of nucleophilic substitution, suitable for application to those pseudo-first order reactions in which the reagent is in large excess, has been based on the circumstance that in bimolecular substitution, the product is determined in a single reaction stage, of which the rate can be measured, whereas in unimolecular substitution it is

formed, not in the rate-measured stage, but in a subsequent fast stage.

Like all ionizations, the preliminary stage of the unimolecular mechanism is a reversible one. This fact has been experimentally demonstrated by L. C. Bateman and E. D. Hughes<sup>6</sup> who showed that the rate of reaction of tertiary butyl chloride with water in formic acid solution is of the first order and independent of the (small) concentration of water. The reversible nature of the reaction was shown by the action of tertiary butyl alcohol with hydrochloric acid in aqueous formic acid.

Essentially, though both mechanisms require first-order kinetics for substitutions in which the reagent is a sufficiently important constituent of the solvent to have a buffered concentration, it is only true as a limit for the unimolecular ( $S_N1$ ) substitution and large deviations of a highly characteristic nature are possible. This provides a unique test to determine whether a given reaction follows one or the other of these mechanisms ( $S_N1$  or  $S_N2$ ). The reversibility gives rise to a distinctive type of retardation ("mass-law" effect) in what may be a completely "irreversible substitution."<sup>7, 8</sup>

An outgrowth of the fact of the first-order kinetics for both mechanisms was the hypothesis that all solvolytic

reactions, whether apparently first or second order kinetically, are actually unimolecular. This is what is meant when we meet the term the "unimolecular theory of solvolysis."<sup>9</sup> This hypothesis has not met with complete empirical verification and additional theories regarding the manner of solvolysis have been proposed.<sup>10</sup> One must also admit that there are intermediate orders concerned in borderline cases. Further, one important difficulty often encountered should be kept in mind, namely, that of separating the two (extreme) mechanisms and the two kinetic orders when binary solvent mixtures are employed.

Although the importance of solvation in ionic dissociation is fully recognized in the concept of the unimolecular theory, the  $S_N1$  mechanism is termed "unimolecular" because only one reactant,  $RX$ , is undergoing covalency change in the rate-determining stage.<sup>11</sup> The terms "unimolecular" and "bimolecular" refer, then, to the type of mechanism involved independently of the reaction order.

Since the unimolecular type displacement<sup>12</sup> depends on ionization, it naturally presupposes an ionizing solvent. From the general theory of solvent effects,<sup>13</sup> we see that for the  $S_N2$  reaction there is subdivision of charge in the transition state so that addition of inert salt or charge to

a more ionizing solvent will lead to a decrease in rate. In the  $S_N1$  reaction, there is generation of charge in the transition state so the effect of solvent change will be opposite in sign.

While in ionizing media the solvolytic reactions of tertiary halides are essentially unimolecular, those of primary halides are at least partly (predominantly in some solvents) bimolecular.

The rates for the tertiary halides are greater than for the corresponding secondary halides by factors of the order of  $10^4$ . The greater part of this difference is represented by the variation in the B factor of the Arrhenius equation ( $k = Be^{-E/RT}$ ).<sup>14</sup> In 80% aqueous ethanol, B is approximately  $10^{13}$  (a "normal" value) for tertiary halides. For the isopropyl halides, B is approximately  $10^9$ , so these compounds show "slow" unimolecular reactions. The hydrolyses of the tertiary butyl halides can be made "normal" or "slow" according to the solvent in which they are carried out. In fact, it is not impossible that the unimolecular mechanism may give place to the bimolecular mechanism near the limit of low water content in a given solvent. Bateman, Cooper, Hughes and Ingold<sup>5</sup> have stated that on making small additions of a "rapid" to a "slow" (or inactive) solvent, initial proportionality between the specific rate and the

concentration of the minor solvent constituent is to be expected on the unimolecular mechanism, i.e., when there is no stoichiometric intervention by water in the rate-measured process.

Through the years, there have been various methods used to determine the mechanism in solvolytic substitutions. These methods are six in number and are the following:

- (1) from the kinetic form of the substitution reaction;
- (2) from the effect of structural changes in the compound substituted on the reaction rate;
- (3) from the effect of systematic changes in the substituting agent on the reaction rate;
- (4) from the effect of solvent changes on the reaction rate and on the products;
- (5) from the effect of salt additions on the reaction rate and on the products;
- (6) from the stereochemical course of the substitution.

