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CHROMATOGRAPHIC AND ELECTROPHORETIC STUDY OF ARYLOXYALKYL AMMONIUM COMPOUNDS

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SUMMARY

The chromatographic and electrophoretic behaviour of aryloxyalkyl ammonium compounds, such as 1-alkylpiperidinium bromides, pyridinium bromides, benzyldimethylammonium bromides and trimethylammonium bromides, were studied. The group constants for the aromatic, alkyl and basic parts of the molecules of the compounds studied were determined in the chromatographic system formamide–1,1′,2,2′-tetrachlorethane. In all cases there was good agreement between the calculated and the experimental R_F values. The relationship between the structure of the aryloxyalkyl ammonium compounds and their chromatographic and electrophoretic properties is discussed.

INTRODUCTION

Organic quaternary nitrogenous compounds represent a pharmaceutically interesting group of substances with antimicrobial, fungicidal, local anaesthetic, sympatholytic and other effects. Their surface-active and solubilizing properties[1] are also of importance.

Soon after 1943 when RAWLINS *et al.*[2] prepared a series of these compounds with germicidal activity, increasing interest in them became apparent[3–11]. The solubilizing properties of ammonium salts of the $(Ar\text{-}O(CH_2)_n\text{–}\overset{|}{\underset{|}{N}}\text{–})^+Br^-$ type depend to a great extent on the structure of the solubilizer and on the type of solubilized substance[12]. Basic information concerning the relationship between structure and chemical behaviour of organic ammonium salts can be obtained by partition paper chromatography and electrophoresis. In addition to this, both these methods can be used for a quick check on identity and purity during their preparation.

MATERIALS AND METHODS

Chemicals

The quaternary nitrogenous compounds studied, listed in Table I, were prepared by synthesis according to previously described procedures[12]. The chemicals

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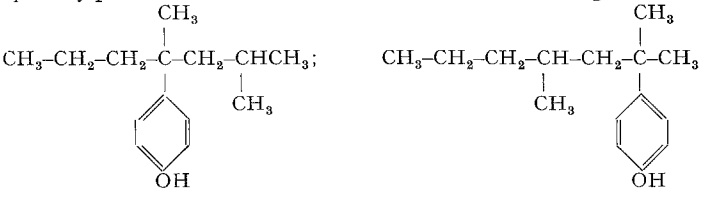
TABLE I

