326. *The Dissociation Constants of the Isomeric (—)-Ephedrinium and (+)-ψ-Ephedrinium Ions in Water from 0° to 60°.*

By D. H. Everett and J. B. Hyne.

The thermodynamic acid dissociation constants from 0° to 60° of the positive ions of the isomeric amino-alcohols, (−)-ephedrine and (+)-ψ-ephedrine in water have been determined by an e.m.f. method. The changes in the thermodynamic parameters accompanying the dissociations have been calculated. They are discussed in relation to the stereochemistry of the ephedrine molecules and their positively charged ions, and compared with the corresponding changes for other positively charged (Brönsted–Lowry) acids.

The method of Everett and Wynne-Jones[1,2] for determining the thermodynamic dissociation constants of positively charged acids at a series of temperatures has been extended to the positively charged isomeric (—)-ephedrinium and (+)-ψ-ephedrinium ions in water. The method involves the use of cells with liquid-junction potentials, and the results are analysed in a manner similar to that established in previous papers.[1,2,3]

Experimental

The cells and methods of measurement of e.m.f. were identical with those of Everett, Landsman, and Pinsent.[4] The initial equilibrium in the cells was established at 0° some four hours after commencement of the hydrogen flow. Readings of e.m.f. were normally made at 10° intervals from 0° to 60°, but a few intermediate determinations were made at the lower temtemperatures. 10—12 Hours were required to cover the whole temperature range. Readings were generally reproducible to within ±0·10 mv, although the overall consistency was less satisfactory than in work with simpler amines. After the system had been heated to 60°, the e.m.f.s at lower temperatures were reproduced, showing that no irreversible changes (and in particular no reduction at the hydrogen electrode) occurred during the experiment.

The experimental cell was:

H_2–Pt	Ephedrine hydrochloride [Eph,HCl] (c_2) Ephedrine [Eph] (c_1) KCl (c_3)	KCl (sat.)	HCl (c_4) KCl (c_3)	H_2–Pt

In all cells $c_1 = c_2 = c_4 = c =$ stoicheiometric concentration and $c_3 = (I - c)$ where $I =$ ionic strength.

Materials and Preparation of Solutions.—*(−)-Ephedrine.* Anhydrous (−)-ephedrine was obtained by distilling (−)-ephedrine hemihydrate (from B.D.H.) ($[\alpha]_D^{20}$ +15·5° in H_2O; −4·7° in EtOH) ($[\alpha]_D^{20}$ values are based on weight of ephedrine contained in the hemihydrate) under vacuum and collecting the distillate in a tared flask (b. p. 106—108°/0·5 mm.). A measured volume of hydrogen-saturated conductivity water was added, and after carbon dioxide-free hydrogen had been bubbled through the solution for several hours, it was titrated with standard hydrochloric acid.

(+)-ψ-Ephedrine. (+)-ψ-Ephedrine (from Messrs. Hopkin and Williams Ltd.) was recrystallised once from water and dried by vacuum-desiccation. Its purity (99·7 ± 0·3%) was checked by titration of a weighed amount dissolved in water, and confirmed by measurement of optical rotation ($[\alpha]_D^{20}$ +40·0° in H_2O; +53·0° in EtOH). Solutions were prepared from weighed samples of the recrystallised solid.

Potassium chloride. "AnalaR" potassium chloride was recrystallised from conductivity water, with hot filtration, dried at 140° for 16 hr., and stored over freshly dried silica gel.

Hydrochloric acid. A stock solution of hydrochloric acid was prepared from constant-boiling acid and conductivity water saturated with hydrogen. The acid was stored in a Jena-glass bottle attached to a burette-dispenser. Accurate determination of the normality was made by gravimetric analysis for chloride.

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[1] Everett and Wynne-Jones, *Proc. Roy. Soc.*, 1938, *A*, **169**, 190.

[2] *Idem, ibid.*, 1941, *A*, **177**, 499.

[3] Everett and Pinsent, *ibid.*, 1952, *A*, **215**, 416.

[4] Everett, Landsman, and Pinsent, *ibid.*, p. 403.

Solutions were made up immediately before use with water having a specific conductivity less than $1\cdot0 \times 10^{-6}$. Solutions of the free base were half-neutralised with hydrochloric acid, and weighed amounts of potassium chloride added to bring the ionic strength to the required value. Calibrated Pyrex flasks and Grade A burettes were used. To minimise atmospheric contamination, solutions were transferred to the cells in the presence of a stream of pure hydrogen.