Original theory<sup>15</sup> provided only two methods, numbers 2 and 3. Cowdrey, Hughes, Ingold, Masterman, and Scott<sup>16</sup> then added method 6 and Bateman, Hughes, and Ingold,<sup>17</sup> method 4. In 1940, Hughes, Ingold and their co-workers<sup>18</sup> added the two remaining methods, 1 and 5.

We shall be concerned only with method four, the effect of the solvent on the reaction rate and on the products.

Olson and Halford<sup>19</sup> made the first contribution in this field. They applied the transition-state theory<sup>20</sup> to the hydrolysis and alcoholysis of tertiary butyl chloride and derived a rate expression for binary solvent mixtures based on the viewpoint that all solvolyses of alkyl halides were bimolecular. Their rate formula for an alcohol-water solvent mixture is as follows:  $\text{rate} = (k_a p_a + k_w p_w) \text{PRX}$ , where "a" refers to alcohol, "w" to water, and the p's are vapor pressures. This expression is a combination of the partial rates of formation of the products, ROme (for instance, if methanol is the alcohol) and ROH. The partial rates of formation are the first and second terms of the binomial, respectively. By observing rates in two mixtures at the extremes of solvent composition, the constants  $k_a$  and  $k_w$  were determined.

Although it was later shown by Bateman, Bird, Hughes and Ingold<sup>17, 21</sup> that the solvolysis of tertiary butyl chloride is actually unimolecular in the solvents employed by Olson and Halford, the O-H formula for the total rate of solvolysis of the alkyl halide could serve to calculate product compositions (alcohol and ether) if the mechanism is bimolecular because the products were formed in the reaction whose rate was measured. On the other hand, if the mechanism were unimolecular, Bateman, Hughes, and Ingold<sup>17</sup> thought that

the measured rates had no connection with the compositions of the products, which are formed in a different reaction stage than the one measured. They concluded that the mechanism of such reactions could be deduced only after the kinetic form is known and after the products of the reaction have been isolated and their percentage concentrations determined. Following this thought, they applied, successfully, the O-H rate formula (for a binary solvent system) to the solvolysis of n-butyl bromide in aqueous alcohol mixtures to calculate both product compositions and rate constants. They used the formula for calculating product compositions:  $\frac{(ROAlk)}{(ROAlk+ROH)} = \frac{k_a p_a}{k_a p_a + k_w p_w}$ , and for the specific rate:  $k_1(\text{sec.}^{-1}) = \frac{\text{rate}}{(RX)} = (k_a p_a + k_w p_w) \frac{P_{RX}}{(RX)}$  or  $(k_a p_a + k_w p_w) H_{RX}$ , where the values in parentheses are concentrations (in mole per liter) and  $H_{RX}$  is Henry's law constant for the alkyl halide (in mm. of mercury). (The units of  $k_a$  and  $k_w$  are  $\text{g-mole} \cdot \text{mm. Hg}^2 \cdot \text{l.}^{-1} \cdot \text{sec.}^{-1}$ ) Later, Grunwald and Winstein<sup>22</sup> showed that unless mole fraction rather than mole per liter was substituted in the derived formula--even if the reaction is bimolecular--the same two constants could not be used to calculate both product compositions and rate constants.



Kinetic data for some substitutions is conclusive, but not for all. For the hydrolysis of alkyl halides in aqueous solvents the kinetics are not determinative and other criteria of mechanism have been advanced.

Additional complexity enters when the incursion of the possible elimination reaction (e.g.,  $\text{OH}^- + \text{C}_3\text{H}_7\text{Br} \longrightarrow \text{C}_3\text{H}_6 + \text{H}_2\text{O} + \text{Br}^-$ ) is considered. (The Hughes-Ingold school considers that any olefin formed merely represents so much halide diverted from the competing substitution processes.) As the rate-controlling step in both substitution and elimination is the ionization of the alkyl halide, the ionizing power of the solvent has been of considerable interest.

The ionizing power of a solvent is thought to be a function both of its basicity and of its dielectric constant. Grunwald, Jones and Winstein<sup>23</sup> have made a significant advance in this field by attempting to correlate the solvolysis rates with the so-called ionizing power of the solvent. They defined a term,  $Y$ , which is a quantitative measure of a solvent's ionizing power which, in turn, determines  $k_1$ , the rate constant for the rate-determining ionization to a cationic intermediate:  $\text{RX} \xrightarrow{k_1} \text{R}^+ + \text{X}^-$ . This important mechanism they have termed "A," in contrast with that they term "B," the solvolysis mechanism wherein the

