Induced Circular Dichroism. Part III.[1,2] Chiroptical Properties and Ion-pair Equilibria in 2-Benzoylbenzoic Acid–Amphetamine

By **Shunsuke Takenaka, Keizo Kondo, and Niichiro Tokura,*** Department of Applied Chemistry, Faculty of Engineering, Osaka University, Suita, Osaka 565, Japan

The molecular ellipticity of the induced circular dichroism (i.c.d.) of the 2-benzoylbenzoic acid–amphetamine system is highly dependent not only on the polarity of solvent but also on the concentration of the salt and the change in temperature. The i.c.d. effect at various concentrations of the salt indicates that the ion-pair dissociates at concentrations below 10^{-3}M, and aggregates to form triple and/or quadruple ions at concentrations over 10^{-2}M in non-polar solvents. The magnitude of the i.c.d. effect is affected mainly by two factors, the intramolecular rotation and the ion-pair equilibrium. The enthalpy of chiroptical induction, ΔH, due to the intramolecular rotation is estimated as 1 ± 0.5 kcal mol^{-1} which is independent of the polarity of the solvent. The ΔH value due to ion-pair equilibrium is very large and strongly dependent on the solvent polarity. A plot of the ΔH *versus* E_T for various solvents resulted in two straight lines, one for benzenoid solvents and the other for aliphatic solvents. The significance of the ΔH values is discussed.

It has been reported that the 2-benzoylbenzoic acid–amphetamine system (1 : 1 salt) shows a large Cotton effect for the *n*–π* transition of the carbonyl group in various solvents[1] except those of high polarity. The induced circular dichroism (i.c.d.)[2-5] in this system is the first instance in which the effect is highly dependent on the polarity of the solvent giving an inversely linear relationship between the solvent polarity (E_T values of Dimroth and Reichardt[6]) and the molecular ellipticity $[\theta]_{max.}$. Using the assumption that the solvent effect on the i.c.d. arises from ion-pair equilibria, the effect of solvents on the magnitude of i.c.d. has been investigated for many ethereal solvents.[2] These results indicate that the progress of ion-pair dissociation due to solvation of the organic cation by ethers is the cause of the reduction of the size of the i.c.d. and the presence of a contact ion-pair is the origin of the i.c.d. Consequently, the effect of solvent on the i.c.d. must arise from an equilibrium between the contact and solvent separated ion-pairs. We report here an investigation into the effect of equilibrium of both ion-pairs on the i.c.d. in various aromatic, aliphatic, and ethereal solvents. For this purpose, concentration and temperature effects on the i.c.d. were also investigated. To estimate the contribution of free ions to the i.c.d., conductivity measurements on the salt were also carried out.

EXPERIMENTAL

R-(−)-Amphetamine, b.p. 85—87° at 18 mmHg, $[\alpha]_D^{20}$ −33.0° (neat), was used. Solvents of analytical grade were distilled twice before use. Other preparations were described previously.[2]

C.d. measurements were taken with a JASCO model J-10 automatic spectrometer using a quartz cell of 1 or 10 cm width. The molecular ellipticity, $[\theta]_{max.}$, was evaluated by the equation $[\theta]_{max.} = 3\,300\ A_{lr}/cl$ where A_{lr} is a difference absorbance between the left and right circularly polarized lights, l is the path length of the light (1 or 10 cm), and c is the concentration of the salt. Temperature variation was kept within ±1°. Conductivity measurements were made with Yanagimoto Seisakusho model MY-64 apparatus using a cell (cell constant, 0.301 mho cm^{-1}) at 22 ± 1°. Direct conductivity measurements for the individual solvents were estimated using the equation $L = R \times S \times C$ where L, R, S, and C are true conductivity reading, reading on scale, range factor, and cell constant, respectively.

RESULTS

Conductivity Measurements on the I.c.d. System.—Conductivity of the i.c.d. system of 2-benzoylbenzoic acid–amphetamine (1 : 1 salt) was measured in various solvents with results shown in Table 1. An approximation of the

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[1] Part I, N. Tokura, T. Nagai, S. Takenaka, and T. Oshima, *J.C.S. Perkin II*, 1974, 337.

[2] Part II, S. Takenaka, K. Kondo, and N. Tokura, *J.C.S. Perkin II*, 1975, 1749.