ARYLOXYALKYL AMMONIUM COMPOUND INVESTIGATED

Number	*Chemical name*	*Formula*
I	1-(2-Phenoxycthyl)-1-ethylpiperidinium bromide	$C_{15}H_{24}BrNO$
II	1-(3-Phenoxypropyl)-1-ethylpiperidinium bromide	$C_{16}H_{26}BrNO$
III	1-(4-Phenoxybutyl)-1-ethylpiperidinium bromide	$C_{17}H_{28}BrNO$
IV	1-(5-Phenoxypentyl)-1-ethylpiperidinium bromide	$C_{18}H_{30}BrNO$
V	1-[4-(2-Methoxyphenoxy)butyl]-1-ethylpiperidinium bromide	$C_{18}H_{30}BrNO_2$
VI	1-[4-(3-Methoxyphenoxy)butyl]-1-ethylpiperidinium bromide	$C_{18}H_{30}BrNO_2$
VII	1-[4-(4-*tert.*-Butylphenoxy)butyl]-1-ethylpiperidinium bromide	$C_{21}H_{36}BrNO$
VIII	1-{4-[4-(1,1,3,3-Tetramethylbutyl)phenoxy]butyl}-1-ethylpiperidinium bromide	$C_{25}H_{44}BrNO$
IX*	1-[4-(4-Nonylphenoxy)butyl]-1-ethylpiperidinium bromide	$C_{26}H_{46}BrNO$
X	1-[4-(2-Biphenyloxy)butyl]-1-ethylpiperidinium bromide	$C_{23}H_{32}BrNO$
XI	1-[4-(4-Biphenyloxy)butyl)-1-ethylpiperidinium bromide	$C_{23}H_{32}BrNO$
XII	1-[4-(1-Naphthyloxy)butyl]-1-ethylpiperidinium bromide	$C_{21}H_{30}BrNO$
XIII	1-[3-(2-Naphthyloxy)propyl]-1-ethylpiperidinium bromide	$C_{20}H_{28}BrNO$
XIV	1-[4-(2-Naphthyloxy)butyl]-1-ethylpiperidinium bromide	$C_{21}H_{30}BrNO$
XV	1-[5-(2-Naphthyloxy)pentyl]-1-ethylpiperidinium bromide	$C_{22}H_{32}BrNO$
XVI	1-[6-(2-Naphthyloxy)hexyl]-1-ethylpiperidinium bromide	$C_{23}H_{34}BrNO$
XVII	1-[8-(2-Naphthyloxy)octyl]-1-ethylpiperidinium bromide	$C_{25}H_{38}BrNO$
XVIII	1-[4-(2-Naphthyloxy)butyl]-1-propylpiperidinium bromide	$C_{22}H_{32}BrNO$
XIX	1-[4-(2-Naphthyloxy)butyl]-1-butylpiperidinium bromide	$C_{23}H_{34}BrNO$
XX	1-[4-(2-Naphthyloxy)butyl]-1-pentylpiperidinium bromide	$C_{24}H_{36}BrNO$
XXI	1-[4-(2-Naphthyloxy)butyl]-1-hexylpiperidinium bromide	$C_{25}H_{38}BrNO$
XXII	1-[4-(2-Naphthyloxy)butyl]-1-cyclohexylpiperidinium bromide	$C_{25}H_{36}BrNO$
XXIII	1-[4-(2-Naphthyloxy)butyl]-1-heptylpiperidinium bromide	$C_{26}H_{40}BrNO$
XXIV	1-[4-(2-Naphthyloxy)butyl]-1-octylpiperidinium bromide	$C_{27}H_{42}BrNO$
XXV	1-[4-(2-Naphthyloxy)butyl]-1-nonylpiperidinium bromide	$C_{28}H_{44}BrNO$
XXVI	1-[4-(2-Naphthyloxy)butyl]-1-decylpiperidinium bromide	$C_{29}H_{46}BrNO$
XXVII	1-[4-(2-Naphthyloxy)butyl]-1-undecylpiperidinium bromide	$C_{30}H_{48}BrNO$
XXVIII	1-[4-(2-Naphthyloxy)butyl]-1-dodecylpiperidinium bromide	$C_{31}H_{50}BrNO$
XXIX	1-[4-(2-Naphthyloxy)butyl]-1-tetradecylpiperidinium bromide	$C_{33}H_{54}BrNO$
XXX	1-[4-(4-*tert.*-Butylphenoxy)butyl]pyridinium bromide	$C_{19}H_{26}BrNO$
XXXI	1-{4-[4-(1,1,3,3-Tetramethylbutyl)phenoxy]butyl}pyridinium bromide	$C_{23}H_{34}BrNO$
XXXII*	1-[4-(4-Nonylphenoxy)butyl]pyridinium bromide	$C_{24}H_{36}BrNO$
XXXIII	1-[4-(2-Naphthyloxy)butyl]pyridinium bromide	$C_{19}H_{20}BrNO$
XXXIV	1-[4-(2-Naphthyloxy)butyl]-2-methylpyridinium bromide	$C_{20}H_{22}BrNO$
XXXV	[4-(4-*tert.*-Butylphenoxy)butyl]benzyldimethylammonium bromide	$C_{23}H_{34}BrNO$
XXXVI	{4-[4-(1,1,3,3-Tetramethylbutyl)phenoxy]butyl}benzyldimethylammonium bromide	$C_{27}H_{42}BrNO$
XXXVII*	[4-(4-Nonylphenoxy)butyl]benzyldimethylammonium bromide	$C_{28}H_{44}BrNO$
XXXVIII	[4-(4-Biphenyloxy)butyl]benzyldimethylammonium bromide	$C_{25}H_{30}BrNO$
XXXIX	[4-(2-Naphthyloxy)butyl]benzyldimethylammonium bromide	$C_{23}H_{28}BrNO$
XL	[4-(4-*tert.*-Butylphenoxy)butyl]trimethylammonium bromide	$C_{17}H_{30}BrNO$
XLI	[4-(2-Naphthyloxy)butyl]trimethylammonium bromide	$C_{17}H_{24}BrNO$
XLII	1-(Propyl)-1-ethylpiperidinium bromide	$C_{10}H_{22}BrN$
XLIII	1-(Butyl)-1-ethylpiperidinium bromide	$C_{11}H_{24}BrN$
XLIV	1-(Pentyl)-1-ethylpiperidinium bromide	$C_{12}H_{26}BrN$
XLV	1-(Hexyl)-1-ethylpiperidinium bromide	$C_{13}H_{28}BrN$
XLVI	1-(Heptyl)-1-ethylpiperidinium bromide	$C_{14}H_{30}BrN$
XLVII	1-(Octyl)-1-ethylpiperidinium bromide	$C_{15}H_{32}BrN$
XLVIII	1-(Nonyl)-1-ethylpiperidinium bromide	$C_{16}H_{34}BrN$
XLIX	1-(Decyl)-1-ethylpiperidinium bromide	$C_{17}H_{34}BrN$