nucleophilic character as well as the ionizing power of the solvent is important (e. g., in neutral and acidic solvents). G-J-W's mechanism A corresponds to  $S_1$  and their mechanism B, to  $S_2$ . The term Y is defined as:  $Y = \log k_{\text{Bu}^\gamma\text{Cl}} - \log k_0^{\text{Bu}^\gamma\text{Cl}}$ , where  $\text{Bu}^\gamma\text{Cl}$  is tertiary butyl chloride,  $k_{\text{Bu}^\gamma\text{Cl}}$  is the rate constant at  $25^\circ\text{C}$ . in a given solvent,  $k_0^{\text{Bu}^\gamma\text{Cl}}$ , the rate constant at  $25^\circ\text{C}$ . in 80 % aqueous ethanol. They have successfully applied the Y value concept to several alkyl halides in different solvents by using the relation:  $\log k = mY + \log k_0$ , the parameters ( $\log k_0$  and  $m$ ) of which were evaluated for several compounds by the method of least squares.

The variation of  $m$  with temperature (T) is, as follows:  $2.303 Y \frac{dm}{dT} = \frac{E^\ddagger - E_0^\ddagger}{RT^2}$ . Values of  $E^\ddagger$ , Arrhenius activation energies, for any one compound are fairly insensitive to solvent change for unimolecular solvolysis.<sup>22</sup> Y is zero in 80 % ethanol, a solvent often employed and of intermediate reactivity, and varies from about +4 to -3 for the common solvolyzing media. Although  $25^\circ\text{C}$ . is chosen as the reference temperature for computing values of Y, it is clear from the near constancy of  $E_{\text{Bu}^\gamma\text{Cl}}^\ddagger$  in various solvents that any other reference temperature would give an almost identical set of Y values. Y values for solvents and correlation data have been summarized in appendix

A. Arner<sup>27</sup> derived equations to predict the effect of  $D$  and  $\mu$ .

The theoretical derivation of the quantitative scheme for correlating solvolysis rates includes the fundamental Bronsted-Debye-Scatchard theory<sup>24</sup> regarding ionic mechanisms in solution. Grunwald and Winstein's data<sup>22, 23</sup> shows that the ionizing power of the solvent does affect ionic reactions as would be expected on the basis of theory discussed by Debye and Pauling<sup>25</sup> and that extended by Moelwyn-Hughes.<sup>26</sup> However, it has been observed that the effect on ionizing power of a solvent is not simply a matter of its nucleophilic character. The functional relationship between  $Y$  and the composition of mixed solvents is apparently not simple. Plots of  $Y$  versus weight % or volume % of water in aqueous ethanol and methanol have considerable curvature. Even the plot of  $Y$  versus mole fraction of water (see figure 1), although more nearly rectilinear, still shows curvature.

For ionic reactions at constant temperature, the dielectric constant is thought to be the most prominent factor in determining the rate of reaction, provided the salt effects have been eliminated (i.e., the velocity constant considered at zero ionic strength,  $k^0$ ). On the assumption that ionic reaction rates are functions only of temperature, dielectric constant ( $D$ ) and ionic strength ( $\mu$ ), Svirbely and

Warner<sup>27</sup> derived equations to predict the effect of  $D$  and  $\mu$  upon the critical increment (the energy of activation). The predictions agree satisfactorily with observed effects in the reaction between ammonium ions and cyanate ions to form urea in water solution at  $30^\circ$  and  $70^\circ$  C., and in methanol-water mixtures at  $D=63.5$  and  $D=55.0$ .

One would expect that changing the water concentration in a solvent (addition of which increases the dielectric constant) would increase the rate of an ionic reaction. Bateman and Hughes<sup>28</sup> observed that there is an invariance with changing water concentration of the rate of reaction of tertiary butyl chloride in formic acid solution containing water, while the rate for *n*-butyl bromide increased linearly with the water concentration. It appeared that *t*-butyl chloride reacted by mechanism A ( $S_N1$ ) and that *n*-butyl bromide reacted via mechanism B ( $S_N2$ ). These workers investigated the solvolysis of *n*-butyl bromide only in aqueous alcohol mixtures containing 0% to approximately 45% water.