RESULTS

Twenty-four solutions (twelve for each ephedrine) of various ionic strengths (I) and buffer concentrations (c) were studied over the temperature range 0—60°. In three runs the e.m.f.s differed from those expected by more than 5 mv and these results were rejected. The e.m.f.s at round temperatures were obtained by interpolation over small temperature intervals from large-scale graphs, and from them the apparent equilibrium concentration products, $K^{c'}$, of the dissociation $EphH^+ + H_2O \rightleftharpoons Eph + H_3O^+$ were calculated as described previously.[2] Hydrolysis of the amino-alcohol was neglected, as the correction term was small in comparison with the accuracy of the results. The values of $-\log K^{c'}$ are given in Tables 1 and 2. The consistency of results within any one run was much better than the reproducibility in successive runs.

TABLE 1. —log $K^{c'}$ *at various ionic strengths and buffer concentrations for cells containing* (—)-*ephedrine.*

		$-\log K^{c'}$						
I	c	0°	10°	20°	30°	40°	50°	60°
0·30	0·040	10·3730	10·0722	9·7861	9·5131	9·2519	9·0009	8·7532
	0·030	10·3606	10·0603	9·7722	9·4966	9·2260	8·9642	8·7063
	0·020	10·3832	10·0821	9·7958	9·5244	9·2659	9·0190	8·7831
	* 0·000	10·354	10·048	9·767	9·493	9·236	8·980	8·735
0·20	0·060	10·3592	10·0634	9·7785	9·5074	9·2505	9·0080	—
	0·050	10·3587	10·0554	9·7667	9·4928	9·2338	8·9883	—
	0·030	10·3370	10·0370	9·7526	9·4828	9·2252	8·9778	8·7397
	0·020	10·3380	10·0390	9·7562	9·4870	9·2293	8·9820	8·7450
	* 0·000	10·320	10·022	9·737	9·469	9·209	8·968	8·726
0·10	0·030	10·3079	10·0199	9·7397	9·4726	9·2125	—	—
	0·020	10·2986	10·0043	9·7246	9·4562	9·1985	—	—
	0·010	10·2881	9·9917	9·7110	9·4410	9·1796	8·9259	—
	* 0·000	10·283	9·992	9·710	9·443	9·184	—	—

* Extrapolated values.

TABLE 2. —log $K^{c'}$ *at various ionic strengths and buffer concentrations for cells containing* (+)-ψ-*ephedrine.*

		$-\log K^{c'}$						
I	c	0°	10°	20°	30°	40°	50°	60°
0·30	0·030	10·5559	10·2441	9·9504	9·6723	9·4069	9·1547	8·9146
	0·020	10·5615	10·2494	9·9563	9·6788	9·4142	9·1634	8·9226
	0·010	10·5488	10·2403	9·9483	9·6705	9·4073	9·1567	8·9205
	0·005	10·5255	10·2142	9·9216	9·6435	9·3791	9·1286	8·8897
	* 0·000	10·552	10·240	9·947	9·672	9·404	9·163	8·914
0·20	0·030	10·5173	10·2187	9·9271	9·6405	9·3737	9·1179	8·8707
	0·020	10·5163	10·2102	9·9185	9·6426	9·3791	9·1269	8·8860
	0·010	10·5308	10·2215	9·9299	9·6538	9·3917	9·1404	8·8950
	0·005	10·5073	10·1964	9·9005	9·6181	9·3451	9·0749	8·8111
	* 0·000	10·514	10·208	9·915	9·636	9·371	9·123	8·883
0·10	0·020	10·4688	10·1675	9·8795	9·6068	9·3490	9·1001	8·8557
	0·010	10·4905	10·1841	9·8946	9·6202	9·3607	9·1095	8·8625
	0·005	10·4735	10·1646	9·8749	9·5994	9·3334	9·0710	—
	* 0·000	10·475	10·169	9·882	9·604	9·345	9·099	8·854

* Extrapolated values.

