456. *Unstable Optical Activity in the* N-*Benzoyldiphenylamine-2-carboxylic Acid Series. Part V.**

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The optical stabilities of some substituted *N*-benzoyldiphenylamine-2-carboxylic acids are discussed from the viewpoint of newly determined racemisation velocity constants and of E, A, and $\Delta S^{\ddagger}$ values.

MUCH evidence [1,2,3] supports a certain sequence of optical stabilities in the series of substituted *N*-benzoyldiphenylaminecarboxylic acids (I) † which owe their optical activity to restriction of rotation about one, or perhaps two, carbon–nitrogen bonds. The velocity constants for racemisation of six such acids (the more optically stable) were measured at 20° in chloroform containing 2·5% of ethanol; [3] we now report the measurement of racemisation velocity constants for four more acids (the less optically stable) under identical conditions of solvent and concentration, so that the optical stabilities of ten acids closely related structurally can now be strictly compared at one temperature (Table 1).

TABLE 1. *Racemisation velocity constants k (min.*$^{-1}$*) for substituted* N-*benzoyldiphenylamine-2-carboxylic acids, A at* 20° *in* $CHCl_3$–2·5% EtOH *and B at* 9·9° *in* $CHCl_3$.

Acid	4	6	2′	4′	*k* (*A*)	*k* (*B*)	$t_{\frac{1}{2}}$ (*A*) (min.)	$t_{\frac{1}{2}}$ (*B*) (min.)
(I*a*)	—	Me	—	—	0·72	0·146	0·96	4·7
(I*b*)	—	Me	Me	—	0·61	—	1·1	—
(I*c*)	Br	Br	—	—	0·50	—	1·4	—
(I*d*)	Br	Br	—	Br	0·44	—	1·6	—
(I*e*)	—	Me	F	—	0·214 (0·209 *)	—	3·2	—
(I*f*)	—	Me	Cl	Me	0·166 (0·167 *)	—	4·2	—
(I*g*)	—	Me	Cl	—	0·147 *	—	4·7	—
(I*h*)	—	Me	Br	—	0·119 (0·115 *)	—	5·8	—
(I*i*)	—	Me	Cl	Cl	0·0929 *	—	7·5	—
(I*j*)	—	Me	Cl	Br	0·0862 *	—	8·0	—
(I*k*)	—	Me	—	Me	—	0·158	—	4·4

* See ref. 3.

These four acids, too unstable for resolution, were obtained optically active by crystallisation of alkaloidal salts in which a single diastereoisomer separated in approximately 100% yield (second-order asymmetric transformation). Yet another acid, *N*-benzoyl-6 : 4′-dimethyldiphenylamine-2-carboxylic acid (I*k*), could not be obtained active in this way as none of its alkaloidal salts crystallised. However, a chloroform solution of the (—)-acid was prepared by asymmetric transformation in solution (first-order) in presence of cinchonidine: the alkaloid was then removed by washing with hydrochloric acid, and the remaining chloroform solution washed, dried, and used immediately for determination of the racemisation rate. Thus a velocity constant in chloroform was obtained which could be compared with one, measured also under these enforced conditions, for *N*-benzoyl-6-methyldiphenylamine-2-carboxylic acid (I*a*). The predicted order of optical stabilities [3] has been upheld. Acid (I*a*) was not previously known as an optically active solid, although the active acid had been obtained in solution.

Racemisation velocity constants still form the most widely used criterion for comparing optical stabilities; in this work they provide a series of values which, in a roughly qualitative way, accords with predictions based on the bulk and inductive effects of groups substituted in a common skeleton. Any group added to the skeleton may change the racemisation rate in three ways: by direct electrical effects, by transmitted electrical effects, or, if it is suitably placed, sterically. It was at first somewhat surprising that

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* Parts I—IV, *J.*, 1938, 1646; 1940, 264; 1955, 145, 4152.

† *Correction*: In Part IV, formula (III) (p. 4153), the R which appears in position 4 should read R′.

[1] Jamison and Turner, *J.*, 1938, 1646.

[2] *Idem, ibid.*, 1940, 264.

