

- [14] *A. Mouton & J. Jollès*, FEBS Letters 4, 337 (1969); *J.-P. Périn & P. Jollès*, unpublished data.
[15] *E. Maron, R. Armon, M. Sela, J.-P. Périn & P. Jollès*, Biochim. biophysica Acta 214, 222 (1970).
[16] *D. C. Phillips*, Scient. American 215, 78 (1966).
[17] *J. Saint-Blancard, P. Chuzel, Y. Mathieu, J. Perrot & P. Jollès*, Biochim. biophysica Acta 220, 300 (1970).
[18] *A. Faure & P. Jollès*, FEBS Letters 10, 237 (1970).
[19] *A.-C. Dianoux & P. Jollès*, Bull. Soc. Chim. biol. 51, 1559 (1969).
[20] *M. Inouye, M. Imada & A. Tsugita*, J. biol. Chemistry 245, 3479 (1970).
[21] *J. B. Howard & A. N. Glaser*, J. biol. Chemistry 244, 1399 (1967); *I. Bernier, E. van Leemputten, M. Horisberger, D. A. Bush & P. Jollès*, FEBS Letters 14, 100 (1971).

286. The Reaction of Methyl Tosylate with Halide Ions in Pyridine-Dimethylformamide

by **Paul Müller** and **Bernard Siegfried**

Département de Chimie Organique de l'Université, 1211 Genève 4

(11. VIII. 71)

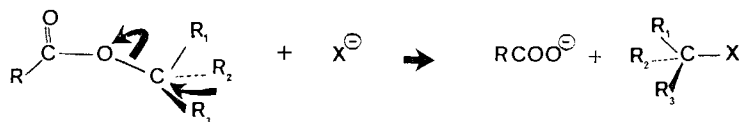
Summary. The reactivity of the lithium halides in 83.3% pyridine-dimethylformamide changes from $\text{Cl}^- > \text{Br}^- > \text{I}^-$ to $\text{Br}^- > \text{I}^- > \text{Cl}^-$ with increasing concentration of the salt from 0 to 0.35M. This behaviour is explained by ion pairing which reduces the concentration of reactive free nucleophiles. Equilibrium constants K for ion pair dissociation and rate constants k_2 for the reaction of the free nucleophiles were determined from the variation of the observed rate constant with the total halide concentration and from conductivity measurements.

The normal order of nucleophilic reactivity of the halide anions with $\text{I}^- > \text{Br}^- > \text{Cl}^-$ is based on measurements in water or other protic solvents [1]. This order can be reversed if the medium is changed to a dipolar aprotic solvent of high dielectric constant [2]. The rationalizations used in the past for nucleophilic reactivity, based on polarizability [3], oxidation potentials [4] and other physical properties are of little value considering the reactivity changes upon transfer from protic to aprotic solvents. The most important factor governing nucleophilic reactivity now appears to be solvation of the nucleophile [2]. The stability of a given nucleophile in a particular solvent with respect to a reference solvent can be expressed by the solvent activity coefficient [2] [5]. Rates of many bimolecular substitution reactions correlate reasonably well with the solvent activity coefficients of the attacking nucleophiles, whereas solvent activity coefficients of organic substrates and transition states are usually of minor importance [2] [6]. Among the halide anions, chloride is the most stable in protic, and the least stable in aprotic solvents. Accordingly, it is the least reactive in protic and the most reactive in aprotic reaction media.

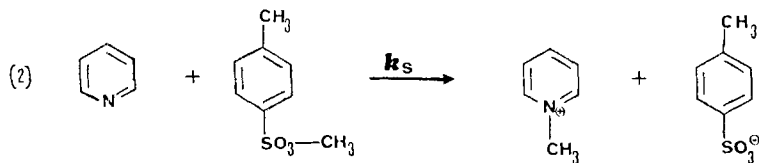
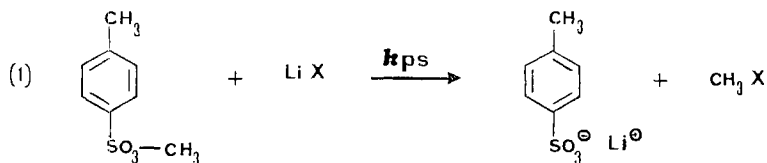
In aprotic solvents of low dielectric constant the situation appears to be more complicated. Thus, in liquid sulfur dioxide, bromide is more reactive than chloride, an anomaly still awaiting explanation [7], and in acetone the observed reactivity sequence of the halide anions corresponds to that obtained in water and not, as would be expected, to that for dipolar aprotic solvents [8]. The behaviour of the halide ions in acetone is easily understood if incomplete dissociation of the inorganic salts in this