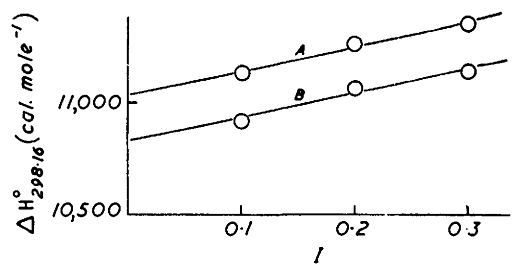
In the usual method of analysis of results[2] liquid-junction effects are eliminated by extrapolation at each ionic strength to zero buffer concentration, and the thermodynamic dissociation constants are obtained by extrapolation to zero ionic strength. The heat, heat capacity, and entropy changes associated with the equilibrium at infinite dilution are then calculated from the temperature dependence of the thermodynamic dissociation constants by using, for example, the equation:

$$\log K = A/T + B \log T + C \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where $A = \Delta H_0^0/2{\cdot}303\boldsymbol{R}$, $B = \Delta C_p^0/\boldsymbol{R}$, and $C = (\Delta S_0^0 - \Delta C_p^0)/2{\cdot}303\boldsymbol{R}$.[5]

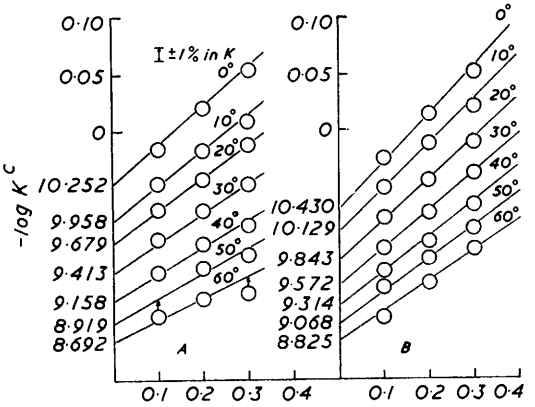
This procedure, using the method of least squares with Gauss multipliers,[6] was followed in the first analysis. However, the lower reproducibility achieved in the present work, compared with that on simple amines, made it difficult to ensure that the heat and heat-capacity values were not influenced by systematic errors introduced in the extrapolations. To eliminate this uncertainty, a second analysis was made in which the results of each individual run were analysed by the method of Everett and Wynne-Jones.[5] It was found that for a given ephedrine B did not vary systematically with either I or c; the mean values were $+10{\cdot}9$ and $+9{\cdot}0$ for (−)-ephedrine and (+)-ψ-ephedrine respectively, with standard deviations of the mean of $\pm 0{\cdot}8$ and $\pm 0{\cdot}3$. Rounded values of 11·000 and 9·000 were used in the subsequent analysis. It was then found that at a given ionic strength A showed no regular variation with c; but the mean values of A at fixed ionic strength varied linearly with I, and enabled A at infinite dilution to be obtained by extrapolation. The values of $\Delta H^0{}_{298{\cdot}16}$ corresponding to the values of A and B are shown as a function of ionic strength in Fig. 1. Although the standard deviations of ΔH may be as high as ±60 cal. mole^{-1}, the difference of 200 cal. mole^{-1} between the results for the two ephedrines is observed at each ionic strength, and indicates that this difference is real. A similar conclusion had been reached in the first analysis.

FIG. 1. *Variation of heat of dissociation of ephedrinium ions at 25° with ionic strength.*



A, (+)-ψ-*Ephedrine.* *B*, (−)-*Ephedrine.*

FIG. 2. *Classical dissociation constants (as* − log K^c*) of ephedrinium ions as a function of ionic strength at various temperatures. [Variation of slope of lines with temperature calculated from data in Fig. 1, extrapolated values from equation* (1) *with appropriate constants. Zero of ordinates not fixed; scale of* − log K^c *given on upper part of ordinates.]*



A, (−)-*Ephedrine.* (*B*), (+)-ψ-*Ephedrine.*

The constant C was then obtained by inserting the values of log K extrapolated to infinite dilution from the first analysis into equation (1) with the appropriate values of A and B; the mean value of C was found and on insertion in equation (1) gave a set of " calculated values " of log K. The self-consistency of the analysis is shown by Fig. 2, where the values of log K^c at each ionic strength are plotted against I. The extrapolated values of log K at zero ionic strength are those calculated from the appropriate equation (1), while the slopes of the lines were obtained in the following way. The slope at one temperature [20° for (−)-ephedrine,

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[5] Everett and Wynne-Jones, *Trans. Faraday Soc.*, 1939, **35**, 1380.