* *p*-Nonylphenol used here could be the mixture of following:



constituting the chromatographic system, the universal Britton–Robinson buffer and other auxiliary chemicals were commercial products of analytical grade purity. Similarly the phenols used for the determination of the group constants of the aromatic part of the molecule of the substances studied, were also commercially available products.

Paper chromatography

A descending chromatographic technique was used with a formamide–1,1′,2,2′-tetrachlorethane system. Both phases of the system were mutually saturated. Prior to impregnation of the paper (Schleicher–Schüll 2043b Mgl) the formamide phase was mixed with methanol in the ratio 1:1. The compounds studied were 25 μg samples of the compounds in ethanolic solution, spotted onto the impregnated chromatogram. The chromatograms were kept in chambers saturated with 1,1′,2,2′-tetrachlorethane. The development period took 4–5 h for the front to run a distance of 40 cm from the start. Compounds with a R_F value lower than 0.1 were chromatographed by using an overrun technique. In this case, compound XX was used for front indication. Chromatograms were detected with Dragendorff's reagent after drying the chromatogram at a temperature which did not exceed 110°. All R_F values listed in Table III are averages from 20 chromatograms, where the deviation of the R_F value from that of control substance XX was not more than $\pm$ 0.03.

Electrophoresis

Electrophoretic mobility was determined on Whatman 31 ET paper. We worked with contact platinum electrodes directly on the electropherogram and no buffer reservoir. Britton and Robinson's universal buffer (0.04 M H_3PO_4, 0.04 M H_3BO_3, 0.04 M CH_3COOH and variable amounts of 0.2 M NaOH) was used adjusted to a constant ionic strength of $\mu = 0.2$ by NaCl. Electrophoresis was performed for 1 h with a potential gradient of 10 V/cm and a temperature of 15°. Tetraethylammonium bromide was used as a standard of mobility. Mobilities u ($cm^2 \cdot V^{-1} \cdot sec^{-1}$) were not corrected for electroosmosis.

RESULTS AND DISCUSSION

From the theoretical concepts of paper chromatography the ΔR_M values for the individual parts of molecules of a substance A can be added according to the formula:

$$R_{M(A)} = x\Delta R_{M(m)} + y\Delta R_{M(n)} + z\Delta R_{M(o)} + \ldots K$$

where:

x, y, z = number of functional groups m, n, o in the substance A,

K = constant for the chromatographic system and paper.

Thus, a prerequisite is given for the study of the relationship between structure and chromatographic behaviour of substances.

In the case of substances of the $(Ar\text{-}O(CH_2)_n\text{–}\overset{|}{\underset{|}{N}}\text{–})^+Br^-$ type we have determined constants for the individual parts of the molecule as indicated in the schematic diagram. The suitability of the chromatographic system used is illustrated by the linear dependence of R_M on the number of carbons in homologous series (Fig. 1).

