

Induced Circular Dichroism. Part II.¹ Induced Circular Dichroism of the 2-Benzoylbenzoic Acid–Amphetamine System in Ethereal Solvents

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

Solvent effects on the induced circular dichroism (i.c.d.) of 2-benzoylbenzoic acid–amphetamine (1 : 1 salt) were investigated for various ethers and indicated that there is a strong dependence on the nature of the solvent. The strength of the i.c.d. effect in di-isopropyl ether and di-n-butyl ether, which are weakly polar and very poor cation-solvating media, was extremely large whereas in powerful cation-solvating media such as tetrahydrofuran and oxetan it was greatly reduced. The strength of the i.c.d. effect is strongly dependent on the polarity, basicity, and steric nature of the solvents. From these results, it is concluded that only the contact ion-pair of the salt exhibits large i.c.d. The i.c.d. of the solvent-separated ion-pair decreases rapidly on increasing the solvation number of the solvent. Therefore, solvent effects on the i.c.d. of the salt originated from changes in the ion-pair equilibria. Temperature effects on the i.c.d. were also examined.

INDUCED circular dichroism (i.c.d.) is a phenomenon in which an achiral compound is induced to demonstrate

chirality and show a Cotton effect when in the presence of a chiral compound.²⁻⁴ The induced Cotton effect has

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

² S. F. Mason and B. J. Norman, *Chem. Comm.*, 1965, 335.

³ B. Bosnich, *J. Amer. Chem. Soc.*, 1966, **88**, 2006.

⁴ B. Bosnich, *J. Amer. Chem. Soc.*, 1967, **89**, 6143.

been attained by various methods.⁵⁻¹⁰ As reported previously,¹ 2-benzoylbenzoic acid-amphetamine in non-polar solvents shows Cotton effects 10—100 times larger than those hitherto reported^{1,11-14} for the $n-\pi^*$ transition of a carbonyl group; the i.c.d. effect is highly dependent on the solvent polarity. The solvent effects have been assumed to arise from the nature of the salt, *i.e.* whether an ion-pair equilibrium is formed.

It is the purpose of this paper to clarify the relationship between the strength of the i.c.d. effect and the extent of solvation of the 1:1 salt. Although the concept of contact and solvent-separated ion-pairs may not apply completely to the 2-benzoylbenzoic acid-amphetamine system where the sizes of the cations and anions are so large, it is still useful and effective in investigating solvent effects upon i.c.d. Therefore, the i.c.d. of the salt was investigated for 17 ethers. It is known that ethers are good solvating agents for cations, *e.g.* organo-metallic salts such as fluorenyl-alkali metal are solvated and give contact and solvent-separated ion-pairs.^{15,16}

EXPERIMENTAL

(*R*)-(-)-Amphetamine (Aldrich) was redistilled *in vacuo* before use, b.p. 85—87° at 18 mmHg, $[\alpha]_D^{20} -33.0^\circ$ (neat). 2-Benzoylbenzoic acid was prepared by the method of Friedel *et al.*¹⁷ and recrystallized from benzene to give needles, m.p. 126—127°. The solvents (Nakarai Chemicals) were purified by two distillations.

C.d. and i.r. spectra were taken with a JASCO J-10 automatic spectrometer and a Hitachi 225 spectrometer, respectively. The molecular ellipticity $[\theta]_{\max}$ was evaluated by the equation¹⁸ $[\theta] = 3300\Delta A_{lr}/cl$ where ΔA_{lr} is a difference in absorbance between the left and right circularly polarized light, l is the path length of the light (1 cm) and c is the concentration of the 1:1 salt ($1.02 \times 10^{-2}M$). Since the salt is assumed to be in equilibrium between the different ion-pairs in the solvent and the concentration of the ion-pair which exhibits i.c.d. is difficult to determine, $[\theta]_{\max}$ is the apparent $[\theta]_{\max}$ for the 1:1 salt.