The effect of the dielectric constant of the solvent on the solvolytic velocity constants of alkyl halides is seen from figures 2a-d and 10 (in which  $\log k$  versus  $1/D$  is plotted) to be "variable." In the aqueous alcohol solvents, especially, one notes some deviation which appears to be notably large for methanol-water mixtures. The curves

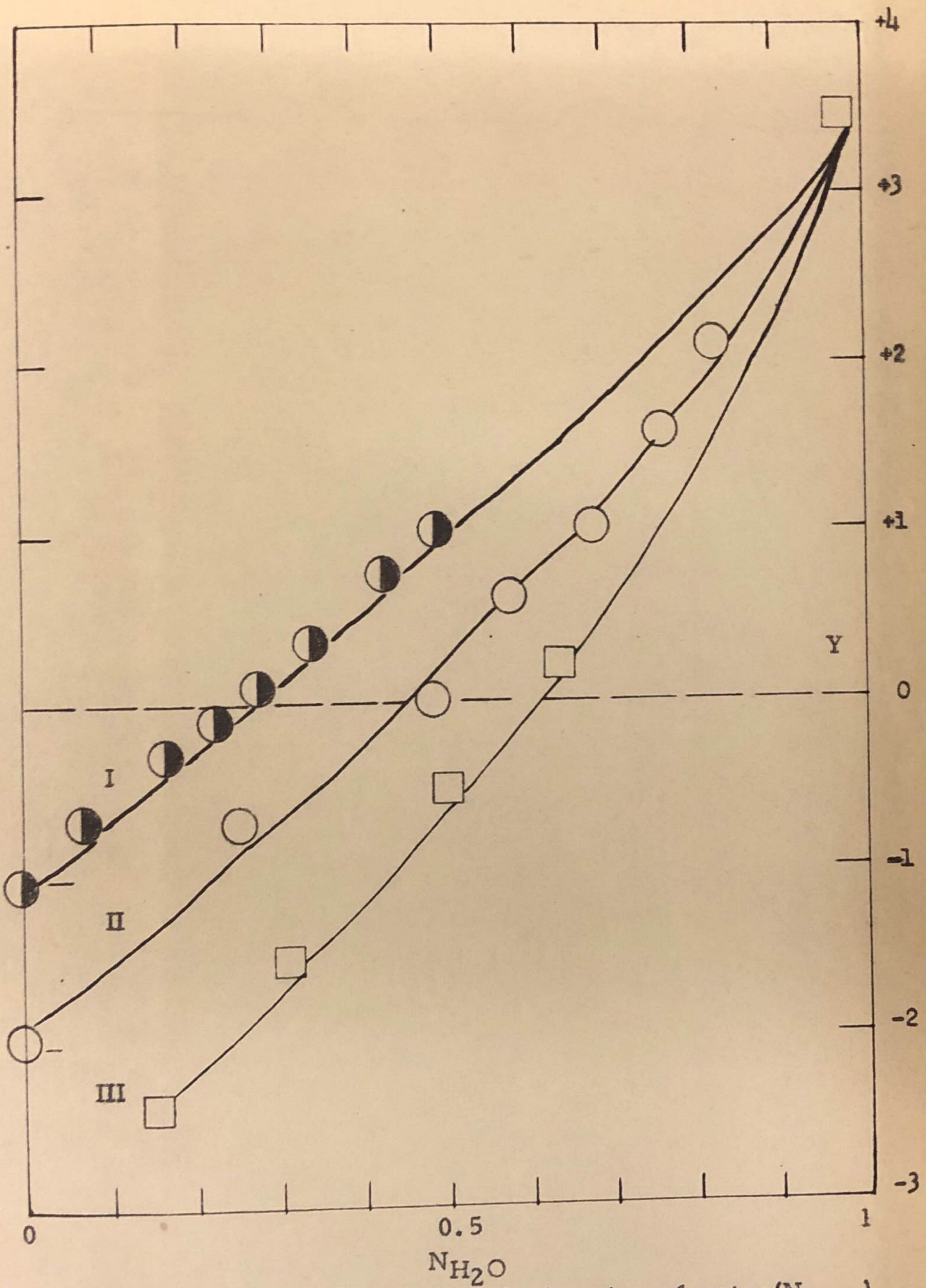


Fig. 1 Plot of Y versus mole fraction of water ( $N_{H_2O}$ )  
 for: I, H<sub>2</sub>O-MeOH; II, H<sub>2</sub>O-EtOH; III, H<sub>2</sub>O-Me<sub>2</sub>CO.