solvent is taken into account. Ion pairs have been shown to be less reactive than free ions [7] [9], and their presence in high concentration leads, in the case of acetone as solvent, to a reversed apparent reactivity order of the halide anions. The reactivity sequence of the free halide anions in acetone is $\text{Cl}^- > \text{Br}^- > \text{I}^-$, corresponding to the order in other aprotic solvents [8]. Ion pairs are also of importance in dimethylformamide (DMF), but their effect is not as striking as in acetone [10].

In this work we have studied the nucleophilicities of the lithium halides in pyridine toward methyl tosylate. This system was selected in view of our interest in the attack of halide anions on carboxylic esters in aprotic solvents. This reaction, which has been studied by *Cherbuliez* [11], *Elsinger & Eschenmoser* [12] and *Taschner & Liberek* [13], is believed to proceed by the $B_{\text{Al}}2$ mechanism, *i.e.* bimolecular nucleophilic substitution on the O-alkyl group (see Chart). It is reported that with pyridine as



solvent, the ease of the reaction increases in the order $\text{Cl}^- < \text{Br}^- < \text{I}^-$, although no precise rate data have been published [13]. This deviation from the normal reactivity sequence for aprotic solvents is of considerable interest, because reactivity sequences with protic solvents cannot generally be associated with sequences with dipolar aprotic solvents [14]. Since no conclusive evidence for the $B_{\text{Al}}2$ mechanism for ester cleavage with halide ions in pyridine has been presented, we wanted to determine whether this reactivity order is normal for bimolecular nucleophilic substitutions in this solvent and, if affirmative, for which reason.



The use of neat pyridine as solvent proved to be impractical since it lead to heterogenous reaction mixtures [12]. Therefore a limited amount ($\sim 16\%$) of dimethylformamide was added as cosolvent. Since the reaction of lithium halides with methyl tosylate in dimethylformamide has already been investigated [10], the effect of this solvent change was expected to be easily accounted for. Methyl tosylate was selected as a model for carboxylic esters, since it permitted rate constants with half-lives in the order of *ca.* 5 min to be obtained. An additional advantage with methyl tosylate is that the reaction mechanism with halide ions in dimethylformamide is firmly established to be S_N2 [10].

The kinetic scheme of the reaction between the lithium halides and methyl tosylate in pyridine is complex, because of the competing reaction with the solvent. The following steps are observable.

The disappearance of methyl tosylate can be measured under pseudo-first order conditions as a function of time. Reaction (3) is of no importance provided that an excess of nucleophile is maintained. Two parallel pseudo-first order reactions then take place. The observed rate constant k_{obs} is obtained from conventional semi-logarithmic plots. As the solvent rate expressed by k_s can be measured separately the rate constant k_{ps} for reaction (1) is given by (4). For X = Br and I, pseudo-first