[3] S. F. Mason and B. J. Norman, *Chem. Comm.*, 1965, 335.

[4] B. Bosnich, *J. Amer. Chem. Soc.*, 1966, **88**, 2006; 1967, **89**, 6143.

[5] J. Bolard, *J. Chim. Phys.*, 1969, **66**, 389, 550.

[6] K. Dimroth and C. Reichardt, *Z. Analyt. Chem.*, 1966, **215**, 334.

[7] R. M. Fuoss and F. Accasina, 'Electrolytic Conductance,' Interscience, New York, 1959.

dissociation constant for the ion-pair according to Fuoss [7] indicates that the contribution of free ions is very low even in methanol. Table 1 does not show any correlation between the magnitude of the i.c.d. and the conductivity reading.

TABLE 1

Direct conductivity measurements of 2-benzoylbenzoic acid–amphetamine (1 : 1 salt; 1.02×10^{-2}M) at 22 ± 1°; all experiments were carried out in duplicate

Solvent	$[\theta]_{max.}$	Direct conductivity reading (mho cm^{-1})
t-Butyl alcohol	329	
1,4-Dioxan	324	
Acetonitrile	229	3.0×10^{-5}
Tetrahydrofuran	224	
Propan-2-ol	191	4.9×10^{-6}
n-Propanol	124	1.6×10^{-5}
Ethanol	76	6.8×10^{-5}
Methanol	0	3.3×10^{-4}

Effect of Salt Concentration on the I.c.d. Strength.—The effect of salt concentration on the $[\theta]_{max.}$ values was investigated and the logarithm of the values was plotted against the logarithm of the salt concentration as shown in Figure 1.

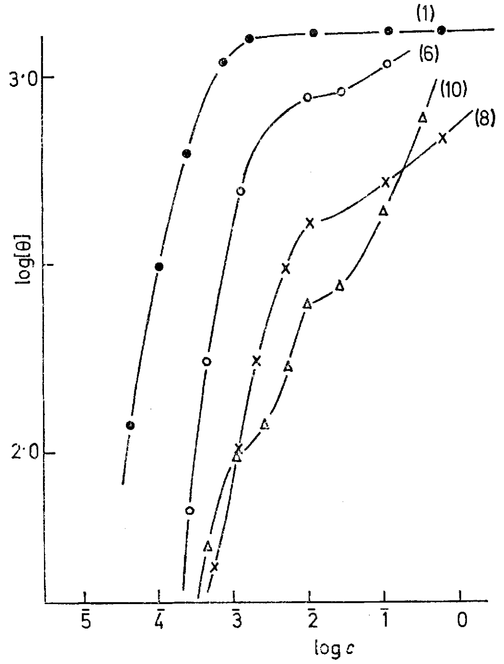

FIGURE 1 Effect of salt concentration *c* (2-benzoylbenzoic acid–amphetamine, 1 : 1) on the i.c.d. (see Table 2 for solvents)

The i.c.d. strength of the ion-pair is constant with $[\theta]_{max.}$ 1 010 and 1 239 units over the concentration range 10^{-1}—10^{-3}M and decreases rapidly below this range in non-polar solvents such as benzene and toluene, suggesting that the ion-pair is stable over a wide range of the salt concentration. In solvents such as chloroform and anisole, on the other hand, a plateau region is no longer seen and the magnitude of the i.c.d. decreases gradually below 10^{-1}M and then rapidly below 10^{-3}M. In acetonitrile, a solvent of high dielectric constant, the plot shows a rapid decrease over the whole region with two inflection points in the neighbourhood of 9.0×10^{-1} and 1.0×10^{-3}M. The rate of decrease of the i.c.d. in the region above 10^{-2}M is proportional to the solvent polarity. The slope of this plot is *ca.* 0 in benzene or toluene, 2 200 in anisole, 2 300 in chloroform, and 5 000 units mol^{-1} in acetonitrile.