[3] Harris, Potter, and Turner, *ibid.*, 1955, 145.

there was so little difference between the velocity constants of racemisation of the 6-methyl- and the 6 : 2′-dimethyl-acid (I*a*) and (I*b*). The experimental results could be explained, to some extent at least, if addition of the second (2′) methyl group in the 6 : 2′-dimethyl-acid (I*b*) had opposing influences on the optical stability : the bulk of the methyl group increasing it and the electron-releasing power decreasing it (see ref. 3). The 6 : 4′-dimethyl-acid (I*k*) was synthesised to test this hypothesis : here the bulk effect of the methyl group is removed from the sphere of hindrance but its electrical effect remains the same as in the 6 : 2′-dimethyl-acid (I*b*). Acid (I*k*) proved to be slightly but definitely *less* stable than the 6-monomethyl-acid (I*a*) at 9·9°; therefore the remote methyl group exercises an accelerating influence on the racemisation. It should be noted in comparison that the 2′-fluoro-6-methyl-acid (I*e*) is much more stable optically than the 6 : 2′-dimethyl-acid (I*b*) in spite of the fact that the van der Waals radii of the fluorine atom and the methyl group are respectively 1·35 and 2·05 Å ; [4] in the 2′-fluoro-6-methyl-acid (I*e*) both the steric and the electrical influences of the fluorine atom appear to be decelerating relative to hydrogen.

The Arrhenius parameters *E* and *A* have been measured [1, 5, 6] for the racemisation of a variety of compounds owing their optical activity to restriction of rotation. Comparisons between the values so determined have not been entirely satisfactory [7, 8] owing, partly, to the diversity of structure in the compounds concerned and also to the different solvents and other conditions used in determining the necessary velocity constants of racemisation. As a preliminary experimental approach, racemisation velocities have been measured over a range of temperatures and *E*, *A*, and the entropies of activation $\Delta S^{\ddagger}$ (Table 2) have been calculated for the five substituted acids, 6-methyl-, 4 : 6-dibromo-, 2′-fluoro-6-methyl-, 2′-chloro-6 : 4′-dimethyl-, and 2′-bromo-6-methyl- (I*a*, *c*, *e*, *f* and *h*), in chloroform containing 2·5% of ethanol; two other sets of determinations for the 4 : 6 : 4′-tribromo- (I*d*) and the 2′-chloro-6-methyl-acid (I*g*), were made in different solvents.

TABLE 2. *Velocity constants, Arrhenius parameters, and entropy factors for racemisation.*

Acid	10^2k (sec.$^{-1}$)	Temp.	*E* (kcal. mole^{-1})	*A* (sec.$^{-1}$)	$\Delta S^{\ddagger}$ (e.u.)
Solvent : Chloroform containing 2·5% of ethanol (by volume).					
(I*a*)	1·20	20·0°	16·2	$10^{10\cdot1}$	−14·1
	0·660	13·8			
	0·327	6·9			
	0·162	0·6			
(I*c*)	0·833	20·0	19·3	$10^{12\cdot0}$	− 4·1
	0·288	10·8			
	0·0858	1·0			
	0·0817	0·6			
(I*e*)	0·663	27·4	14·9	$10^{8\cdot6}$	−20·9
	0·357	20·0			
	0·109	6·9			
(I*f*)	0·654	29·8	15·7	$10^{9\cdot1}$	−18·6
	0·277	20·0			
	0·108	10·2			
	0·0410	0·7			
(I*h*)	0·601	32·0°	16·4	$10^{9\cdot5}$	−16·9
	0·562	31·8			
	0·198	20·0			
	0·0795	10·8			
	0·0274	0·6			
Solvent : Ethanol					
(I*d*)	0·448 [a]	17·7	18·7	$10^{12\cdot2}$	− 6·9
	0·185	9·5			
	0·0603	0·65			
Solvent : Chloroform containing 6·9% of ethanol (by volume).					
(I*g*)	0·483 [b]	25·4	16·6	$10^{9\cdot7}$	−15·4
	0·308	20·6			
	0·0738	6·3			

[a] See ref. 1. [b] Potter, Thesis, London, 1953.

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[4] Waters, " Physical Aspects of Organic Chemistry," Routledge, London, 1950, p. 58.

[5] Kuhn and Albrecht, *Annalen*, 1927, **455**, 272; **458**, 221; Li and Adams, *J. Amer. Chem. Soc.*, 1935, **57**, 1565; Kistiakowsky and Smith, *ibid.*, 1936, **58**, 1043; Mills and Kelham, *J.*, 1937, 274; Adams and Kornblum, *J. Amer. Chem. Soc.*, 1941, **63**, 188; Rieger and Westheimer, *ibid.*, 1950, **72**, 19; Newman and Powell, *J.*, 1952, 3747; Hall, *ibid.*, 1956, 3674.