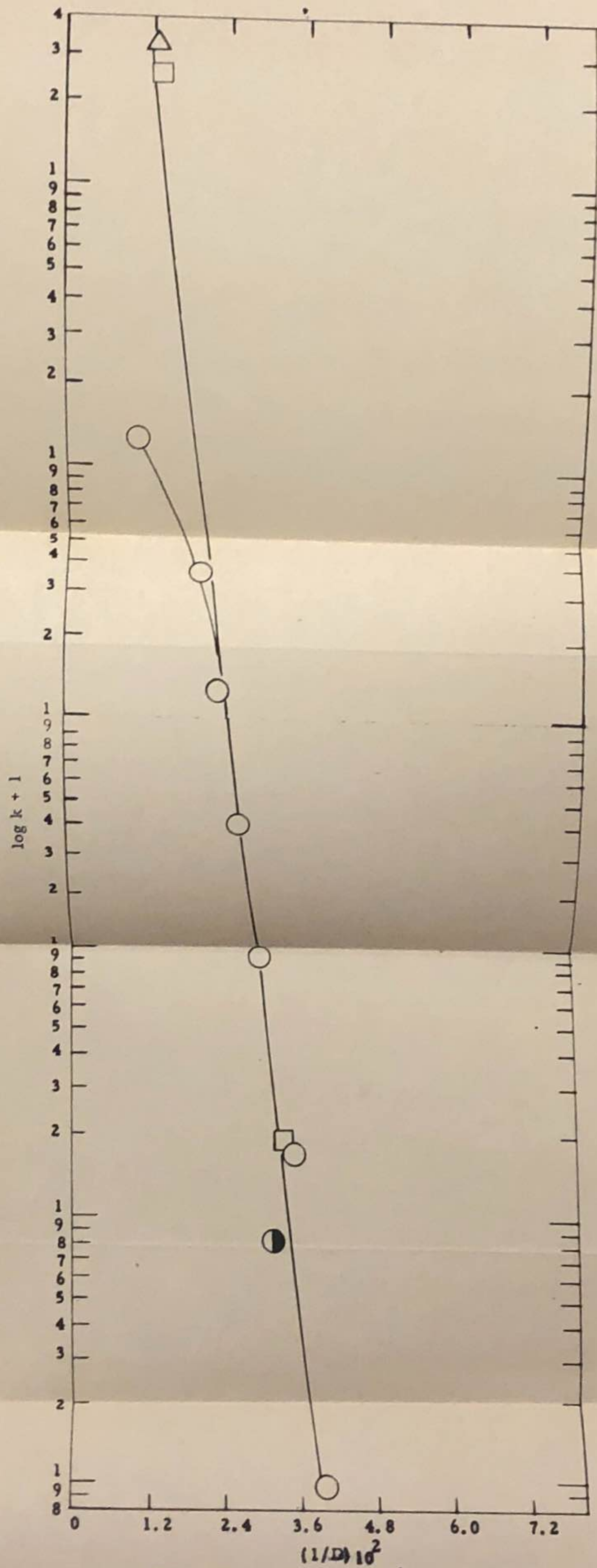


Fig. 2a Plot of  $\log k_1$  (sec.<sup>-1</sup>) versus  $1/D$  for *t*-Butyl chloride at 25°C., in solvents: □, acetone-water; ○, ethanol-water; ◐, methanol-water; △, water.