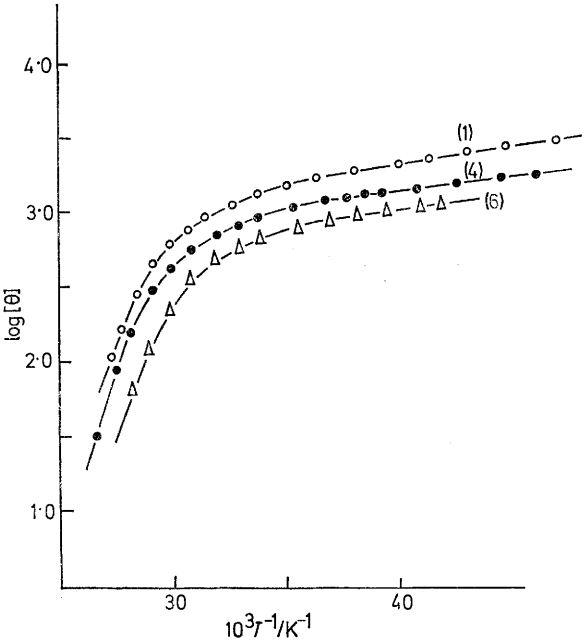

FIGURE 2 Effect of temperature on the i.c.d. of the 1 : 1 salt (1.02×10^{-2}M) (for solvents see Table 2)

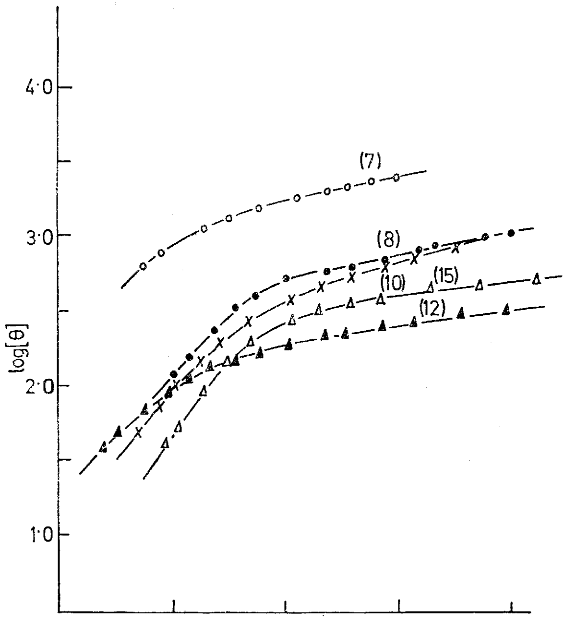

FIGURE 3 Effect of temperature on the i.c.d. of the 1 : 1 salt (1.02×10^{-2}M) (for solvents see Table 2)

Temperature Dependence of the I.c.d. Effects.—The dependence of $[\theta]_{max.}$ on temperature is shown in Figures 2—4 which are plots of the logarithm of $[\theta]_{max.}$ against T^{-1} to estimate the enthalpy change of chiroptical induction, ΔH,* as summarized in Table 2. Figures 2 and 3 undoubtedly indicate that the i.c.d. change of 2-benzoylbenzoic acid–

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* This is defined as the enthalpy change estimated from the temperature-dependent variation of chiral induction.

amphetamine originates from two different factors. On the other hand, similar plots for *N*-(3-benzoylbenzoyl)-amphetamine in benzene and ethanol, and 2-benzoylbenzoic acid in amphetamine are straight lines.

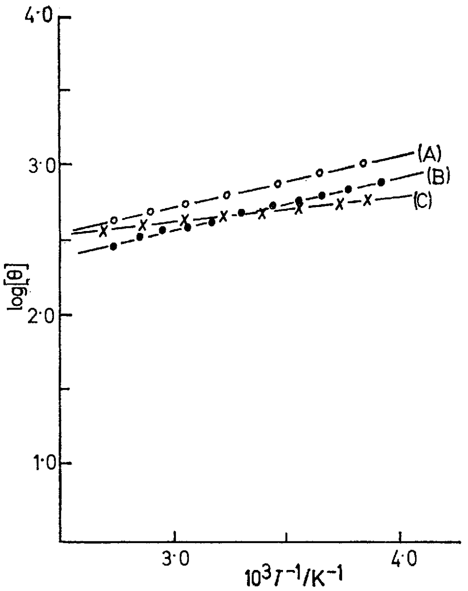

FIGURE 4 Effect of temperature on the i.c.d. of: (A) *N*-(3-benzoylbenzoyl)amphetamine in benzene; (B) *N*-(3-benzoylbenzoyl)amphetamine in ethanol; (C) 2-benzoylbenzoic acid (1.02×10^{-2}M) in amphetamine