RESULTS

Molecular asymmetry was induced in 2-benzoylbenzoic acid by the presence of an equimolar amount of amphetamine; large Cotton effects were observed for the $n-\pi^*$ carbonyl transition at 310—320 nm (Table I). As Table I shows there is a positive Cotton effect for all the solvents and neither irregular shifts in wavelength of the i.c.d. band maxima nor multiple bands were observed. A rough correlation between $\log [\theta]_{\max}$ and the E_T values of Dimroth and

⁵ E. R. Blout and L. Stryer, *Proc. Nat. Acad. Sci. U.S.A.*, 1959, **45**, 1591.

⁶ S. F. Mason and A. J. McCaffery, *Nature*, 1964, **204**, 468.

⁷ R. A. Berg and B. A. Haxby, *Mol. Cryst. Liquid Cryst.*, 1970, **12**, 93.

⁸ F. D. Saeva and J. J. Wysocki, *J. Amer. Chem. Soc.*, 1971, **93**, 5928.

⁹ B. Bosnich and J. MacB. Harrowfield, *J. Amer. Chem. Soc.*, 1972, **93**, 989.

¹⁰ E. Axelrod, G. Barth, and E. Bunnenberg, *Tetrahedron Letters*, 1969, 5031.

¹¹ L. D. Hayward and R. N. Totty, *Canad. J. Chem.*, 1971, **49**, 624.

¹² J. Bolard, *J. Chim. Phys. Physicochim. Biol.*, 1969, **66**, 389.

¹³ J. Bolard, *J. Chim. Phys. Physicochim. Biol.*, 1970, **67**, 550.

¹⁴ K. Noack, *Helv. Chim. Acta*, 1969, **52**, 2501.

Reichardt¹⁹ was observed for solvents (2), (5), and (7)—(9) (Figure 1).

Solvent Basicity and Steric Effects.—It is apparent that an increase in the basicity of the ethers causes a decrease in the

TABLE I
Solvent effects on the i.c.d. of 2-benzoylbenzoic acid-amphetamine at $22 \pm 1^\circ$
[2-benzoylbenzoic acid] = [amphetamine] = $1.02 \times 10^{-2}M$

Solvent	λ_{\max}/nm	$[\theta]_{\max}$
Oxetan	(1) 326	63.1
Tetrahydrofuran	(2) 325	199.4
2-Methyltetrahydrofuran	(3) 324	387.9
3-Methyltetrahydrofuran	(4) 327	183.4
Tetrahydropyran	(5) 324	319.1
Oxepan	(6) 328	108.2
Di-isopropyl ether	(7) 323	1200
Di-n-butyl ether	(8) 322	1550
Anisole	(9) 323	618.7
Diphenyl ether	(10) 324	638.2
Dioxan	(11) 327	264.8
Diethoxyethane	(12) 325	87.9
Dimethoxyethane	(13) —	0
1,3-Dimethoxybenzene	(14) 323	306.1
2,2-Dimethoxypropane	(15) 324	605.6
Diglyme	(16) 322	104.2
Triglyme	(17) 324	130.2

$[\theta]$ value. The order of the basicity of the cyclic ethers measured by a variety of methods is (1) > (6) > (2) > (5)²⁰ or (1) > (2) > (5) > (6).^{21,22} The largest $[\theta]$ value is for the six-membered ether (5), the weakest base among

