

### 300. Nucleophilic Substitution in Dipolar Aprotic Solvents: Hexamethylphosphoric Triamide

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*Summary.* The rate of the reaction between ethyl tosylate and chloride as well as bromide ion has been measured in hexamethylphosphoric triamide in the presence of several counterions. Rate constants for the free ions at 25.0° are 14.4 mole<sup>-1</sup> for chloride and 2.0 mole<sup>-1</sup> min<sup>-1</sup> for bromide, both independent of the cation used. The equilibrium constants for ion pair dissociation of lithium-, ammonium- and tetra-*n*-butylammonium chloride are  $3.97 \times 10^{-2}$ ,  $1.52 \times 10^{-3}$  and  $6.36 \times 10^{-3}$  mole, and for the corresponding bromides  $3.30 \times 10^{-2}$ ,  $9.65 \times 10^{-3}$ , and  $9.62 \times 10^{-3}$  mole.

Within the group of dipolar aprotic solvents hexamethylphosphoric triamide appears to be the most interesting one. The physical and chemical properties of this 'super solvent' are well documented [1]. Nucleophilic substitutions of neutral substrates with charged nucleophiles are in general faster in hexamethylphosphoric triamide than in other solvent systems. Kinetic studies of the reaction between azide ion and *n*-butylbromide [2] and between bromide ion and methyl tosylate [3] demonstrate the ability of hexamethylphosphoric triamide to accelerate nucleophilic substitution reactions more than any other aprotic solvent. An explanation for this behaviour may be found on the basis of solvent activity coefficients [4] [5]. However, very little rate data of substitution reactions in this solvent are known, and the possible contribution of other factors to the rate acceleration in hexamethylphosphoric triamide has not been excluded.

In this paper we report on a kinetic study of the reaction of chloride and bromide ion with ethyl tosylate, using lithium-, ammonium-, and tetra-*n*-butylammonium salts as the source of nucleophiles. This series was selected in order to investigate the importance of ion pairing, counterion effects on the reactivity of the free halide ions and the reactivity of ion pairs in this system.

The rate constants were determined under pseudo-first order conditions in a UV.-cell, thermostated at 25.0°, by monitoring the change in absorbance at 273 nm. The concentration range studied was 0.02–0.2M in halide salt and  $2.25 \times 10^{-3}$ M initial tosylate concentration. The observed rate constants  $k_{\text{obs}}$ , in mole<sup>-1</sup> min<sup>-1</sup>, are represented in Fig. 1 (chloride) and Fig. 2 (bromide).

From the plot it becomes immediately apparent that the reaction rate does not depend in a simple manner on the total salt concentration. The rates of lithium salts are always higher than those of the corresponding tetra-*n*-butylammonium salts. This is just the opposite to the situation in acetone where the rates of lithium salts are much more reduced (by ion pairing) than the rates of tetra-*n*-butylammonium salts [6] [7] [8]. On the basis of the rate data one might in fact conclude that in hexamethylphosphoric triamide lithium salts are more dissociated than tetra-*n*-butyl-