TABLE 2

Enthalpy of chiroptical induction, ΔH, of 2-benzoylbenzoic acid–amphetamine in various solvents

	$-\Delta H$ (kcal mol^{-1})	
Solvent	Low temperature region	High temperature region
Toluene (1)	1.24	19.2
Benzene (2)	1.43	18.9
Biphenyl (3)		18.1
Chlorobenzene (4)	0.70	17.0
Bromobenzene (5)	1.14	17.2
Anisole (6)	0.80	18.1
Carbon tetrachloride (7)	1.37	9.14 [a]
Chloroform (8)	1.07	7.78
Dichloromethane (9)	0.73	7.59
Acetonitrile (10)	1.78	6.54
Propan-2-ol (11)	1.10	6.16
Butan-1-ol (12)	1.04	5.93
Propan-1-ol (13)	1.22	5.31
Ethanol (14)	*b*	*b*
Tetrahydrofuran (15)	0.71	11.5
Dioxan (16)		20.0
Methanol	*c*	*c*
2-Benzoylbenzoic acid in amphetamine	1.51	
N-(3-Benzoylbenzoyl)amphetamine in benzene	1.53 [d]	
N-(3-Benzoylbenzoyl)amphetamine in ethanol	0.94 [d]	

[a] Value was obtained by the extrapolation from Figure 3 because the b.p. is too low to measure the change of i.c.d. [b] $[\theta]_{max.}$ too small to measure exactly. [c] I.c.d. not observed in the range 50 to −50°. [d] *N*-(3-benzoylbenzoyl)amphetamine used instead of the 2-benzoylbenzoyl derivative which was difficult to obtain.[8]

I.c.d. Effect in Mixed Solvents.—As is evident from Figure 5 where the magnitude of the i.c.d. is plotted against the mole fraction of the added solvent, the stepwise solvation by benzene of the ion-pair is assumed to be a characteristic in aromatic solvents. The $\Delta\theta$ values for the first, second, and third solvation steps are 42, 172, and 99, respectively. It is possible to explain the curve qualitatively (see Discussion section) but quantitative analysis is not easy. However, the curve in mixed solvents such as (7)—(16) and (7)—(15) decreases in a simple fashion which is possible to analyse by the solvation model (1) where S is

$$S + 2D = SD_2 \qquad (1)$$

the salt and D is a solvent such as dioxan or tetrahydrofuran. The calculated values (dotted lines in Figure 5), with 9.83×10^{-2} (in dioxan) and 0.43 (in tetrahydrofuran) for the formation constants and 2 for the solvation number, were in good agreement with experiment.

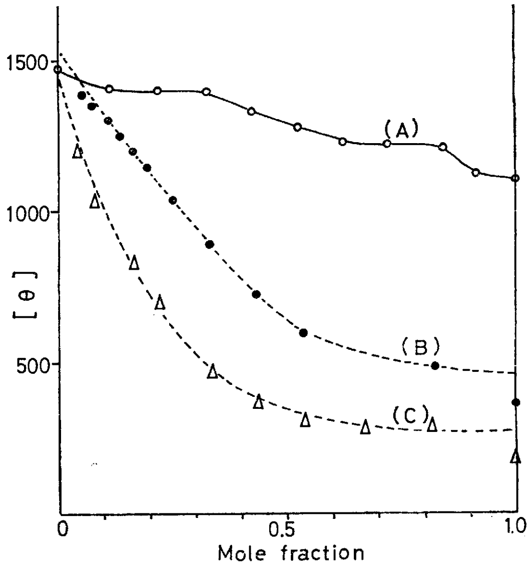

FIGURE 5 I.c.d. in mixed solvents: (A) (7)—(2); (B) (7)—(16) (● observed, — — — — calculated); (C) (7)—(15) (△ observed, — — — — calculated) at 16°