[6] Goulden, " Methods of Statistical Analysis," 2nd edn., Wiley, New York, pp. 138—142.

30° for (+)-ψ-ephedrine] was taken from the best straight line through the experimental points, and that at other temperatures was calculated from the equation: [2]

$$\frac{\partial}{\partial I}\left(\frac{\Delta H}{RT^2}\right) = \frac{\partial}{\partial T}\left(\frac{\partial \ln K}{\partial I}\right) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

The variation of ΔH with I was taken from Fig. 1, and equation (2) was then integrated to obtain the slopes d log K/dI at other temperatures. Apart from a few results for (–)-ephedrine at 50° and 60°, the internal consistency of the analysis is better than ±1% in K. However, the uncertainties in extrapolation to zero buffer concentration may introduce a systematic error up to 2—3% in absolute values of K. The method of analysis ensures, however, that any error influences only ΔG^0 and not ΔH^0 and $\Delta C_p{}^0$.

The parameters of equation (1) and thermodynamic functions at 25° are collected in Table 3 while the final values of log K are given in Table 4 where they are compared with previous work.

Table 3. *Parameters of equation* (1) *and thermodynamic functions at* 25° *for the dissociation of* (–)-*ephedrinium and* (+)-ψ-*ephedrinium ions in water.*

Parameter and thermodynamic function	(–)-Ephedrinium	(+)-ψ-Ephedrinium	Parameter and thermodynamic function	(–)-Ephedrinium	(+)-ψ-Ephedrinium
A (degrees)	–942·96	–1246·07	ΔS^0 (cal. mole^{-1})	–7·35 ± 0·5	–7·42 ± 0·5
B	9·000	11·000	(J mole^{-1})	–30·75 ± 2·0	–31·05 ± 2·0
C	33·601	27·797	ΔC_p (cal. mole^{-1})	22 ± 4	18 ± 2
ΔG^0 (cal. mole^{-1})	13,020 ± 15	13,245 ± 10	(J mole^{-1})	92 ± 16	75 ± 9
(J mole^{-1})	54,475 ± 60	55,420 ± 40			
ΔH^0 (cal. mole^{-1})	10,830 ± 80	11,030 ± 80			
(J mole^{-1})	45,310 ± 350	46,150 ± 350			

(The limits given are approximately twice the standard deviations of the means.)

Table 4. *Thermodynamic dissociation constants of ephedrinium ions* (–log K_a).

Temp.		0°	10°	17·6°	20°	22°	25°	30°	31°	38°	40°	50°	60°
(–)-Ephedrinium	(*a*)	10·252	9·958	9·745	9·679	9·625	9·544	9·413	9·387	9·213	9·158	8·919	8·692
	(*b*)		9·942	9·720			9·522		9·364	9·205			
	(*c*)					9·58 †	9·58 ‡						
(+)-ψ-Ephedrinium	(*a*)	10·430	10·139		9·843	9·787	9·706	9·572			9·314	9·068	8·833
	(*c*)					9·74 †							

(*a*) Calc. from equation (1) with values of A, B, and C from Table 3. (*b*) Values from Äyräpää.[7] (*c*) Other values: † Prelog and Häfliger [8]; ‡ Leffler, Spencer, and Burger.[9]

Äyräpää [7] has determined the dissociation constant of the (–)-ephedrinium ion in water, using a hydrogen–calomel electrode cell with liquid junctions over the temperature range 10—38°. In this range our values of K_a are on the average 4% lower than his. Other workers report figures at a single temperature [8, 9] and, despite the fact that they do not appear to have made a correction for ionic strength, the agreement with the present work is reasonably good. For (+)-ψ-ephedrine only a single value at 22° due to Prelog and Häfliger [8] is available; the agreement with the present determination is only fair.

DISCUSSION OF THERMODYNAMIC FUNCTIONS

The thermodynamic functions for the dissociation of positively charged acids have been discussed by Everett and Wynne-Jones,[2, 5] Everett and Pinsent,[3] Evans and Hamann,[10] and by Everett.[11] The results of the present work can be discussed in essentially similar terms; the relevant data are given in Table 5.