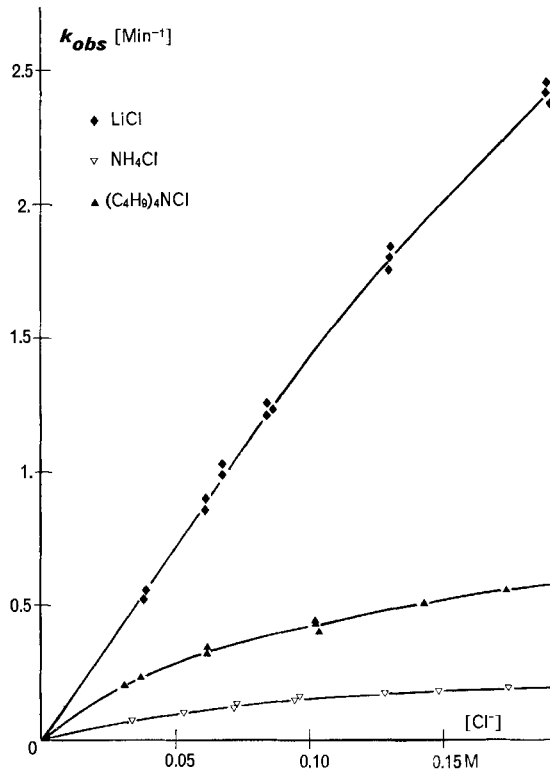


Fig. 1. Pseudo-first order rate constants  $k_{obs}$  for chloride ion with ethyl tosylate in hexamethylphosphoric triamide, as a function of salt concentration ( $T = 25.0^\circ$ )

ammonium salts. *Normant* has already pointed out [9] the high degree of dissociation of lithium chloride in hexamethylphosphoric triamide.

Ion pair dissociation constants of the bromides and chlorides were determined from conductivity measurements (Fig. 3 and 4). The calculations used for the determinations of the ion pair dissociation constants in the literature are developed from the *Fuoss-Onsager* theory [10] and the *Debye-Hückel* equation for the mean activity coefficients of the ions [11]. In all these treatments there are certain ambiguities because the reference function that should represent the conductance of the completely dissociated electrolyte is not really known [12]. For example variation of the ion size parameter in the *Debye-Hückel* equation leads to different degrees of dissociation ( $\alpha$ ) and different dissociation constants ( $K_D$ ) for the ion pairs [8] [13]. The treatment of *Justice* [14] uses a modified *Fuoss-Onsager* equation of the form

$$A = A_0 - Sc^{1/2} + E_1 (A_0 - 2E_2) C\alpha \log C\alpha + JC\alpha + J_{3/2} C^{3/2}\alpha^{3/2} - \frac{1}{K_D} C\alpha f_{\pm}^2 A \quad (1)$$

In this treatment ion pairs are defined to exist if ions of opposite charge are within a distance  $q - a$ , where  $q$  stands for the minimum approach distance, calculated with the theory of *Bjerrum* [15], and  $a$  for the contact distance. The equation of *Justice*

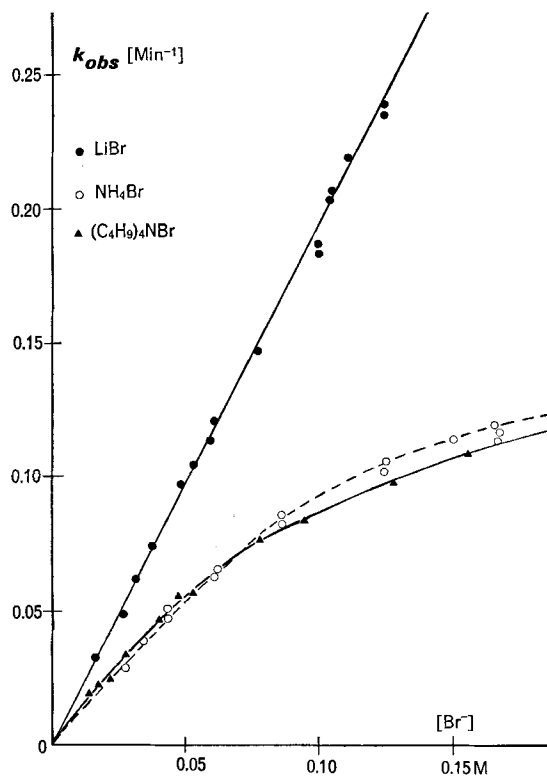


Fig. 2. Pseudo-first order rate constants  $k_{obs}$  for bromide ion with ethyl tosylate in hexamethylphosphoric triamide, as a function of salt concentration ( $T = 25.0^\circ$ )