$$k_{ps} = k_{obs} - k_s . \quad (4)$$

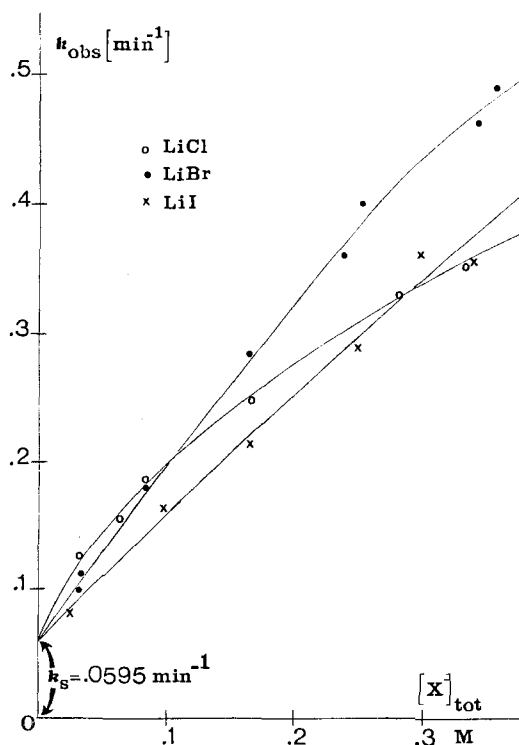


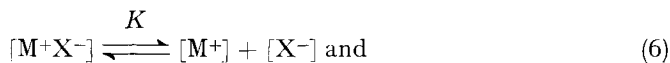
Fig. 1. Variation of the observed rate constant k_{obs} with total nucleophile concentration $[X^-]_{tot}$

order conditions are maintained even if the concentration of the nucleophile is of the same order as that of the substrate, because step (3) is rapid compared to (2). Hence, the nucleophile is rapidly regenerated, and its concentration remains essentially constant. Unfortunately, this is not true for $X = Cl$. The reaction of methyl chloride with pyridine is much slower than step (2), so that pseudo-first order conditions are only maintained with excess chloride present. For this reason, concentrations of nucleophile higher than 0.05 M with 0.022 M methyl tosylate were employed. The rate constants obtained with chloride concentrations between 0.05 and 0.1 M are probably somewhat too low. Nevertheless, considering the contribution of the solvent rate to the disappearance of the substrate, the chloride concentration, even with only 0.05 M starting concentration, does not vary much more than 20%¹⁾.

In Fig. 1 the observed rate constants, k_{obs} , for the nucleophiles are plotted against the total lithium halide concentration, $[X^-]_{tot}$. The curves originate at the same point, the ordinate representing k_s , the rate constant for the reaction of the solvent. The shapes of the curves indicate that the reaction is not first-order with respect to $[X^-]_{tot}$, and that the reactivity order of the halide ions changes from $Cl^- > Br^- > I^-$ to $Br^- > Cl^- > I^-$ with increasing nucleophile concentration. The data were fitted to the mechanistic model developed by *Weaver* [10] where the concentration dependence of k_{obs} is ascribed to incomplete dissociation of the lithium halides. In this treatment, activity coefficients are neglected and the reactivity of ion pairs is considered to be of no importance. With these assumptions the rate constant k_2 for the reaction of the free nucleophile and the equilibrium constant K for ion pair dissociation, are determined as follows:

The rate for the reaction of the free nucleophile with methyl tosylate is given by the relation (5). Assuming simple mass law equilibria for ion pair dissociation

$$\text{rate} = k_2 [X^-] [\text{MeTos}] \quad (5)$$



$$K = \frac{[M^+][X^-]}{[M^+X^-]}, \quad (7)$$

the dependence of k_{obs} on the total nucleophile concentration $[X^-]_{tot}$ is given by equation (8) [10]²⁾:

$$k_{obs} = \frac{k_2}{2} \left\{ -K + \sqrt{K^2 + 4K[X^-]_{tot}} \right\} + k_s. \quad (8)$$

As k_s can be measured separately it is convenient to substitute eq. (4) in (8). It is then possible to solve for $[X^-]_{tot}$.

$$[X^-]_{tot} = \frac{k_{ps}^2}{k_2 K} + \frac{k_{ps}}{k_2}. \quad (9)$$

¹⁾ Scattering in the data was too high as to allow to treat the system as parallel first and second order reaction [15].

²⁾ The equation (8) corresponds to the one by *Weaver & Hutchinson*, but the pseudo-first order rate constant k_{obs} is used instead of $k_{2obs}[X^-]$ and the term for the solvent rate k_s is added.