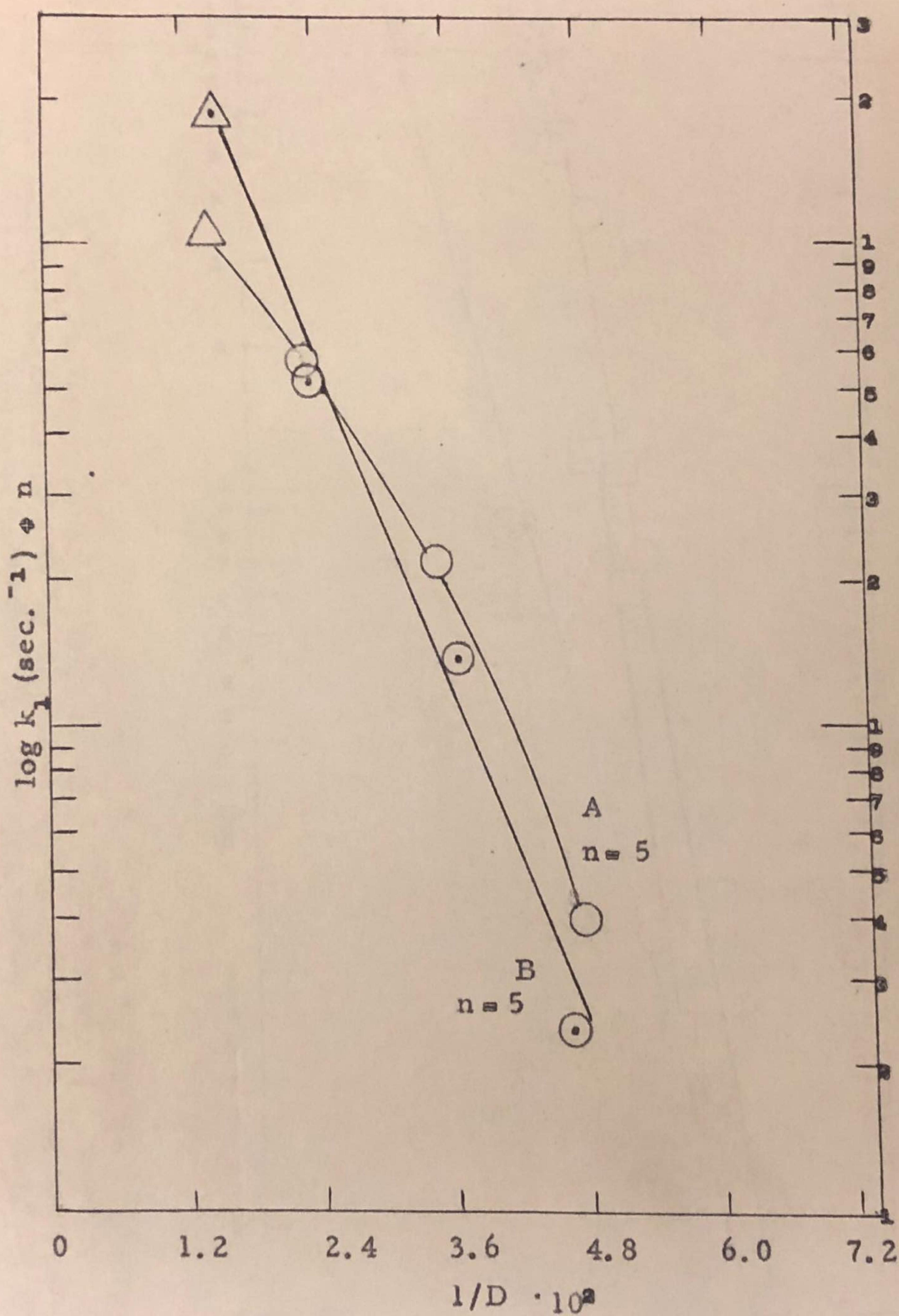


Fig.2b Plot:  $\log k_1$  versus  $1/D$  for: A, MeBr, 50°C.; B, EtBr, 55°C. Solvents:  $\circ, \odot$ , EtOH- $H_2O$ ;  $\triangle, \blacktriangle$ , Water.

Fig.2c Plot:  $\log k_1$  versus  $1/D$  for: C, isopropyl bromide,  $50^\circ\text{C}$ .,  $k_1$  ( $\text{sec.}^{-1}$ ); D, t-butyl bromide,  $24.95\text{--}25^\circ\text{C}$ .,  $k_1$  ( $\text{sec.}^{-1}$ ); E, p, p -dimethylbenzhydryl chloride,  $0.0^\circ\text{C}$ .,  $k$  ( $\text{sec.}^{-1}$ ). Solvents:  $\circ$ , EtOH-H<sub>2</sub>O;  $\square$ , Me<sub>2</sub>CO-H<sub>2</sub>O;  $\triangle$ , H<sub>2</sub>O. For C and D,  $n=4$ ; for E,  $n=3$ .