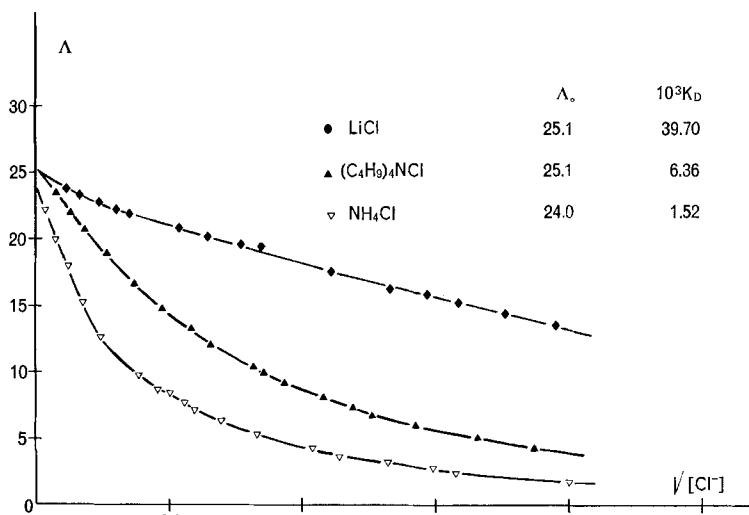


Fig. 3. Conductivity of lithium-, ammonium-, and tetra-n-butylammonium chloride in hexamethylphosphoric triamide ( $T = 25.0^\circ$ ,  $\Lambda$  in Ohm<sup>-1</sup> cm<sup>2</sup> eq<sup>-1</sup>,  $c$  in mole l<sup>-1</sup>)

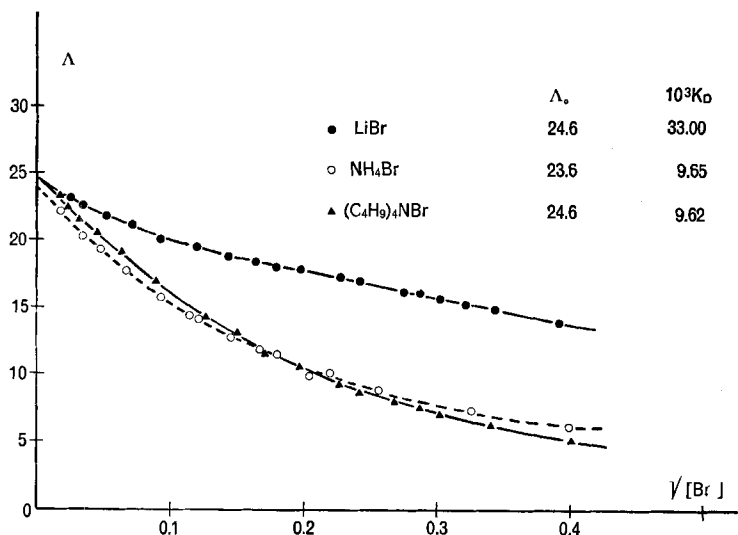


Fig. 4. Conductivity of lithium-, ammonium- and tetra-*n*-butylammonium bromide in hexamethylphosphoric triamide ( $T = 25.0^\circ$ ,  $\Lambda$  in  $\text{Ohm}^{-1} \text{cm}^2 \text{eq}^{-1}$ ,  $c$  in  $\text{mole l}^{-1}$ )

accommodates existing conductivity data in a better way than the *Fuoss-Onsager* theory. Our measurements were analyzed in terms of equation (1) by Prof. *Justice* and his co-workers<sup>1)</sup> by means of a computer program. The results of the compilation are given in Table 1. With both, chloride and bromide ion, the dissociation is indeed highest, if lithium is the counterion. Ammonium and tetra-*n*-butylammonium ions are paired to a much greater degree. The trend is quite clear, although there might be some doubt concerning the reliability of the conductivity data. Measurements from different laboratories with hexamethylphosphoric triamide as solvent lead to

Table I. Analysis of conductivity data in hexamethylphosphoric triamide ( $T = 25.0^\circ$ )