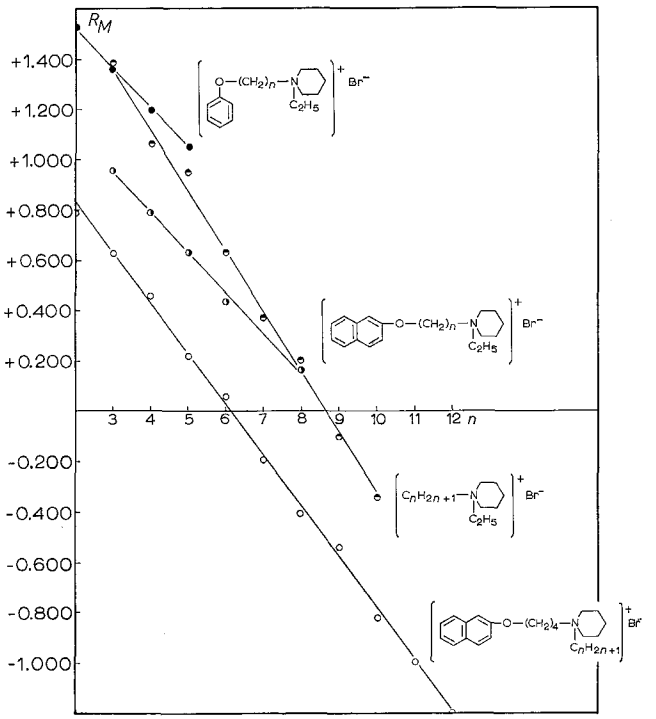


Fig. 1. Dependence of R_M values on the number carbons in an homologous series.

For the aromatic parts of the molecule the group constants (ΔR_M) were computed from the R_F value of relevant phenols according to the formula:

$$\Delta R_M = \log\left(\frac{1}{R_F} - 1\right) - K$$

In this way it is possible to determine the ΔR_M values for all monohydric phenols which display, in the system used, reliable and measurable R_F values. The selection of the phenols (Table II) was determined by the anticipated use of this type of aryloxyalkyl ammonium salt as a solubilizing agent. Further resolution of the aryloxy group into the effect of the substituent, its position etc., would only be of theoretical significance.

Increasing of the number of C atoms in the alkyl substituent on the aromatic nucleus, on the connecting bridge and the nitrogenous part of the molecule influences separation in favour of the non-polar mobile phase (Table III). In an homologous series, C_nH_{2n+1}, where substitution is on the N atom the latter effect is more pronounced than in the case where the series C_nH_{2n} is attached to the connecting bridge. This difference is probably caused by the orientation of the carbon chain of the connecting bridge in the direction of the aromatic nucleus. Such an arrangement in space had been confirmed experimentally in the case of 2-phenoxyethylamine[13] and can be explained as a manifestation of the interaction owing to the varying potential of π–σ bonds[14].

TABLE II

GROUP CONSTANTS

Group	ΔR_M
K-constant for paper and solvent system	−0.024
Carbon atom C_nH_{2n+1}	−0.201
C_nH_{2n}	−0.162
Piperidinium bromide	+2.175
Pyridinium bromide	+2.259
2-Methylpyridinium bromide	+1.963
Benzyldimethylammonium bromide	+1.616
Trimethylammonium bromide	+2.289
Phenoxy	+0.252
2-Methoxyphenoxy	+0.046
3-Methoxyphenoxy	−0.051
2,3-Dimethylphenoxy	−0.407
2,4-Dimethylphenoxy	−0.471
2,5-Dimethylphenoxy	−0.504
2,4,6-Trimethylphenoxy	−0.761
4-*tert.*-Butylphenoxy	−0.683
4-(1,1,3,3-Tetramethyl)phenoxy	−1.143
4-Nonylphenoxy*	−1.380
2-Methyl-5-isopropylphenoxy	−0.850
2-Biphenyloxy	−0.812
4-Biphenyloxy	−0.558
1-Naphthyloxy	−0.371
2-Naphthyloxy	−0.295

* See note to Table I.

Direct determination of group constants for the basic parts of the molecules of the substances studied is impossible in the system used. Data listed in Table II were computed from the differences between the R_M values found and known group constants. Table III shows good agreement of the values found with the ones computed for all compounds studied (with an R_F value not exceeding $\pm$ 0.04). The courses of the mobility curves of the compounds studied (Figs. 2–5) are affected not only by the electromigration phenomena, but also by adsorption on paper. In the case of tetraethylammonium bromide (TEAmmBr), adsorption was not observed.

Measurement of electrophoretic mobility in the series of 2-naphthyloxybutyl nitrogenous quaternary salts (Fig. 2) shows a decrease in mobility in the order trimethylammonium > pyridinium > 2-methylpyridinium > 1-ethylpiperidinium > benzyldimethylammonium. The ΔR_M values for these basic groups also decrease in the same order. Electrophoretic mobility in the series of 1-[4-(2-naphthyloxy)butyl]-1-alkyl piperidinium bromides follows a different course to the mobility of TEAmmBr (Fig. 3). The change in the shape of the curves occurring from C_8 up in the 1-alkylpiperidinium part is caused by the surface activity of these substances (approximatively 40 dyne·cm^{-1} in a concentration of 0.02 *M* (ref. 12)), which is also responsible for the change in the shape of the spots from circular to longitudinal. Lengthening of the connecting carbon bridge between the aromatic part and the basic group results in a decrease of electrophoretic mobility (Fig. 4). Mobilities of 1-alkyl