We find that the entropies of dissociation of the two ephedrinium ions (which are secondary ammonium ions) are identical (–7·4 cal. deg.$^{-1}$ mole^{-1}) and lie between values

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[7] Äyräpää, *Svensk Kem. Tidskr.*, 1950, **62**, 135.

[8] Prelog and Häfliger, *Helv. Chim. Acta*, 1950, **33**, 2021.

[9] Leffler, Spencer, and Burger, *J. Amer. Chem. Soc.*, 1951, **73**, 2612.

[10] Evans and Hamann, *Trans. Faraday Soc.*, 1951, **47**, 34.

[11] Everett, *Ind. Chim. belge*, 1951, **16**, 647.

characteristic of simple secondary (*e.g.*, dimethylammonium $\Delta S^0 = -9{\cdot}5$) and primary (*e.g.*, methylammonium, $\Delta S^0 = -4{\cdot}7$) ammonium ions, while the heat-capacity changes are also nearly identical (22 and 18 cal. deg.$^{-1}$ mole^{-1}) and are within experimental error equal to the value characteristic of a simple secondary amine (*e.g.*, dimethylammonium, $\Delta C_p = +19$).

TABLE 5. *Thermodynamic functions for the dissociations of some positively charged acids in water at 25°.*

Acid	ΔG^0 (cal. mole^{-1})	ΔH^0 (cal. mole^{-1})	ΔS^0 (cal. deg.$^{-1}$ mole^{-1})	$\Delta C_p{}^0$ (cal. deg.$^{-1}$ mole^{-1})	Ref.
Ammonium	12,562	12,400	$-0{\cdot}5$	$0{\cdot}0$	1, 12
Methylammonium	14,484	13,092	$-4{\cdot}7$	$+7{\cdot}5$	2, 5
Ethylammonium	14,500	13,580	$-3{\cdot}1$	—	10
Propylammonium	14,360	13,850	$-1{\cdot}7$	$\sim+8$	10, *a*
Butylammonium	14,450	14,070	$-1{\cdot}3$	$\sim+9$	10, *a*
Dimethylammonium	14,721	11,880	$-9{\cdot}5$	$+19{\cdot}0$	2, 5
Trimethylammonium	13,384	8,828	$-15{\cdot}3$	$+41{\cdot}0$	2, 5
2-Hydroxyethylammonium	12,960	12,090	$-2{\cdot}9$	$-1{\cdot}2$	*b*
(−)-Ephedrinium	13,020	10,830	$-7{\cdot}4$	$+22$	This work
(+)-*ψ*-Ephedrinium	13,245	11,030	$-7{\cdot}4$	$+18$	

a, Landsman, unpublished work. *b*, Bates and Pinching, *J. Res. Nat. Bur. Stand.*, 1951, **46**, 349.

The less negative value of ΔS, compared with that of dimethylammonium, may be evidence for a " chain stiffening " effect in the ion, perhaps (see below) associated with restricted rotation in the molecule: we have postulated previously[4] that this influences ΔS much more than ΔC_p. The magnitude of the change is comparable with that observed on passing from the methyl group of methylammonium to the three-carbon chain of propylammonium. The hydroxyl group might, on general grounds, be expected to influence ΔS; but the data for ethylammonium and 2-hydroxyethylammonium suggest that this is not a large effect. That the heat-capacity changes are the same as that for dimethylammonium suggests an almost exact balancing of the effect of introducing additional hydrocarbon substituents near the charge centre, which according to our previous views[4] causes a substantial increase in ΔC_p, and that of the hydroxyl group, which from a comparison of hydroxyethylammonium with other primary amines decreases ΔC_p. If the slightly smaller value for ΔC_p for (+)-*ψ*-ephedrinium is real, this indicates that in its influence on the solvent the hydroxyl group competes more effectively with the hydrocarbon constituents in the *ψ*-ephedrine conformation; if, as suggested below, the *N*-methyl group and the hydroxyl group are adjacent in the *ψ*-ephedrine molecule this effect would be not unexpected.

Because of the similarity between the entropy and the heat-capacity changes of dissociation of the two ephedrine ions, the difference in acid strength [$\delta(\Delta G^0) = 225$ cal. mole^{-1}] is, within the experimental accuracy, attributable to the difference between the heats of dissociation [$\delta(\Delta H^0) = 200$ cal. mole^{-1}]. Consequently our discussion of acid strengths can be limited to a consideration of energy terms. We shall interpret our results on the assumption that the isomeric ephedrine molecules differ in the relative dispositions of the hydroxyl and methylamino-groups, while in the isomeric ions these groups are similarly disposed.