[6] Armarego and Turner, *ibid.*, 1956, 3668.

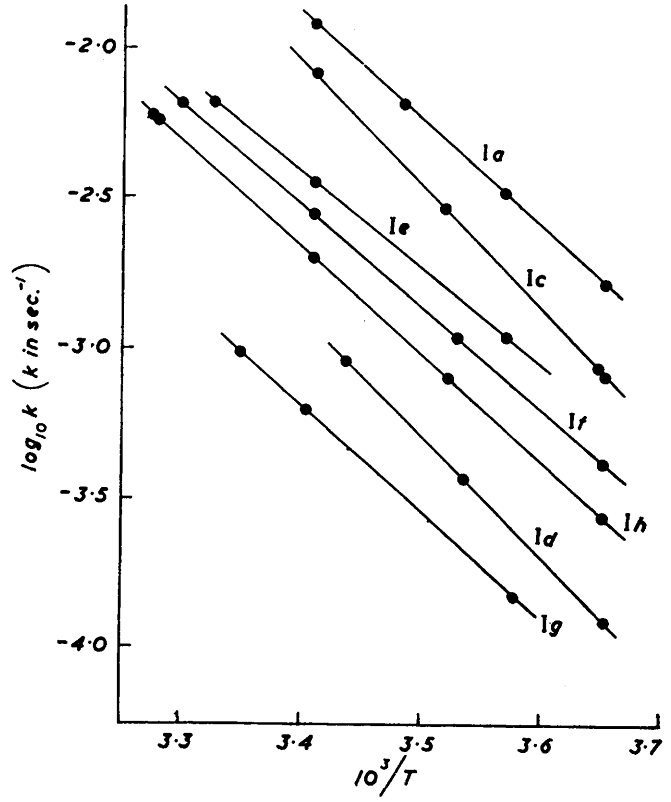
[7] Cagle and Eyring, *J. Amer. Chem. Soc.*, 1951, **73**, 5628.

[8] de la Mare, " Progress in Stereochemistry," Vol. I, Butterworths, London, 1954, p. 120.

The range of temperature employed in the determination of E is to a large extent dictated by the rapidity of racemisation at the higher temperatures and by the solubility (including the rate of dissolution) at the lower ones. Chloroform containing 2·5% of ethanol by volume has been the most generally useful solvent for the present series of acids.

The racemisation velocity constants k are calculated from $k = (1/t) \ln (\alpha_0/\alpha_t)$; as there is no asymmetric influence present, a rate constant, measured for racemisation, is twice the rate constant for inversion of configuration, the physical process occurring on the molecular scale. In Fig. 1 $\log_{10}k$ is plotted against the reciprocal of the absolute temperature: the relation is closely linear. $\Delta S^\ddagger$ is calculated from the formula (see Appendix)

FIG. 1. *Arrhenius plots for racemisation of substituted* N-*benzoyldiphenylamine-2-carboxylic acids.*



The plots for I*d* and I*g* have been displaced 0·7 unit lower on the $\log_{10} k$ scale.

$$k = \kappa e(\boldsymbol{k}T/\boldsymbol{h}) \exp (\Delta S^\ddagger/\boldsymbol{R} - E/\boldsymbol{R}T)$$

in which E is the experimentally determined energy of activation; the transmission coefficient κ has been assumed to be unity.

It is immediately apparent that arguments based on racemisation velocity constants measured at one temperature may lead to different conclusions from those based on E values for racemisation. One can speak of either the 6-methyl- (I*a*) or the 2′-fluoro-6-methyl-acid (I*e*), for example, as the more optically stable of the two according to which criterion is used.

Scrutiny of the E, A, and $\Delta S^\ddagger$ values (Table 2) shows that the acids fall into two groups: (1) Those with a 6-methyl substituent have rate equations of racemisation whose energies of activation are 14·9—16·6 kcal. mole^{-1}, *A* factors $10^{8·6}$—$10^{10·1}$ sec.$^{-1}$, and entropies of activation —14·1 to —20·9 e.u. (2) Those with a 6-bromo-substituent have the values, respectively, 18·7 and 19·3 kcal. mole^{-1}, $10^{12·0}$ and $10^{12·2}$, —4·1 and —6·9 e.u. The grouping of these figures is compatible with the view that among the various acids so far examined it is the resistance to relative rotation about bond (*a*) [see (I)] which is responsible for optical stability.