TABLE III

R_F VALUES OF AMMONIUM COMPOUNDS

Number	*Found*		*Calculated*	
	R_F	R_M	R_F	R_M
I*	0.029	+1.525	0.022	+1.677
II*	0.042	+1.359	0.030	+1.515
III*	0.060	+1.196	0.042	+1.353
IV*	0.082	+1.048	0.059	+1.191
V*	0.10	+0.954	0.08	+1.055
VI*	0.09	+1.005	0.08	+1.050
VII	0.26	+0.454	0.28	+0.418
VIII	0.54	−0.070	0.53	−0.042
IX	0.68	−0.327	0.66	−0.279
X	0.33	+0.308	0.34	+0.289
XI	0.24	+0.501	0.22	+0.543
XII	0.15	+0.753	0.16	+0.730
XIII	0.10	+0.954	0.10	+0.968
XIV	0.14	+0.788	0.14	+0.806
XV	0.19	+0.630	0.19	+0.644
XVI	0.27	+0.432	0.25	+0.482
XVII	0.43	+0.122	0.41	+0.158
XVIII	0.19	+0.630	0.20	+0.605
XIX	0.26	+0.454	0.28	+0.404
XX	0.38	+0.213	0.38	+0.203
XXI	0.47	+0.052	0.50	+0.002
XXII	0.40	+0.176	—	—
XXIII	0.61	−0.194	0.61	−0.199
XXIV	0.72	−0.410	0.72	−0.400
XXV	0.78	−0.545	0.80	−0.601
XXVI	0.87	−0.826	0.87	−0.802
XXVII	0.91	−1.005	0.91	−1.003
XXVIII	0.94	−1.195	0.94	−1.204
XXIX	front	$-\infty$	0.98	−1.606
XXX	0.12	+0.865	0.11	+0.904
XXXI	0.26	+0.454	0.26	+0.444
XXXII	0.34	+0.288	0.38	+0.207
XXXIII	0.06	+1.195	0.05	+1.292
XXXIV	0.09	+1.005	0.08	+1.060
XXXV	0.33	+0.308	0.35	+0.261
XXXVI	0.64	−0.250	0.62	−0.199
XXXVII	0.73	−0.432	0.73	−0.436
XXXVIII	0.25	+0.475	0.24	+0.496
XXXIX	0.20	+0.602	0.20	+0.595
XL*	0.08	+1.061	0.10	+0.934
XLI*	0.06	+1.195	0.05	+1.322
XLII*	0.04	+1.380	0.07	+1.146
XLIII*	0.08	+1.061	0.10	+0.945
XLIV	0.11	+0.954	0.15	+0.744
XLV	0.19	+0.630	0.22	+0.543
XLVI	0.30	+0.368	0.31	+0.342
XLVII	0.39	+0.194	0.42	+0.142
XLVIII	0.56	−0.105	0.53	−0.060
XLIX	0.69	−0.347	0.65	−0.261

* A run-off technique was used.

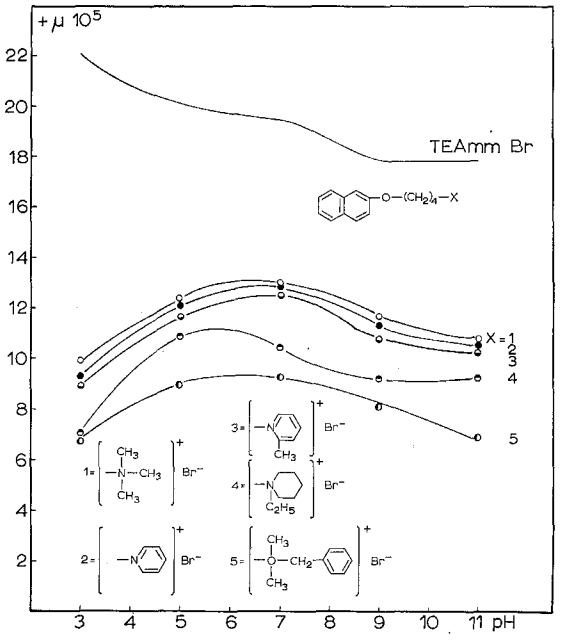


Fig. 2. Electrophoretic mobility of nitrogenous quaternary bromides of general formula as shown.