Salt	N <sup>a)</sup>	$\Lambda_0$ $\text{ohm}^{-1} \text{cm}^2 \text{eq}^{-1}$	$J_1$	$J_{3/2}$	$R_{J_{3/2}} \times 10^8 \text{ cm}$	$10^3 K_D [\text{M}]$	$a_{\text{K}}^{\text{B}} \times 10^8 \text{ cm}$
LiCl	14	$25.10 \pm 0.31$	$768 \pm 0.5$	$-1555 \pm 36.2$	$7.8 \pm 0.1$	$39.70 \pm 4.30$	4.9
<i>n</i> -Bu <sub>4</sub> NCl	18	$25.10 \pm 0.17$	$770 \pm 0.3$	$-2876 \pm 63.2$	$10.5 \pm 0.1$	$6.36 \pm 0.24$	2.0
NH <sub>4</sub> Cl	18	$23.98 \pm 0.24$	$734 \pm 0.2$	$-4575 \pm 295.0$	$13.2 \pm 0.4$	$1.52 \pm 0.06$	1.6
LiBr	16	$24.66 \pm 0.13$	$754 \pm 0.2$	$-1418 \pm 20.2$	$7.5 \pm 0.1$	$33.00 \pm 1.20$	4.3
<i>n</i> -Bu <sub>4</sub> NBr	19	$24.67 \pm 0.20$	$756 \pm 0.3$	$-2372 \pm 45.8$	$9.7 \pm 0.1$	$9.62 \pm 0.45$	2.3
NH <sub>4</sub> Br	16	$23.61 \pm 0.20$	$722 \pm 0.3$	$-1922 \pm 60.5$	$8.9 \pm 0.1$	$9.65 \pm 0.46$	2.3

<sup>a)</sup> N is the number of measurements. For explanation of the symbols see ref. [14]. A value of  $9.34 \text{ \AA}$  was used for the parameter of *Bjerrum*,  $q$ .

<sup>1)</sup> We are deeply indebted to Prof. *Justice* for the computation of our data.

quite different results [16]. We found it necessary to use the solvent within 24 hours of purification. Otherwise irreproducible data were often obtained.

One consequence of the high ion pair dissociation constant of the lithium salts is that the reactivity scale of the halide ions appears to be inverted, if one compares the rate constant of lithium bromide with ammonium chloride (Fig. 5) at concentrations above 0.1M. It may also be of interest to note that addition of dicyclohexyl-18-crown-6-ether to lithium bromide or chloride produces no acceleration of the reaction with ethyl tosylate in hexamethylphosphoric triamide, although in other solvents reactivities of nucleophiles are often enhanced by the addition of cyclic polyethers [17]. In fact with lithium halides in hexamethylphosphoric triamide dicyclohexyl-18-

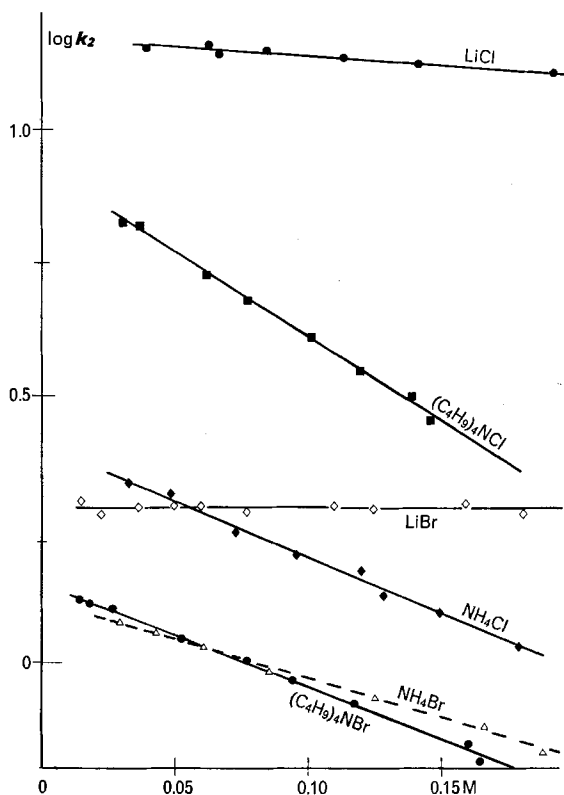


Fig. 5. Comparison of second order rate constants ( $k_2 = k_{obs}/c$ ) of chlorides and bromides. Data from Fig. 1 and Fig. 2. The curves are drawn for clarity and have no significance.  $k_2$  in  $\text{mole}^{-1} \cdot \text{min}^{-1}$ .

crown-6-ether produces a rate retardation, which is believed to be caused by impurities in the commercially available sample. The absence of rate enhancement upon addition of crown ethers is not unexpected, as the ability of crown ethers to break up ion pairs [18] and thus to increase reaction rates is of no consequences in a system where ion pairs are essentially absent.