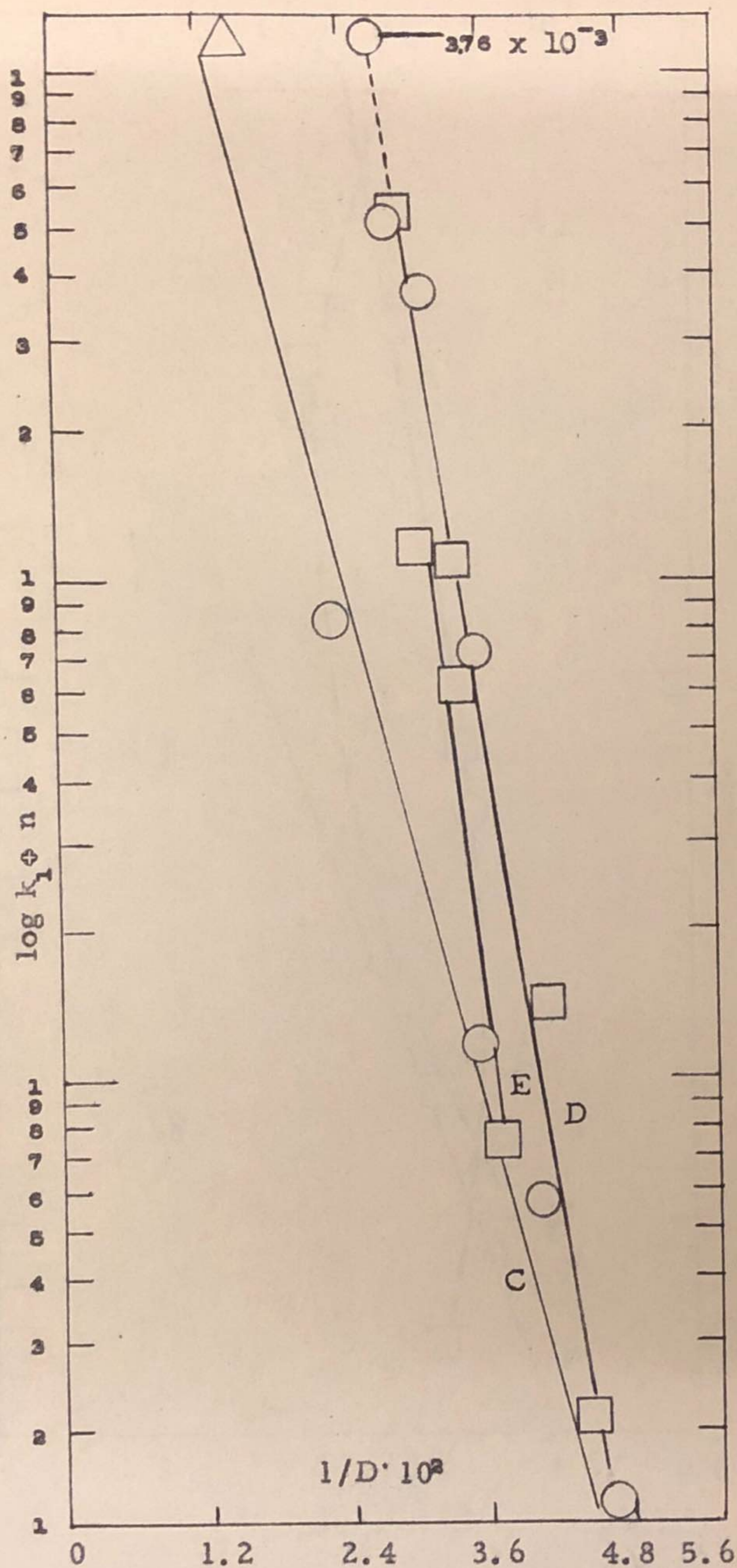
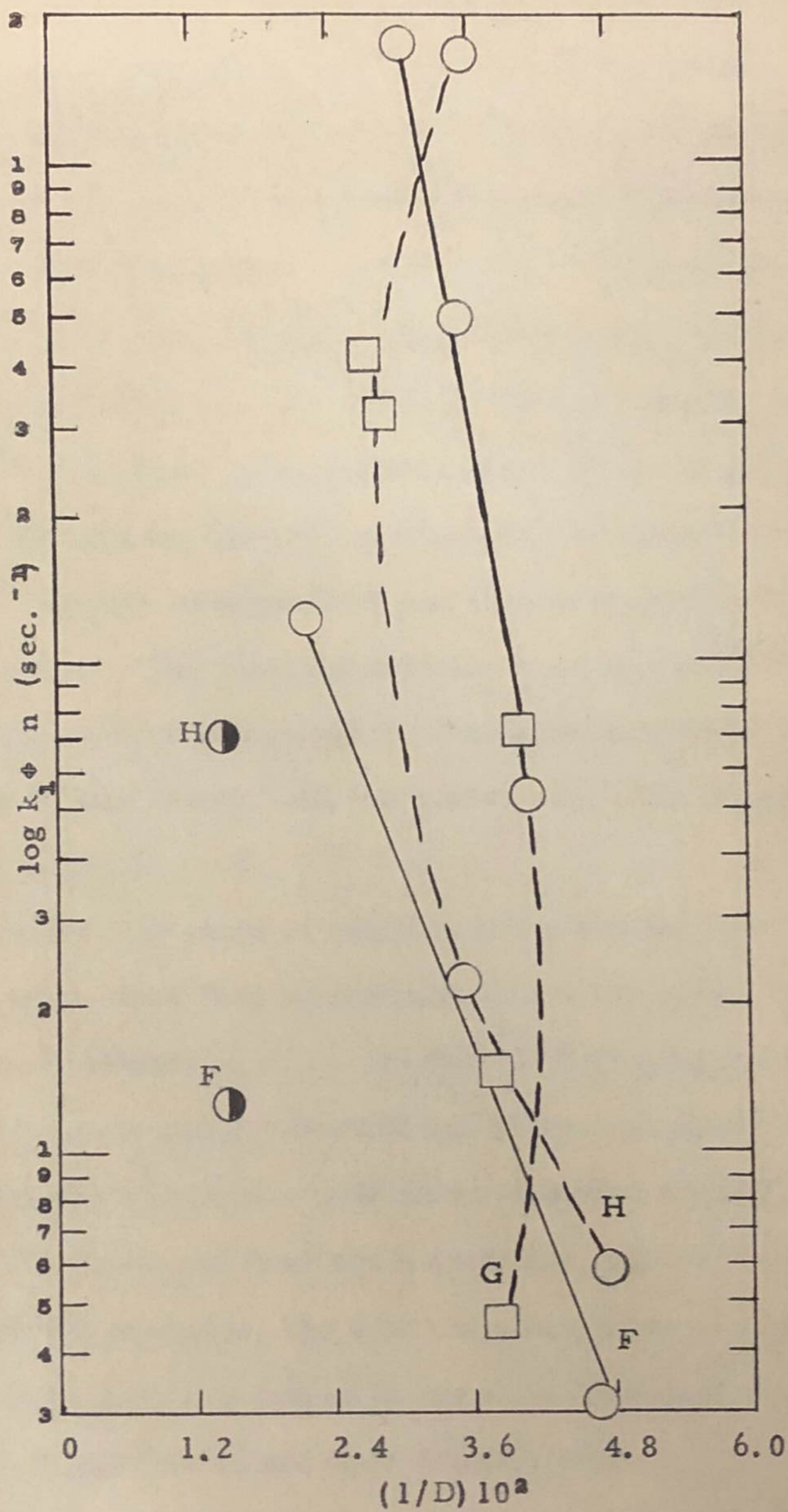