The constants k_2 and K are determined by computer³⁾ using a least square calculation with appropriate weighing. The values obtained for the various halide ions are given in the table. The rate constants k_2 , corresponding to the reactivities of the free nucleophiles are clearly in the order $\text{Cl}^- > \text{Br}^- > \text{I}^-$ (see Table). Ion pairing is more

Calculated rate and equilibrium constants k_2 and K , for lithium halides LiX

X	k_2 [$\text{M}^{-1}, \text{min}^{-1}$]	K [M]	K [M] conductometric
Cl	2.8	0.046	0.00015
Br	1.5	1.4	0.0035
I	1.0	3.0	0.0085

important with the chloride owing to the stronger interionic forces between ions of high charge density. Theoretical curves for the dependence of the second-order rate constant $k_{\text{ps}}/[\text{X}^-]_{\text{tot}}$ on $[\text{X}^-]_{\text{tot}}$ (see Fig. 2) were calculated using the constants in the Table. In this representation k_2 corresponds to the ordinate at concentration Zero.

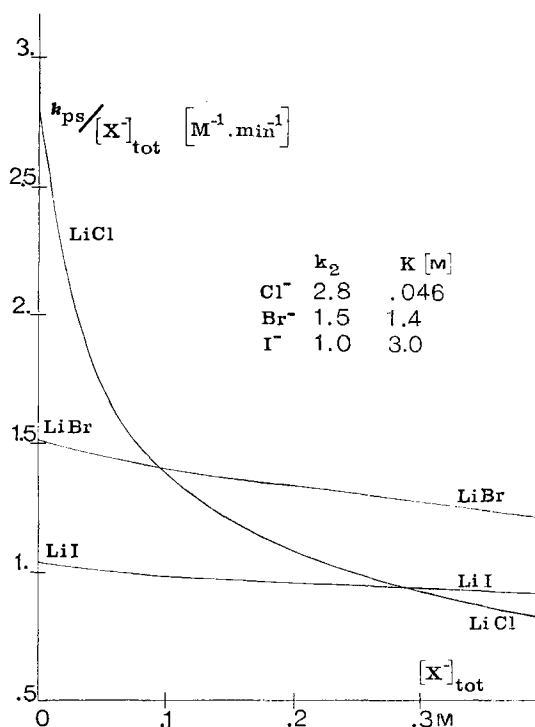


Fig. 2. Plot of the calculated second order rate constant $k_{\text{ps}}/[\text{X}^-]_{\text{tot}}$ against $[\text{X}^-]_{\text{tot}}$ using the constants from table

³⁾ The authors are indebted to Mrs. F. Barbalat-Rey for the computer program and the calculations.

The shapes of the curves are determined by K . A low value for K as in the case of the chloride leads to considerable decrease of the rate constant at high nucleophile concentration, while for bromide and iodide the change is not very important. In fact, as K becomes large, the curves tend to flatten, so that variation of K has little influence on the shape of the curves and on k_2 . For this reason the values of K for bromide and iodide have to be considered with caution. Although we believe the uncertainty of the rate constants k_2 to be not larger than ca. 10%, the difference between the equilibrium constants for bromide and iodide is within experimental error.

Additional evidence in favour of *Weaver's* [10] mechanistic scheme was obtained by rate measurements using tetrabutyl ammonium halides, which are stronger electrolytes than lithium halides. Since bulky cations decrease interionic forces the extent of ion pairing is usually low. We found that in 83.3% pyridine-dimethylformamide the observed rate constants for 0.165M tetrabutyl ammonium halides are of the same order as those calculated for the free halides [16].

In view of the uncertainty about the equilibrium constants for lithium bromide and iodide it was desirable to obtain more precise values for K by conductivity measurements. In Fig. 3 the conductance Δ of lithium halide solutions is plotted against the square-root of concentration. The Δ_0 -values were obtained by simple *Fuoss-Kraus* plots (Fig. 4) [17] using free-hand extrapolation of the plots in Fig. 3 to determine the initial values needed for the calculation. Activity coefficients were assumed to be 1, as in *Weaver's* calculation. The equilibrium constants were calculated from the intercept (Δ_0), of the straight lines in the *Fuoss-Kraus* plots and with the equation of *Ostwald* (10). These constants are included in the Table. For experimental

$$K = \text{conc.} \cdot \frac{\Delta^2}{\Delta_0(\Delta_0 - \Delta)} \quad (10)$$