There are, of course, two paths by which a rotation about bond (*a*) might take place; the benzoyl group might pass the carboxylic acid group in position 2 (II) or, alternatively, it might pass the substituent in position 6 (III). If position 6 carries hydrogen only, the optical stability is very slight indeed and mutarotation is not detectable at room temperatures, even when ring A carries a chlorine atom or a methyl group in an *ortho*-position. [Interference with rotation will be less than appears in formulæ (II) and (III); for example the plane of ring A in the passing position probably lies roughly perpendicular to the plane of ring B.] It is probable that structure (III) represents the most favourable passing position for the 6-methyl compounds studied, since the >C=O group would, presumably, avoid passing the similarly negative $-CO_2H$ group: Hall, Ridgwell and Turner [9] have summarised evidence which indicates that polar repulsions between two suitably placed carboxylic acid groups can exert a strongly accelerating influence on a diphenyl-type racemisation. The repulsive force envisaged in the present case would be smaller, but probably large enough to determine which of two alternative paths should be followed.

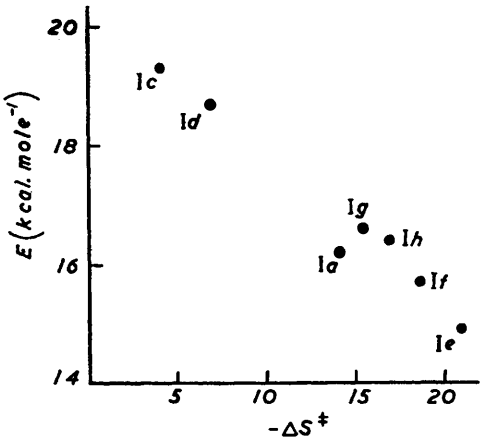
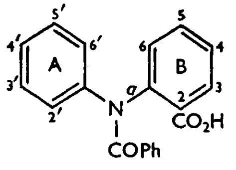
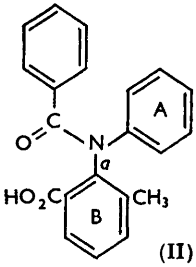


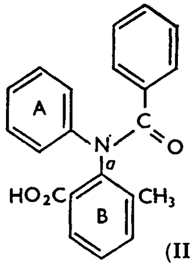
FIG. 2. *The grouping of the energies and entropies of activation.*



(I ; for key see Table I)



(II)



(III)

The variations of $\Delta S^{\ddagger}$ appear to make a positive contribution to the interpretation of of the optical stabilities. First, the grouping (Fig. 2) suggests a difference between the

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[9] Hall, Ridgwell, and Turner, *J.*, 1954, 2498.

4 : 6-di- and the 4 : 6 : 4′-tri-bromo-acids (I*c*) and (I*d*) and the others; reference to models, and the high values of the energies of activation, support the possibility that the alternative passing position [represented by (II), but with bromine in place of methyl] might be used in these two cases. Secondly, as Cagle and Eyring [7] have pointed out in discussing the optical stability of another type of compound showing restriction of rotation, high negative values of $\Delta S^{\ddagger}$ would be expected when the transition state for racemisation is an improbable arrangement of the molecule. Foster, Cope, and Daniels,[10] studying the rearrangement of α-*cyclo*hex-1-enylallylmalononitrile to 2-allyl*cyclo*hexylidenemalononitrile by following the change in refractive index, found a fairly large negative entropy of activation and attributed it to the complicated and improbable shape which the molecule must attain for the rearrangement to take place. Models of the molecules now under discussion show that rings A and B not only must each take up favourable positions but their movements must also be synchronised for rotation about bond (*a*) to occur. Such synchronisation should be easier in the 6-methyl- (I*a*), 4 : 6-dibromo- (I*c*), and 4 : 6 : 4′-tribromo-acids (I*d*) because ring A is both unsubstituted in the *ortho*-positions and axially symmetrical; the bromo-acids (I*c*) and (I*d*) have the small negative $\Delta S^{\ddagger}$ values already noted, while the methyl-acid (I*a*) has the smallest negative value of all the 6-methyl-acids so far investigated. An *ortho*-substituent in the ring A, *i.e.*, in the 2′-fluoro-, 2′-chloro-, and 2′-bromo-6-methyl-acids (I*e*, I*f*, I*h*, and I*g*), will, both by its bulk and by its polar attractions and repulsions, lower the number of ways of attaining the transition state and will cramp movement in it. Restriction of oscillation and rotation in the activated state would be expected to be accompanied by a relatively high negative value of $\Delta S^{\ddagger}$ and such is found to be the case.