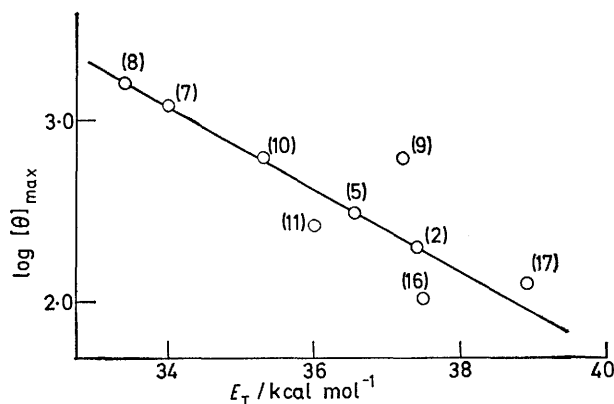


FIGURE 1 $\log [\theta]_{\max}$ against E_T for $1.02 \times 10^{-2}M$ -2-benzoylbenzoic acid-amphetamine in various ethers. For key to solvents see Table I

the ethers, and $[\theta]$ becomes progressively smaller in the order (5) > (2) > (6) > (1). This order is in good agreement

¹⁵ Michael Szwarc, 'Ions and Ion Pairs in Organic Reactions,' Wiley, New York, 1972.

¹⁶ T. E. Hogen Esch and J. Smid, *J. Amer. Chem. Soc.*, 1965, **87**, 669; 1966, **88**, 307, 318.

¹⁷ C. Friedel and J. M. Crafts, *Compt. rend.*, 1878, **86**, 1368.

¹⁸ L. Vellz, M. Legrand, and M. Grosjean, 'Optical Circular Dichroism: Principles, Measurements, and Applications,' Verlag Chemie, Weinheim, 1965.

¹⁹ K. Dimroth and C. Reichardt, *Z. Analyt. Chem.*, 1966, **215**, 344.

²⁰ E. M. Arnett and C. Y. Wu, *J. Amer. Chem. Soc.*, 1962, **84**, 1684.

²¹ S. Searles, M. Tamres, and E. R. Lippincott, *J. Amer. Chem. Soc.*, 1953, **75**, 2775.

²² M. Brandon, M. Tamres, and S. Searles, *J. Amer. Chem. Soc.*, 1960, **82**, 2129.

with the inverse basicity order of Arnett and Wu.²⁰ Steric factors are also of some importance in determining the strength of the i.c.d. effect. A bulky substituent adjacent to the oxygen atom undoubtedly causes an increase in i.c.d. probably due to poor solvation of the cation by the ether, as is evident in the series (2)—(4) or (11)—(13).

The behaviour of the salt is more complicated in ethers possessing two or more oxygen atoms. In solvents such as (11)—(15) the $[\theta]$ values are extremely small and the $[\theta]$ versus E_T plot is non-linear. The ion-pair equilibria must be more complex in this case.

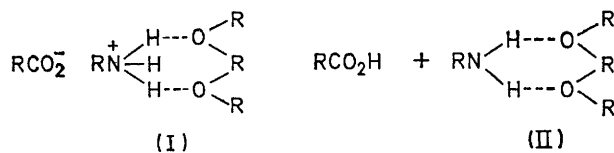
I.r. Spectra of the Carbonyl Groups.—The formation of ion-pairs is clearly suggested by the i.r. spectra. The salts in these solvents showed strong peaks due to the carboxy-group of monomeric and dimeric 2-benzoylbenzoic acid (Table 2). The characteristic absorption in the carbonyl

TABLE 2
I.r. data for carboxy- and carbonyl groups of 2-benzoylbenzoic acid in the salt ($1.02 \times 10^{-2}M$)^a

Solvent	Carboxy-group		Carbonyl group
	Monomeric	Dimeric	
	$\nu_{\max.}/\text{cm}^{-1}$		
Benzene ^b	1736	1694	1676
Benzene			1660
Chloroform			1665
Tetrahydrofuran			1660
1,2-Dimethoxyethane	1720	1676	^c
1,4-Dioxan	^c	1673	1630
Acetonitrile	1723	1668	

^a Spectra were taken at 22° in a 1 mm cell. ^b In the absence of amphetamine. ^c In the presence of amphetamine.

region due to the carboxy-group of 2-benzoylbenzoic acid occurs at 1694 for the dimer and 1736 cm^{-1} for the monomer in non-polar solvents such as benzene. The peaks at 1720, 1676, and 1673 cm^{-1} for solvents (11) and (13) undoubtedly indicate the presence of monomeric and dimeric 2-benzoylbenzoic acid associated with the solvent by hydrogen bonding. The contribution of solvated species such as (I) and/or



(II) should lead to a reduction in the strength of the i.c.d. effect.