Chemical evidence, concerned mainly with the ease of formation of derivatives of ephedrine and *ψ*-ephedrine, suggests that transition states in which the hydroxyl and methylamino-groups are spatially adjacent are more readily formed by the *ψ*-ephedrines than by the ephedrines.[13] This appears reasonable from a study of molecular models

[12] Everett and Landsman, *Trans. Faraday Soc.*, 1954, **50**, 1221.

[13] Hyne, Ph.D. Thesis, St. Andrews, 1954; Close, *J. Org. Chem.*, 1950, **15**, 1131; Nagai and Kanao, *Annalen*, 1929, **470**, 157; Fodor and Koczka, *J.*, 1952, 850; Welsh, *J. Assoc. Offic. Agric. Chem.*, 1948, **31**, 528; Földi, Földi, and Földi, *Chem. and Ind.*, 1955, 1297.

(Catalin pattern) and is confirmed by approximate calculations we have made of the energetically most favourable conformations, based on a consideration of repulsive interactions between non-bonded atoms and ignoring specific attraction between hydroxyl and methylamino-groups. If we define the conformation by the angle between the planes $C_\beta C_\alpha O$ and $NC_\beta C_\alpha$ (Fig. 3), then in accordance with the generally accepted view[14] the most stable conformations are the staggered orientations at 180° for ephedrine (E_{180}) and 60° for ψ-ephedrine (ψ_{60}). Other, less marked, energy minima are found at 60° (E_{60}) and (E_{300}) for ephedrine, and at 180° (ψ_{180}) and 300° (ψ_{300}) for ψ-ephedrine. The interaction curves are shown schematically in Fig. 4. It is difficult to estimate quantitatively the effect of attractive interactions between hydroxyl and methylamino-groups, but the direction in which they would modify the curves is indicated by the broken lines.

FIG. 3. *The staggered conformations of ephedrine and ψ-ephedrine.* [(+)-*Ephedrine and* (+)-ψ-*ephedrine are shown*]. *Underlined conformations are probable conformations of neutral molecules.*

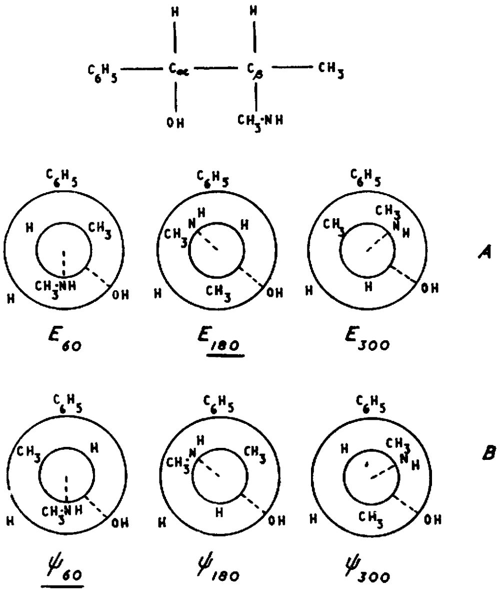
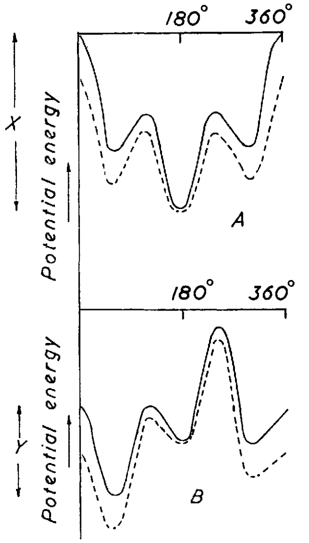


FIG. 4. *Schematic potential energy curves for rotation about the* $C_\alpha C_\beta$ *bond in* (*A*) *ephedrine and* (*B*) ψ-*ephedrine.*



(———) *Ignoring dipole interaction between* OH *and* NHMe.

(– – – –) *Showing probable influence of dipole interaction between* OH *and* NHMe.