DISCUSSION

It has been assumed that the large i.c.d. of 2-benzoylbenzoic acid–amphetamine in non-polar media originates from the ion-pairs, and is largely influenced by the effect on the ion-pairs of solvation by the solvent.[1,2] We briefly discuss the relationship between the ion-pairs and the i.c.d. effect. The bulk ion-pair equilibria can be expressed as in Scheme 1. The hydrogen bonded salt has been reported to show no Cotton effect in this circumstance as mentioned previously.[1,2] There is no contribution from the free ion to the i.c.d., as shown in Table 1. In general, the ion-pairs are known to aggregate readily in organic media to give triple and quadruple ions. Tetraisopentylammonium halide, for example, dissociates to form free ion at low salt concentration below 10^{-4}M and aggregates to form triple ion in higher salt concentration over 10^{-1}M in benzene.[9,10] Similar ion-pair equilibria must occur in 2-benzoyl-

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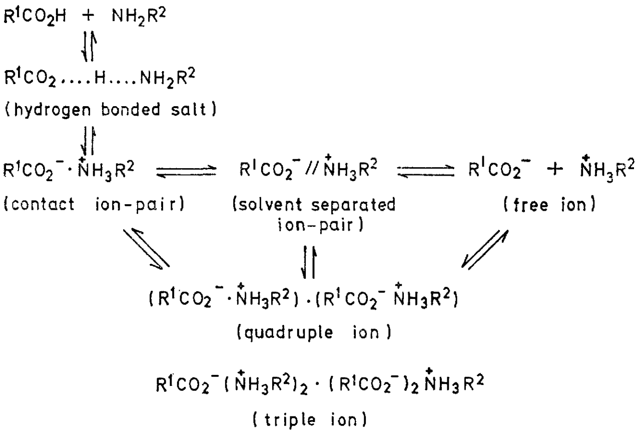
[8] W. Graf, E. Girod, E. Schmid, and W. G. Stoll, *Helv. Chim. Acta*, 1959, **42**, 1085.

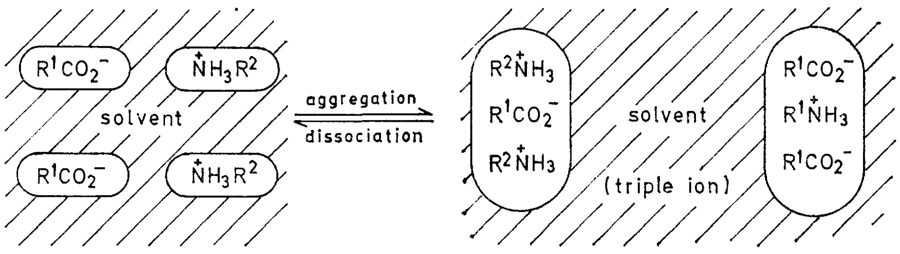
[9] R. M. Fuoss and C. A. Kraus, *J. Amer. Chem. Soc.*, 1933, **55**, 3614.

[10] L. E. Strong and C. A. Kraus, *J. Amer. Chem. Soc.*, 1950, **72**, 166.

benzoic acid–amphetamine, in spite of the difference in size of the anion molecule. The rapid depression of the size of the i.c.d. at lower salt concentrations (Figure 1) must be due to the dissociation of the ion-pairs required by the law of mass action, and the increase of the i.c.d. in the salt concentration above 10^{-2}M in anisole, chloroform, and acetonitrile must be attributed to the aggregation of the ion-pairs. To understand this phenomenon, it is convenient to draw the models in Scheme 2. The anion and cation molecules in triple and quadruple ions are more easily accessible to each other than in the solvent separated ion-pair, and the average distance between a chiral and a carbonyl molecule becomes shorter in consequence of the ion-pair aggregation, resulting in the increased induction of the Cotton effect.



SCHEME 1



SCHEME 2

Although the aggregation of ion-pairs such as benzoylbenzoic acid–amphetamine in benzene and toluene is also expected to be similar to that of tetra-amylammonium halide,[8,9] a corresponding increase of the i.c.d. is not observed, indicating that ion-pair aggregation in toluene or benzene is small under normal conditions (1 : 1 salt; 1.02×10^{-2}M).

The i.c.d. curve of the salt system (Figures 2 and 3) can be extrapolated in two straight lines in regions of high and low temperature. The slope in the low temperature region which is independent of the polarity of the solvent is also seen in *N*-(3-benzoylbenzoyl)-amphetamine in benzene or toluene (Figure 4). The slope (Table 2) is in good agreement with the enthalpy change due to intramolecular rotation of steroidal esters of benzoyl substituted carboxylic acids.[11] Therefore, the gradual change of i.c.d. of the salt system at low temperatures (Figures 2 and 3) must be also attributable to a decrease in the intramolecular rotation to give a conformation which enhances the i.c.d. effect.