Temperature and Solvent Effects on the Enthalpy of Chiral Induction.—I.c.d. in ethers is highly dependent on temperature. The $\log [\theta]_{\max}$ values in various solvents were plotted against the reciprocal of the temperature as shown in Figure 2. In all solvents, the i.c.d. strength decreased upon an increase in temperature, the decrease being more rapid above 30°. The data for the lower and higher temperature regions were extrapolated to give two straight lines and the enthalpy changes (enthalpy of chiral induction) associated with these ranges were evaluated (Table 3). Table 3 shows that the $-\Delta H$ values of tetrahydrofuran (0.71) and anisole (0.80) in the low temperature region are very small compared with those for carbon tetrachloride (1.37), benzene (1.43), and n-butanol (1.04 kcal mol^{-1}). The $-\Delta H$ values in the high temperature region for the ethers can be as large as 15.0—

20.0 kcal mol^{-1} , e.g., that for benzene, and this is much larger than those of n-butanol (5.93) and carbon tetrachloride (9.14 kcal mol^{-1}).

Intramolecular rotation of the ion-pair as observed for the steroidal esters of benzophenonecarboxylic acids²³ may

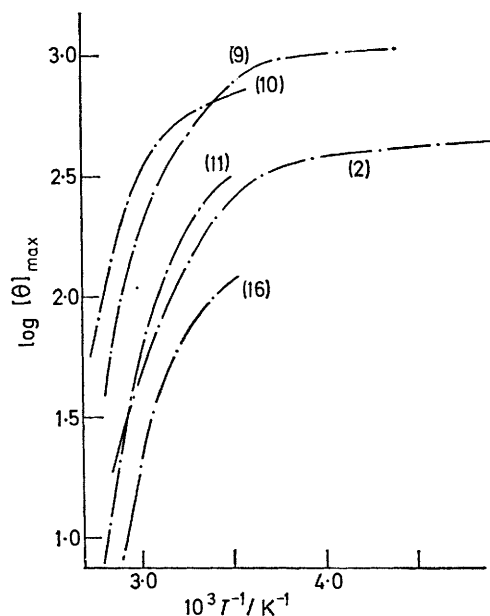


FIGURE 2 Variation of $\log [\theta]_{\max}$ with $1/T$ for $1.02 \times 10^{-2}M$ -2-benzoylbenzoic acid-amphetamine in various ethers. For key to solvents see Table 1

be responsible for the enthalpy change in the lower temperature region. The $-\Delta H$ values in the higher temperature

TABLE 3
Enthalpy of chiral induction

Solvent	$-\Delta H/\text{kcal mol}^{-1}$	
	Lower temperature (below 30°)	Higher temperature (over 30°)
Carbon tetrachloride	1.37	9.14
Benzene	1.43	18.9
n-Butanol	1.04	5.93
Tetrahydrofuran	0.71	11.5
1,4-Dioxan		20.0
Anisole	0.80	18.1
Diphenyl ether		18.1
Tetrahydropyran		19.5
1,3-Dimethoxybenzene		19.5
2,2-Dimethoxypropane		20.1
Diglyme		16.9
Triglyme		15.0

region are very large and may be connected with the changes in the ion-pair equilibrium.