Further, within the set of acids 6-methyl- (I*a*), 2′-fluoro-6-methyl- (I*e*), 2′-chloro-6 : 4′-dimethyl- (I*f*), 2′-bromo-6-methyl- (I*h*), and 2′-chloro-6-methyl- (I*g*), there may be additional rigidity of the transition state arising from polar interactions between the carbonyl and the 6-methyl groups (III). This effect, which would also enhance the negative value of $\Delta S^{\ddagger}$, is absent in the di- and tri-bromo-acids (I*c*) and (I*d*), which have much smaller negative values for $\Delta S^{\ddagger}$.

A possibility which should be considered is that of π-hydrogen bonding between the phenyl group and the methyl group [11] which could become operative if structure (II) represented the passing position. Comparison of the $\Delta S^{\ddagger}$ values for the 6-methyl- and the 2′-fluoro-6-methyl-acid (I*a*) and (I*e*), in which ring A of (I*a*) should be the better electron donor,[12] makes this possibility seem unlikely. The values for the di- and tri-bromo-acids (I*c*) and (I*d*) are too close for valid comparison with each other, particularly as they are derived from measurements in different solvents.

In the development of arguments concerning intramolecular attractions of the hydrogen-bonding type a clear differentiation must be kept between bonds which might stabilise the (+)- and the (−)-form and those which would add rigidity to the transition complex. The former would lead to a decrease in the value of the racemisation velocity constant in the manner indicated by Jaffé, Freedman, and Doak,[13] unless they held the molecule close to the passing position thus overcoming some of the group repulsion; this effect has already been noted where formal bonds are concerned.[6] Hydrogen bonding which operates in the transition state and not (or with diminished strength) in the two interconvertible forms will become apparent in the $\Delta S^{\ddagger}$ values. A study of the effect of solvent in $k_{\text{racem.}}$, E, A, and $\Delta S^{\ddagger}$, on which preliminary experiments have already been made, should throw light on this. Chloroform, for example, might be expected to allow the greater freedom for intramolecular bonding, while ethanol would compete with the substrate and break down internal bonds in both the normal and the transition states.

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[10] Foster, Cope, and Daniels, *J. Amer. Chem. Soc.*, 1947, **69**, 1893.

[11] Braude and Jackman, " Determination of Organic Structures by Physical Methods," Academic Press Inc., New York, 1955, p. 719.

[12] Tamres, *J. Amer. Chem. Soc.*, 1952, **74**, 3375.

[13] Jaffé, Freedman, and Doak, *ibid.*, 1954, **76**, 1548.

EXPERIMENTAL

All measurements of rotation, α_{5461}, were made in a 2-dm. jacketed tube thermostatically controlled. " Solvent X " is chloroform containing 2·5% of ethanol by volume.

N-*Benzoyl-6 : 4′-dimethyldiphenylamine-2-carboxylic Acid*.—This acid was prepared by the general method [14, 1, 2] involving the Chapman rearrangement [15] of the corresponding imidate. (a) *2-Methoxycarbonyl-6-methylphenyl* N-*4′-methylphenylbenzimidate* was crystallised from ethanol, and had m. p. 100—101° (Found: C, 77·0; H, 6·0; N, 3·85. $C_{23}H_{21}O_3N$ requires C, 76·85; H, 5·9; N, 3·9%). (b) The imidate isomerised at 275° giving *methyl* N-*benzoyl-6 : 4′-dimethyldiphenylamine-2-carboxylate* which crystallised from methanol in prisms, m. p. 122° (70% yield) (Found: C, 76·3; H, 5·7; N, 3·7. $C_{23}H_{21}O_3N$ requires C, 76·85; H, 5·9; N, 3·9%). (c) N-*Benzoyl 6 : 4′-dimethyldiphenylamine-2-carboxylic acid*, crystallised from aqueous ethanol and dried (P_2O_5) in a vacuum, had m. p. 158—159° (yield 98%) (Found: C, 76·5; H, 5·53; N, 4·1. $C_{22}H_{19}O_3N$ requires C, 76·5; H, 5·56; N, 4·1).