The reduction of the i.c.d. at high temperatures, on the other hand, is very rapid, especially in benzenoid solvents (Figure 2), and this is not observed in the non-salt system (Figure 4). The rate of the reduction seems to be inversely proportional to solvent polarity. From these facts, it is concluded that the change in the i.c.d. is related to the ion-pair equilibria.

It is believed that the magnitude of an asymmetric induction is proportional to the average distance between the chiral centre of a chiral molecule and the chromophore of an achiral molecule as a vector quantity, though the detailed mechanism of asymmetric induction is not known.[5] The application of this to the i.c.d. system leads to the conclusion that the magnitude of the induced Cotton effect seems to be smaller in the order: contact, solvent separated, and free ions. The aggregate of the ion-pair also shows a large Cotton effect as is seen from the higher concentrations of the salt in anisole, acetonitrile, and chloroform. The i.c.d. effect from a free ion is very small and negligible for low concentrations. Therefore, the large Cotton effect of the salt under these conditions near room temperature originates from the contact and/or solvent separated ion-pairs. It is apparent from Figure 5 that the ion-pair in many solvents seems to be essentially solvent separated. However, this classification of the ion-pair is not decisive in a salt system where the sizes of the cation and anion are very large, since a shift from contact to solvent separated ion-pairs from a structural point of view should be considered as a continuous change.[2] The rapid reduction of i.c.d. effect in the high temperature region may originate from the dissociation of these ion-pair species to free ions. The dissociation constant, *K* for these ion-pair species is given by equation (2). Supposing that the $[\theta]_{\text{max.}}$ values are a function of *K*, this

$$\mathrm{d}(\ln K)/\mathrm{d}T = \Delta H/RT_2 \qquad (2)$$

gives (3). The ΔH values estimated from Figures 2 and 3 and listed in column 3 of Table 2 are inversely

$$\mathrm{d}(\ln[\theta]_{\text{max.}})/\mathrm{d}T = \Delta H/RT_2 \qquad (3)$$

proportional to the solvent polarity and a plot against E_T values [6] indicates the interesting tendency shown in

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[11] R. Breslow, S. Baldwin, T. Flechtner, P. Kalicky, S. Iiu, and W. Washburn, *J. Amer. Chem. Soc.*, 1973, **95**, 3251.

Figure 6. It is apparent from Figure 6 that the solvents can be classified into three types, ethereal, aromatic, and other aliphatic solvents such as carbon tetrachloride, chloroform, acetonitrile, and propan-2-ol. The chiroptical properties were not changed in going from a protic to an aprotic solvent. The ΔH values for aromatic solvents are extremely large and the slope is entirely different from those of aliphatic solvents (0.19 for aliphatic solvents; 0.65 units for aromatic solvents). It is apparent that aromatic solvents exhibit different properties from aliphatic solvents for solvation of the ion-pair. The specific solvation of the aromatic group of the cationic part of the solute (ammonium ion in this case) must be the cause of this difference. The curious pattern in Figure 5 is well explained by the solvation model (Scheme 3) for the ammonium ion postulated by Armstrong *et al.*[12] The second solvation seems to be the most effective on the i.c.d., since the carboxylate ion is drawn apart from the ammonium ion by solvation. The $\Delta\theta$ value for the second step (172) is larger than for the first (42) and the third steps (99).