It seems unlikely that the most stable conformations of the ephedrinium ions will be the same as those of the corresponding neutral molecules. Ion-dipole interaction between $Me \cdot NH_2^+$ and OH will tend to bring these groups together in *both* ions, and may well overwhelm the steric repulsions. Both ions will probably approximate to the 0° conformation, and this may be further stabilised by hydrogen bonding with solvent water. There is no direct evidence for these conclusions, but Phillips[15] has shown by *X*-ray structure analysis that the $Me \cdot NH_2^+$ and OH groups are adjacent in (—)-ephedrinium hydrochloride crystals, while recent measurements of the magneto-optic effect by Fleming and Saunders[16]

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[14] Brown, McDaniel, and Häfliger in " Determination of Organic Structures by Physical Methods," ed. Braude and Nachod, Interscience Publ. Inc., 1955, p. 654.

[15] Phillips, *Acta Cryst.*, 1954, 7, 159.

[16] Fleming and Saunders, *J.*, 1955, 4150.

can be interpreted as supporting the view that the two positive ions have similar conformations in aqueous solutions. If we assume that both ions have the 0° conformation, and denote the most stable conformations of the neutral molecules by E_m and ψ_m respectively, then the ionisation processes can be represented formally as follows:

$$EH_0^+ \longrightarrow E_0 + H^+ \longrightarrow E_m + H^+ \qquad (2)$$

$$\psi H_0^+ \longrightarrow \psi_0 + H^+ \longrightarrow \psi_m + H^+ \qquad (3)$$

$$\Delta G^0(\text{diss}) \qquad \Delta G^0(\text{rot})$$

The overall free-energy change of the reaction is thus the sum of two terms, the first [ΔG^0(diss)] referring to the dissociation of the proton while the molecule is retained in the 0° conformation, and the second [ΔG^0(rot)] to the rotation of the molecule to its most stable form. It is then reasonable to suppose that the first stages are identical from an electrostatic point of view for both ions,* so that we can equate ΔG^0(diss) for the two ions and attribute the difference between the ionisation constants to the difference between the free-energy changes accompanying the rotation processes:

$$\delta(\Delta G^0) = \Delta G^0(E) - \Delta G^0(\psi) = \Delta G^0(\text{rot})(E) - \Delta G^0(\text{rot})(\psi)$$

Expressed in terms of the standard chemical potentials of the various conformations we have:

$$\left.\begin{aligned}\delta(\Delta G^0) &= [\mu^0(E_m) - \mu^0(E_0)] - [\mu^0(\psi_m) - \mu^0(\psi_0)]\\ &= (Y - X)\ (\text{see Fig. 4}) = -225\ \text{cal. mole}^{-1}\end{aligned}\right\} \qquad (4)$$

We conclude therefore that E_m is more stable, relative to E_0, than ψ_m is relative to ψ_0. If chemical reaction in, for example, condensation reaction occurs through a transition state in which the ephedrine or ψ-ephedrine has to achieve the 0° conformation, then we shall expect such reactions to be somewhat faster for ψ-ephedrine, although the effects should not be large. It may be noted, furthermore, that the effect of dipole interaction between hydroxyl and methylamino-group is, for ephedrine, to bring the potential energies of the E_{60} and E_{300} conformations down closer to that of E^{180}: if these energies were equal then, at equilibrium, ephedrine would consist of a mixture of the three conformations in equal amounts. The 0° transition state can be formed directly from E_{60} and E_{300}, but E_{180} can reach the transition state only by passing through E_{60} or E_{300}. If the energy barrier separating E_{180} from the other two conformations were high, then a second factor inhibiting the rate of reaction of ephedrine would result.

An interpretation of the relative strengths of the isomeric ephedrinium ions has been given previously by Prelog and Häfliger.[8, 14] It is, however, not quite clear from their paper whether they suppose the ions to retain the conformation of the neutral molecules. They state that hydrogen bonding of the hydroxyl and methylamino-groups will tend to occur through the solvent structure, and they attribute the difference in acid strength to the fact that this tendency is favoured by the configuration of (+)-ephedrine and opposed by that of (−)-ephedrine.

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* A second-order effect might arise if, for example, the detailed electron-density distribution in a methyl group, and hence its interaction with a proton, were dependent on the nature of the spatially adjacent groups in the molecule.