DISCUSSION

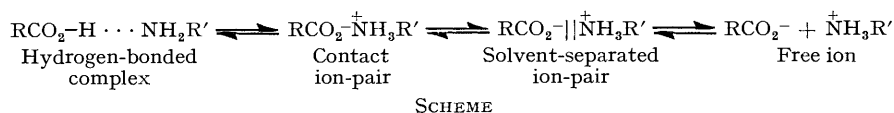
The strength of the i.c.d. effect for 2-benzoylbenzoic acid-amphetamine (1 : 1) in a wide variety of solvents shows a linear correlation with the E_T value of the solvents,¹ except for ethers such as tetrahydrofuran (THF) and

²³ R. Breslow, S. Baldwin, T. Flechtner, P. Kalicky, S. Liu, and W. Washburn, *J. Amer. Chem. Soc.*, 1973, **95**, 3251.

dioxan. In less polar solvents, mainly linear and cyclic ethers, there is also a roughly linear relationship (Figure 1).

The gross equilibria of the system in the solvent is shown in the Scheme. The contribution of the hydrogen-bonded salt to the i.c.d. can be neglected since the salt in

will become smaller as solvation by the solvent increases and the ion-pairs change progressively as contact ion-pair \rightarrow solvent-separated ion-pair \rightarrow free ion. Though ethers are known to be good solvating agents for cations bulky substituents adjacent to the oxygen atom of the ether such as isopropyl and n-butyl might tend to



less polar solvents did not show any i.r. band due to a hydrogen-bonded carboxy-group. Considering that the ester-amphetamine systems, methyl 2-benzoylbenzoate-amphetamine and benzyl 2-benzoylbenzoate-amphetamine in benzene, and 2-benzoylbenzoic acid-amphetamine in a polar solvent (methanol) do not exhibit¹ any Cotton effect under similar conditions, it appears that proximity between the chromophore and the chiral centre or a close relationship between the constituents of the ion-pair is indispensable for developing an i.c.d. effect. Consequently, the large solvent effects on the i.c.d. must be related to the equilibrium between contact and solvent-separated ion-pairs. The effect can be attributed solely to the contact ion-pair. Although it may be somewhat impractical to introduce the concept of the ion-pairs in such a large molecular system it is useful in understanding the large difference in solvent effects among di-isopropyl ether, di-n-butyl ether, tetrahydrofuran, and tetrahydropyran.

The rotational strength of the i.c.d. has been estimated to be proportional to r^{-7} where r is the average distance between a chiral centre and a chromophore, a carbonyl group in this case.¹³ The distance between a cation and an anion is *ca.* 3 Å for a contact ion-pair and 6 Å for a solvent-separated ion-pair in acetonitrile,²⁴ though it is dependent on the solvent and the nature of the entity complexed with the ion-pair. The molar ellipticity $[\theta]$

prevent the solvent-cation interaction. A decrease in solvation will favour contact ion-pair and give rise to large i.c.d. values. The $[\theta]$ values are inversely proportional to the basicity of the ethers,²⁰ the order of the basicity being regarded as a measure of the solvating powers in this case.

It is also of considerable interest to compare the $[\theta]$ values with the ratio of solvent-separated and contact ion-pairs for fluorenyl-lithium in ether solvent (Table 4). There is clearly a correlation between the two sets of data and this is a further indication that the i.c.d. is related to the nature of the ion-pair.

TABLE 4
Comparison of the ratio of ion-pairs for fluorenyl-lithium with $[\theta]_{\text{max}}$ for 2-benzoylbenzoic acid-amphetamine

Solvent	$\frac{(\text{F}^- \text{Li}^+)^b}{(\text{F}^-, \text{Li}^+)}$	$[\theta]_{\text{max}}$
Oxetan	50	63.1
Tetrahydrofuran	4.6	199.4
2-Methyltetrahydrofuran	0.33	387.9
3-Methyltetrahydropyran	0.85	183.4
Tetrahydropyran	0.46	319.1
Oxepan	0.24	108.2
1,3-Dimethoxybenzene	0.01	306.1
1,4-Dioxan	0.01	264.8

[4/1084 Received, 4th June, 197

²⁴ E. Grunwald, *Analyt. Chem.*, 1954, **26**, 1696.