(−)-N-*Benzoyl-6 : 4′-dimethyldiphenylamine-2-carboxylic Acid in Chloroform Solution by First-order Asymmetric Transformation in Presence of Cinchonidine*.—(±)-Acid (0·345 g., 0·01 mole) and cinchonidine (0·294 g., 0·01 mole) were dissolved in chloroform (25 c.c.) and set aside for 2 hr. At time $t = 0$ (min.) the solution was washed with ice-cold concentrated hydrochloric acid, then with ice–water, dried (Na_2SO_4), and filtered into a polarimeter tube previously cooled to 9·9°. At time $t = 2{\cdot}80$ (min.) α was −1·61° and gradually fell to 0·0°; $k_{\text{racem.}} = 0{\cdot}158$. Repetition gave an identical value for k.

Brucine (−)-N-*Benzoyl-6-methyldiphenylamine-2-carboxylate*.—The (±)-acid (3·31 g., 0·1 mole) and anhydrous brucine (3·94 g., 0·1 mole) were each dissolved separately in 100 c.c. of hot acetone. The mixed solutions were evaporated to 75 c.c., light petroleum (b. p. 40—60°) was added until crystallisation started, and the whole kept warm while the salt [brucine (−)-acid] crystallised (yield ≃100%). Decomposition of this salt with cold, anhydrous formic acid, followed by precipitation by dilute hydrochloric acid, gave the (−)-acid [(1) α first observed −1·94° at 0·6°, solvent X, c 0·400, $[\alpha]^{0{\cdot}6^\circ}$ −243°; (2) α first observed −5·11° at 20°, chloroform, c 1·324, $[\alpha]^{20^\circ}$ −193°, half-life 0·96 min. at 20°].

APPENDIX

For a unimolecular reaction in the liquid phase $k = \kappa(\gamma^0/\gamma^\ddagger)(\mathbf{k}T/\mathbf{h})K^\ddagger$, where γ^0 and $\gamma^\ddagger$ are the activity coefficients for normal and activated reactant species respectively; $K^\ddagger = \exp\,(\Delta S^\ddagger/\mathbf{R} - \Delta H^\ddagger/\mathbf{R}T)$ is the expression for the modified equilibrium constant between normal and activated species.[16] If we assume that $\kappa = 1$ and that the activity coefficients are equal because the two species are so similar, and since $E = \mathbf{R}T^2(\mathrm{d}\log_e k/\mathrm{d}T)$ and $\mathrm{d}\log_e k/\mathrm{d}T = 1/T + \mathrm{d}\log_e K^\ddagger/\mathrm{d}T$,

$$E = \mathbf{R}T + \mathbf{R}T^2(\mathrm{d}\log_e K^\ddagger/\mathrm{d}T) = \mathbf{R}T + \Delta H^\ddagger - p\mathrm{d}v^\ddagger$$

where $\mathrm{d}v^\ddagger$ is the increase in volume accompanying activation. For our reactions $\mathrm{d}v^\ddagger = 0$, hence $\Delta H^\ddagger = E - \mathbf{R}T$ and $k = (\mathrm{e}\mathbf{k}T/\mathbf{h})\exp\,(\Delta S^\ddagger/\mathbf{R} - E/\mathbf{R}T)$.

Cagle and Eyring [7] use the equation in the form $k = (\kappa\mathbf{k}T/\mathbf{h})\exp\,(\Delta S^\ddagger/\mathbf{R} - \Delta H^\ddagger/\mathbf{R}T)$. It is not uncommon for the experimentally determined value E to be used in place of $\Delta H^\ddagger$ in this form of the equation, an approximation which has sometimes led to confusion (see refs. 10 and 17) and which seems unnecessary in our calculations. If the approximation were used, all the $\Delta S^\ddagger$ values in Table 2 would be about two units less negative.

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[14] Jamison and Turner, *J.*, 1937, 1954.
[15] Chapman, *ibid.*, 1929, 569.
[16] Wynne-Jones and Eyring, *J. Chem. Phys.*, 1935, 3, 492.
[17] Daniels, " Outlines of Physical Chemistry," Wiley, New York, 1948, p. 382.