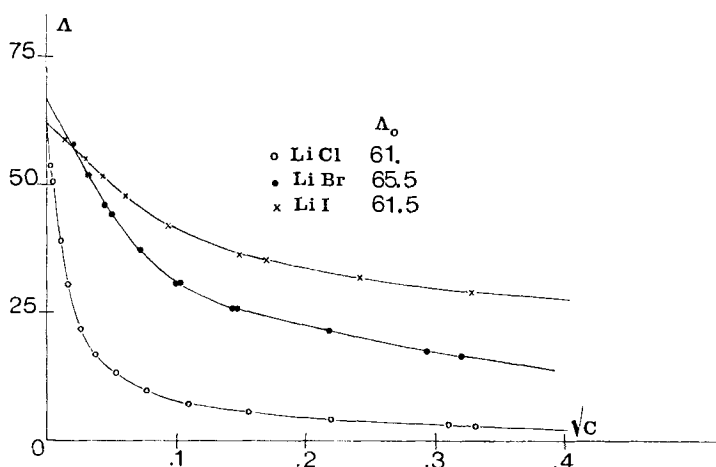


Fig. 3. Conductance Δ of lithium halide salts in 83.3% pyridine-DMF plotted against square-root of salt concentration

Δ in $\text{Ohm}^{-1} \cdot \text{cm}^2 \cdot \text{eq}^{-1}$, c in M

reasons (apparatus and conductance of the solvent) measurements could not be extended to concentrations lower than $10^{-5}M$, where the treatment gives better results. In particular, lithium chloride showed considerable deviations in the *Fuoss-Kraus* treatment in the measured range, owing to the appearance of triple ions [18], and because activity coefficients were neglected. Our constant for the chloride may therefore be somewhat high.

The equilibrium constants determined by our method and those determined by the kinetic method are both in the expected order, but the two sets of results differ by several orders of magnitude. Thus, it seems that *Weaver's* treatment does not adequately describe our system. In fact, considerable discrepancy is found comparing *Weaver's* equilibrium constant for lithium chloride in dimethylformamide with the value determined by conductivity measurements [19]⁴).

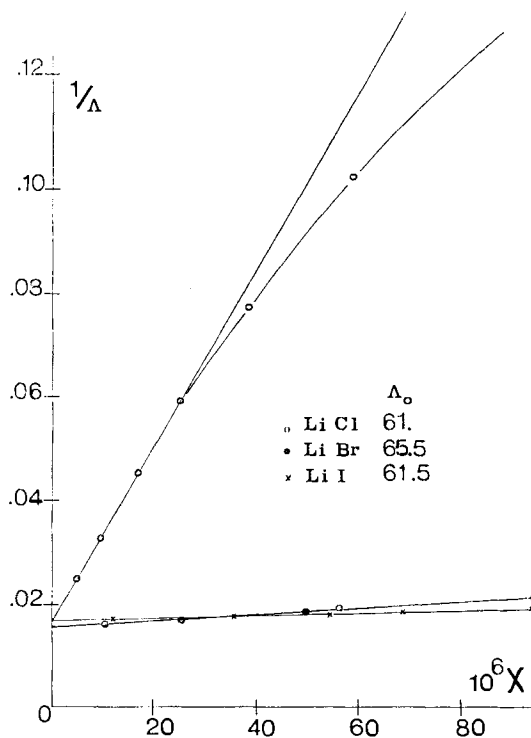


Fig. 4. Fuoss-Kraus plot with data corresponding to Figure 3
 χ in $\text{Ohm}^{-1} \cdot \text{cm}^{-1}$

An explanation for these disagreements may be that the ion pairs are not as unreactive as is assumed. Reactivities of ion pairs have been calculated by *Lichtin* [7] for reactions in liquid sulfur dioxide. The ratio of the reactivities of free anions and ion pairs depends on the nature of the ions and the assumptions used in the calcu-

⁴) Conductivity measurements give 0.026 at 25°, while the kinetic method leads to a constant *K* of 0.18 at 0°. *K* does not increase very much with increasing temperature [20].

lation: values between 160 and 1.5 were found. Hence, as the fraction of ion pairs increases, their contribution to the observed rate becomes considerable and cannot be neglected. At low concentrations of halide ion the free ions are predominant. The extrapolated rate constants (k_2) should, therefore, not be affected too much by the deficiencies of the treatment and, as K -values obtained by conductivity are in the same order as those determined by kinetics, the nucleophilicity order of the free halides estimated by both methods is the same. Ion pair dissociation constants for various salts in neat pyridine are of the order of 10^{-4} M [21], *i.e.* somewhat lower than in pyridine-dimethylformamide. The addition of dimethylformamide as co-solvent to pyridine tends to decrease ion pairing. Otherwise there is no significant effect of the co-solvent since the reaction rate in neat dimethylformamide is close to that in pyridine-dimethylformamide [6].