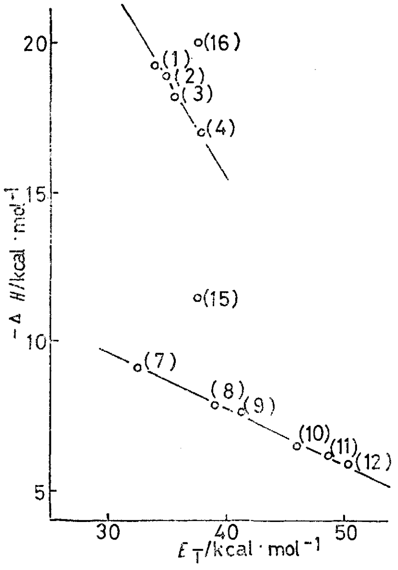
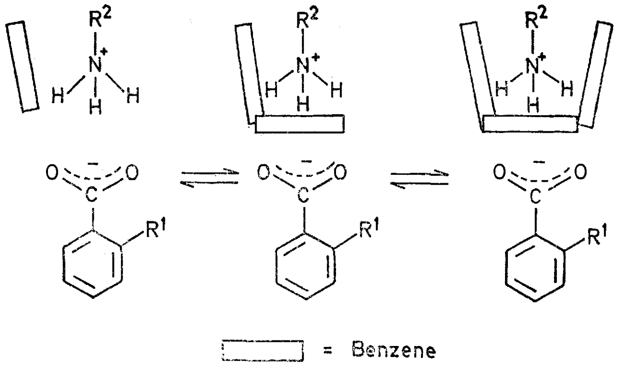


FIGURE 6 Dependence of enthalpy change ($-\Delta H$) for the salt on Dimroth E_T values (for solvents see Table 2)

The ΔH values in ethereal solvents do not show any linear correlation with E_T values. The deviation is related to specific interactions between ammonium ion and ethereal oxygen atom as mentioned previously.[2] It is of interest that the ΔH value for dioxan is about twice that for tetrahydrofuran in view of the number of oxygen atoms of the solvents, in spite of the same solvation number (2, estimated from the plot of Figure 5). The ΔH values for biphenyl and anisole indicate that the contribution of the aromatic substituent is larger than that of the ethereal oxygen atom in solvents for the ion-pair equilibria.

In this way, the ΔH values obtained from Figures 2 and 3 are connected with the ion-pair equilibria and must be similar to the enthalpy change for the dissociation of the ion-pairs to free ions.



SCHEME 3

The ΔH values can be related to the kinetic and bulk thermodynamic parameters of ionic processes such as the Menshutkin and Finkelstein reactions. As a typical example, the rate constants for the reactions of pyridine with methyl iodide[13] and ethyl iodide[14] are plotted against the ΔH values (Figure 7). A good linear correlation is also obtained for the solvents in these plots. Different solvation properties as mentioned above for benzenoid and aliphatic solvents are also apparent.

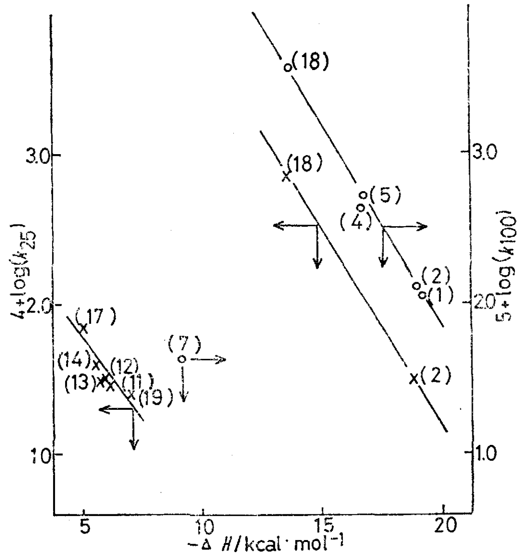


FIGURE 7 Dependence of rate constants for the reaction of methyl iodide (○)[13] and ethyl iodide with pyridine (×)[14] on ΔH values (for solvents see Table 2). The ΔH values of (14), (17), nitrobenzene (18), and n-butanol (19) are extrapolated from Figure 5

It may be concluded that the ΔH value is a useful parameter for measuring solvent polarity similar to the Z value of Kosower[15] and the E_T value of Dimroth.[6]

[4/2205 *Received, 25th October*, 1974]

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[12] R. S. Armstrong, M. J. Aroney, R. K. Duffin, H. J. Stootman, and R. J. W. LeFèvre, *J.C.S. Perkin II*, 1973, 1272, 1362.

[13] N. J. T. Pickles and C. N. Hinshelwood, *J. Chem. Soc.*, 1936, 1353.

[14] J. F. Norris and S. N. Prentiss, *J. Amer. Chem. Soc.*, 1928, **50**, 3042.

[15] E. M. Kosower, *J. Amer. Chem. Soc.*, 1958, **80**, 3253; *J. Chim. phys.*, 1964, **61**, 230.