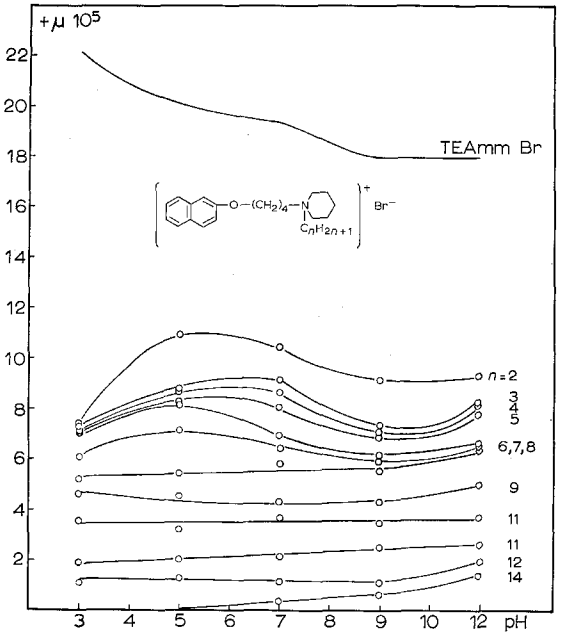


Fig. 3. Electrophoretic mobility of 1-[4-(2-naphthyloxy)butyl]-1-alkyl piperidinium bromides.

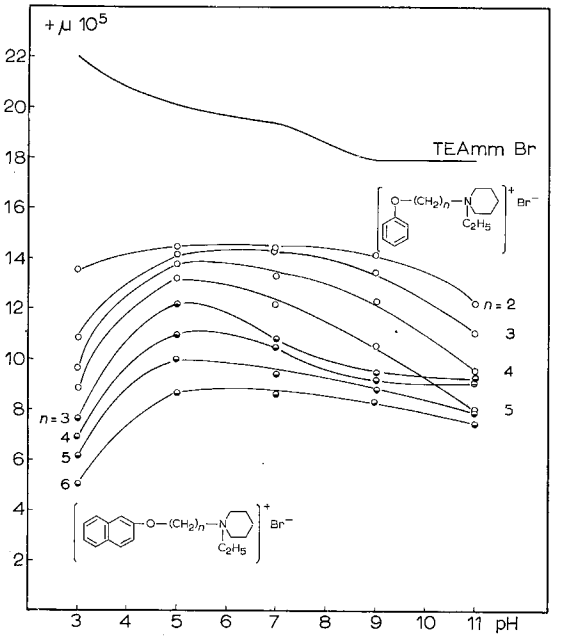


Fig. 4. Effect of chain length on electrophoretic mobility of compounds of general formula as shown.

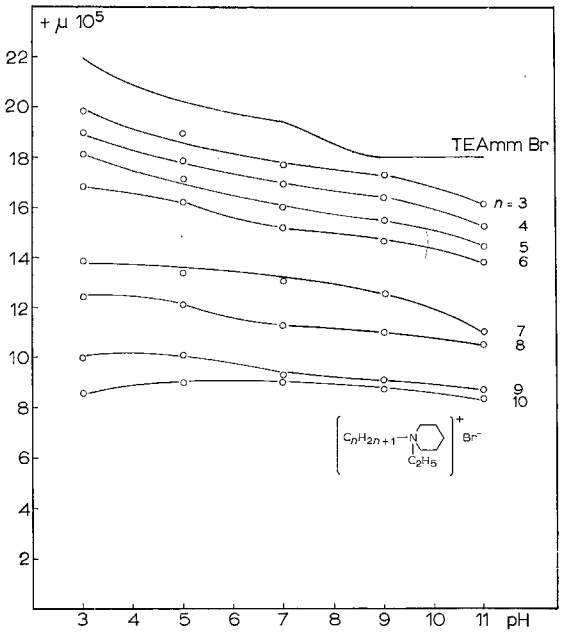


Fig. 5. Electrophoretic mobility of 1-(alkyl)-1-ethylpiperidinium bromides.

ethylpiperidinium bromides with no aryloxy moiety in their molecule (Fig. 5) follow a similar course to TEAmmBr, which is used in the electrophoretic measurements as a standard of mobility.

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