On the basis of our results we are justified in ascribing to the free halide ions in pyridine the same reactivity order, namely $\text{Cl}^- > \text{Br}^- > \text{I}^-$, as is usually found in dipolar aprotic solvents, whereas the inversion of this order observed at high salt concentration can be ascribed to ion pairing. That we were unable to obtain complete inversion of the reactivity scale is probably due to the co-solvent used and to the lower solubility of the salts at 25° compared to 115° , the temperature used by *Taschner & Liberek* [13].

Support of this work by a grant of the *Fonds National Suisse de la Recherche Scientifique* (grant No. 2.251.69) is gratefully acknowledged.

Experimental. – *Materials.* The lithium halides (*Merck*, “Suprapur”) were dried at 180° /12 Torr for 15 h. *N,N*-Dimethylformamide (*Merck*) was refluxed with lithium hydride for 2 hours and distilled *in vacuo* under nitrogen. Pyridine was distilled from calcium hydride after 3 hours of reflux. The absence of water in the solvent was confirmed by NMR. spectroscopy. Spectrograde pyridine and dimethylformamide (*Fluka*), both used without purification, gave the same results. Commercial methyl tosylate was purified according to *Fieser* [22].

Kinetic measurements. Appropriate stock solutions of lithium halide were made up in neat pyridine. Stock solutions of methyl tosylate (0.135 M) in dimethylformamide were used within 3 h after their preparation. Within this time there was no change observable in the NMR. However, stock solutions stored for one week consistently led to higher rates.

For the runs 10 ml of lithium halide stock solution in a stoppered *Erlenmeyer* flask were thermostatted to 25.0° in a *LAUDA* NBS thermostat for at least 15 min. 2 ml of thermostatted methyl tosylate solution were then added by means of a pipette, and the timer started immediately while the content of the flask was thoroughly mixed by shaking. At appropriate time intervals the reaction was quenched with 50 ml of 30% nitric acid and 2.0 ml (25 mg acetophenone) of standard solution of acetophenone in carbon tetrachloride were added. The mixture was extracted with 10 ml of carbon tetrachloride and the organic phase washed twice with distilled water. After drying with calcium chloride the solution was concentrated in the rotatory evaporator at room temperature to *ca.* 0.5 ml. The unreacted methyl tosylate was determined by measuring the NMR. signal for the methyl group of the ester with respect to the methyl signal of the standard acetophenone, using a *Perkin-Elmer* R 12 instrument. The points given in the plots are averages from 2–4 runs and are considered to be good within *ca.* 10%. This high uncertainty is due to the large number of operations necessary and to the difficulty of obtaining reproducible integrals with the NMR. Accordingly, an error of the same order of magnitude is ascribed to k_2 .

Conductivity measurements. The apparatus used was a *Metrohm* Conductoscope E365B with cells having a constant of 0.800 cm^{-1} at 25.0° . Solvent conductivity was in the order of $10^{-6} \text{ Ohm}^{-1} \cdot \text{cm}^{-1}$. This value was subtracted from the conductivity of the salt solution. At low salt concentration the correction was of the order of magnitude of the conductivity of the electrolytes. For this reason the lower concentration limit for measurements was given by 10^{-5} M.