The concentration dependence of the second order rate constant may be interpreted by means of the *Acree* [19] hypothesis, once the dissociation constant  $K_D$  of the ion pairs is known. In the *Acree* equation (2) the second order rate constant  $k_2$  at

$$k_2 = k_1\alpha + k_m(1 - \alpha) \quad (2)$$

a given concentration is broken up in a term for free ions ( $k_1$ ) and a term for ion pairs ( $k_m \frac{1 - \alpha}{\alpha}$ ). The hypothesis predicts no influence of the counterion on  $k_1$ , which, with exceptions, has been experimentally verified [8] [20]. The rate constants in Fig. 5 were fitted to a rearranged *Acree* equation of the form (3) by means of a least-

$$\frac{k_2}{\alpha} = k_1 + k_m \frac{1 - \alpha}{\alpha} \quad (3)$$

square treatment<sup>2)</sup>. The results of the compilation are summarized in Table 2. The only conclusion that may be safely drawn from these calculation is that  $k_1$  remains unchanged upon variation of the counterion. The precision of the data appears to be too low to allow much significance to be ascribed to the  $k_m$ -values. For experimental

Table II. *Analysis of rate data in terms of the Acree hypothesis* [19]. Data from Fig. 5 and Table I.

Salt	$k_1$	$k_m$	$r^a$
LiCl	$14.4 \pm 1.1$	10.5	0.90
$\text{NH}_4\text{Cl}$	$14.4 \pm 0.6$	-0.7	0.80
<i>n</i> - $\text{Bu}_4\text{NCl}$	$14.4 \pm 0.6$	-0.5	0.81
LiBr	$2.0 \pm 0.10$	1.70	0.92
$\text{NH}_4\text{Br}$	$2.0 \pm 0.08$	0.150	0.95
<i>n</i> - $\text{Bu}_4\text{NBr}$	$2.0 \pm 0.10$	0.150	0.91

a) Correlation coefficient [21].

reasons the rate constants could not be determined at sufficiently low concentrations. Further, rate constants were found to be very difficult to reproduce in hexamethylphosphoric triamide.  $k_m$ -Values in the literature are often not comparable because they depend too much on the equation and the choice of parameters used for the analysis of conductivity data [22]. Our results indicate agreement between  $k_m$ -values and the contact distance  $a_{K^B}$  (Table 1), suggesting higher reactivity for pairs in which the distance between the combined ions is large, and low reactivity if the distance is small.

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<sup>2)</sup> A computer program written by Mr. *J. C. Perlberger* was used.

### Experimental

*Materials.* Hexamethylphosphoric triamide (*Fluka*) was refluxed with phosphorous pentoxide and distilled. A second distillation from calcium hydride under nitrogen atmosphere afforded a liquid with a maximum conductivity of  $10^{-7}$  ohm $^{-1}$  cm $^{-1}$ . The solvent was used within 24 h after purification. Lithium chloride and bromide (*Merck*, suprapur) was dried at 180°/12 mm for 3 days. Tetra-*n*-butylammonium bromide (*Fluka*) was dried over phosphorous pentoxide at 60°/10 mm. Tetra-*n*-butylammonium chloride (*Fluka*) was recrystallized from ethyl acetate/ether, filtered under nitrogen atmosphere and dried over phosphorous pentoxide at 100°/10 mm. Ethyl tosylate (*Fluka*) was recrystallized twice from light petroleum, dried under vacuum and stored over phosphorous pentoxide.

*Kinetics and conductivity measurements.* Apparatus and methods for the determination of reaction rates [5] and conductivity [23] of the salts have been described in previous publications.

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