Fig. 2<sup>d</sup> Plot:  $\log k$  versus  $1/D$  for: F, Diphenyl methyl chloride  $50^\circ\text{C}$ .,  $n=5$ ; G, Diphenyl methyl chloride  $25^\circ\text{C}$ .,  $n=3$ ; H, alpha-Chloroethylbenzene,  $50^\circ\text{C}$ .,  $n=3$ . Solvents:  $\bigcirc$ , EtOH- $\text{H}_2\text{O}$ ;  $\square$ ,  $\text{Me}_2\text{CO}$ - $\text{H}_2\text{O}$ ;  $\bullet$ ,  $\text{MeOH}$ - $\text{H}_2\text{O}$ .



for methyl bromide, t-butyl chloride, and alpha-chloroethylbenzene show some tendency to curvature, while those for ethyl bromide, isopropyl bromide, p,p'-dimethylbenzhydryl chloride, t-butyl bromide, and n-butyl bromide show anticipated behaviour. These same curves for diphenylmethyl chloride apparently show both curvature and linearity depending upon some effect, direct or indirect, of the solvent and/or some indirect effect of the temperature. (The data for the construction of these curves has been summarized in appendix B and is representative of available data. The reported velocity constants at other temperatures were calculated for the same temperature when the  $E^\ddagger$  was known. All the curves represent the isothermal values.)

Generally, the rates of reaction in the alcohol solvents for reactions other than substitutions lie in the order of the dielectric constants as do many other of their properties, but nitrobenzene and acetone fall out of line completely. The effect of water upon reactions in alcohol medium is usually that predicted from the increase in dielectric constant which it produces, the effect of other solvents is not.

Nevertheless, it has been known for a long time that the alcohol solvents do not obey Raoult's law.

Although structural effects are beyond the present discussion, we find that the ionizing capacity of the medium exerts an influence here as well. In fact, it can produce an entirely different reaction order.<sup>5</sup>

In 1951, Grunwald, Jones and Winstein<sup>23</sup> added two mechanistic categories: the "limiting" and the "nucleophilic." These have, like their "ancestors," resolved only a small part of the displacements on carbon known as nucleophilic (see table I).

TABLE I

Classification of Nucleophilic Displacements on Carbon\*

I. Hughes and Ingold	$S_N1$	Borderline Cases	$S_N2$
II. Evidence for an intermediate**	positive	negative	
III. Covalent character to solvent-R interaction in the transition state	Lim. (-)	N(+)	

\*Source: Grunwald, Jones and Winstein, J. Am. Chem. Soc., 73, 2701 (1951); \*\* such as a "mass-law" effect or stereochemical effects, see Gleave, Hughes, and Ingold, J. Chem. Soc., 236 (1935).