BIBLIOGRAPHY

- [1] *A. Streitwieser, Jr.*, Chem. Rev. 56, 571 (1956); *C. G. Swain & C. B. Scott*, J. Amer. chem. Soc. 75, 141 (1953).
- [2] *A. J. Parker*, Advances org. Chemistry 5, 1 (1965); Advances phys. org. Chemistry 5, 173 (1965); Quarterly Reviews 16, 163 (1962); Chemical Reviews 69, 1 (1969); *R. F. Rodewald, K. Mahendran, J. L. Bear & R. Fuchs*, J. Amer. chem. Soc. 90, 6698 (1968), *R. Fuchs & K. Mahendran*, J. org. Chemistry 36, 730 (1971).
- [3] *H. R. McCleary & L. P. Hammett*, J. Amer. chem. Soc. 63, 2254 (1941).
- [4] *J. O. Edwards*, J. Amer. chem. Soc. 76, 1540 (1954).
- [5] *M. H. Abraham*, Chem. Commun. 1969, 1307.
- [6] *P. Müller & B. Siegfried*, Helv. 54, 2668 (1971).
- [7] *N. N. Lichtin, M. S. Puar & B. Wasserman*, J. Amer. chem. Soc. 89, 6677 (1967).
- [8] *S. Winstein, L. G. Svedoff, S. Smith, I. D. R. Stevens & J. S. Gall*, Tetrahedron Letters 9, 24 (1960).
- [9] *E. R. Swart & L. J. Le Roux*, J. chem. Soc. 1956, 2210; *L. D. Frashier & F. J. Spieth*, J. phys. Chemistry 55, 860 (1951); *Farhat-Aziz & E. A. Moelwyn-Hughes*, J. chem. Soc. 1959, 2635.
- [10] *W. M. Weaver & J. D. Hutchinson*, J. Amer. chem. Soc. 86, 261 (1964).
- [11] *E. Cherbuliez, P. Leber & M. Bowvier*, Helv. 36, 1203 (1953).
- [12] *F. Elsinger, J. Schreiber & A. Eschenmosev*, Helv. 43, 113 (1960); *F. Elsinger*, Diss. ETH, Prom. 3087, Zurich 1960; Organic Syntheses 45, 7 (1965).
- [13] *E. Taschner & B. Liberek*, Roczniki Chemii 30, 323 (1956) [Chem. Abstr. 51, 1039d (1957)].
- [14] *M. S. Puhar*, J. chem. Education 47, 473 (1970).
- [15] *A. A. Frost & R. G. Pearson*, "Kinetics and Mechanism", 2nd Ed., p. 165, John Wiley and Sons, Inc. New York; *S. W. Benson*, "The Foundation of Chemical Kinetics", p. 32, McGraw-Hill Inc., New York 1960.
- [16] *P. Müller & B. Siegfried*, unpublished results.
- [17] *R. M. Fuoss*, J. Amer. chem. Soc. 57, 488 (1935); *I. M. Kolthoff, S. Bruckenstein & M. K. Chantooni, Jr.*, J. Amer. chem. Soc. 83, 3927 (1961).
- [18] *G. Kortüm*, "Lehrbuch der Elektrochemie", p. 229, Verlag Chemie, Weinheim 1957.
- [19] *J. E. Prue & P. J. Sherrington*, Trans. Farad. Soc. 1961, 1795.
- [20] *A. R. Martin*, J. chem. Soc. 1930, 530.
- [21] *R. A. Robinson & R. H. Stokes*, "Electrolyte Solutions", p. 550, Butterworth, London 1959.
- [22] *L. F. Fieser & M. Fieser*, "Reagents for Organic Synthesis", p. 1180, J. Wiley & Sons, New York 1967.

287. Abschätzung der Alkali- und Erdalkali-Ionenselektivität von elektrisch neutralen Träger-Antibiotica («Carrier-Antibiotica») und Modellverbindungen

von **W. E. Morf** und **W. Simon**

Laboratorium für Organische Chemie, Eidgenössische Technische Hochschule, Zürich

(15. X. 71)

Summary. Using model calculations, the influence of coordination number, properties of ligand groups, dimension of the ligand, steric interactions, and solvent on the complexation of alkali- and alkaline earth metal cations by electrically neutral ligands (carrier antibiotics, model compounds) is discussed. Information is given on the molecular parameters needed to achieve a given ion selectivity in view of the use of such ligands as carriers in ion selective membranes.

1. Einleitung. – Im Jahre 1966 konnten wir zeigen [1], dass die Ionenselektivität gewisser Antibiotica, die als Träger («Carrier-Antibiotica») einen spezifischen Trans-