

Solvent Effects on Circular Dichroism induced in Aroylarene-carboxylic Acids by Optically Active Amines

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When 2-, 3-, or 4-benzoylbenzoic acid, 2-(2,4,6-trimethylbenzoyl)benzoic acid, or 2-acetylbenzoic acid and (-)-(*R*)-amphetamine, (-)-(*R*)-*N*-methylamphetamine, (\pm)-(*R*)- or (-)-(*S*)- α -phenylethylamine, or (\pm)-(*S*)-*s*-butylamine were dissolved together in equimolar proportions in the non-polar solvents benzene or carbon tetrachloride at 25°, induced circular dichroism was observed even at low concentrations. The logarithm of the molecular ellipticity θ , of the mixture of 2-benzoylbenzoic acid and amphetamine inversely correlates with the E_T value of the solvent used. A contact ion pair derived from salt formation between the keto-acid and the optically active amine may be responsible for the phenomenon. In polar solvents such as alcohol the induced c.d. effect is reduced as expected from increased dissociation of the ion pair.

An inherent property of a structurally symmetric compound is that it has neither optical rotatory power nor

exhibits circular dichroism. However, such a compound may show optical activity in the presence of a chiral molecule owing to asymmetry induced by the latter compound.^{1a,b}

¹ (a) S. F. Mason and B. J. Norman, *Chem. Comm.*, 1965, 335; (b) B. Bosnich, *J. Amer. Chem. Soc.*, 1966, **88**, 2006; (c) 1967, **89**, 6143.

For example, benzil and benzophenone show a c.d.

effect in the $n \rightarrow \pi^*$ region in an optically active solvent such as (+)-1-butane-2,3-diol. This phenomenon was described by Bosnich^{1c} and may be named induced c.d. Induced c.d. phenomena have been reported for nitro-compounds,² azo-compounds,³ and thioketones,⁴ and these have given rise to interest in the intermolecular interactions involved. Noack² postulated the formation of a hydrogen-bonded complex between the nitro-compounds and an asymmetric alcohol upon consideration of the effects of steric hindrance, concentration, temperature, and solvent. A similar explanation has also been proposed by Bolard.⁵

Notwithstanding these observations, induced c.d. has been detected in a thioketone–optically active ether system for which it is believed that thioketone is unable to undergo hydrogen bonding with the ether.⁴ The present study is concerned with the induced optical asymmetry produced by interaction between aroylarene-carboxylic acids and optically active amines, and the influence of solvents on this effect.

When an acid and an active amine were dissolved together in equimolar proportions in a non-polar solvent significant induced c.d. was observed even at low concentrations and this is in contrast with previously reported cases such as the ketone–chiral alcohol system. Furthermore, we observed a marked solvent effect: the more polar the solvent, the less is the induced c.d.

The amines (–)-amphetamine, (–)-*N*-methylamphetamine, (+)- and (–)- α -phenylethylamines, and (+)-*s*-butylamine were used as they have no c.d. in the neighbourhood of the carbonyl $n \rightarrow \pi^*$ transition and thus do not hinder the measurement of the induced c.d. of the carbonyl groups of the aroylarene-carboxylic acids.

EXPERIMENTAL

Materials.—(–)-(*R*)-Amphetamine (Aldrich) was distilled *in vacuo*, b.p. 85–87° at 18 Torr, $[\alpha]_D^{20}$ –33.0° (neat). (–)-(*R*)-*N*-Methylamphetamine was prepared by the method of Woodruff *et al.*⁶ from the Schiff's base of amphetamine and benzaldehyde by methylation, b.p. 57–58° at 3 Torr, $[\alpha]_D^{14}$ –7.46° (*c* 3.35, EtOH). It was shown to be free of both amphetamine or the tertiary amine by g.l.c.

(+)-(*R*)- and (–)-(*S*)- α -phenylethylamines were obtained by resolution of the racemic amine with (–) or (+)-tartaric acid.⁷ (+)-(*R*)- α -Phenylethylamine had b.p. 76–77° at 18 Torr, $[\alpha]_D^{15}$ +35.6° (neat), and (–)-(*S*)- α -phenylethylamine had b.p. 76–77° at 18 Torr, $[\alpha]_D^{15}$ –20.7° (neat), the optical purities being 86 and 62% respectively. Racemic *s*-butylamine was resolved to (+)-(*S*)-*s*-butylamine with (+)-tartaric acid by the method of

² K. Noack, *Helv. Chim. Acta*, 1969, **52**, 2501.

³ L. D. Hayward and R. N. Totty, *Canad. J. Chem.*, 1971, **49**, 624.

⁴ E. Axelrod, G. Barth, and E. Bunnenberg, *Tetrahedron Letters*, 1969, 5031.

⁵ J. Bolard, *J. Chem. Phys.*, 1969, **66**, 389.

⁶ E. H. Woodruff, J. P. Lambooy, and W. E. Burt, *J. Amer. Chem. Soc.*, 1940, **62**, 922.

⁷ W. Theilacker and H. Winkler, *Chem. Ber.*, 1954, **87**, 690.

⁸ P. Bruck, I. N. Denton, and A. H. Lambertson, *J. Chem. Soc.*, 1956, 921.

Bruck *et al.*,⁸ b.p. 63–64°, $[\alpha]_D^{14}$ +4.72°, optical yield 63%. 3-Benzoylbenzoic acid was prepared by the method of Smith,⁹ m.p. 162–163° (from benzene). 2-(2,4,6-Tri-methylbenzoyl)benzoic acid, prepared by a Friedel–Crafts synthesis from mesitylene and phthalic anhydride, had m.p. 207–209° (from methanol).¹⁰ 2-Acetylbenzoic acid was prepared by the method of Yale,¹¹ m.p. 114–115° (from ether). 3-Acetylbenzoic acid was prepared by the method of Rupe,¹² m.p. 164–165° (from water). Methyl 2-benzoylbenzoate, m.p. 54–55°, was prepared from 2-benzoylbenzoic acid. β -Benzoylacrylic acid was prepared according to the method of Crummitt *et al.*,¹³ m.p. 94–96° (from benzene). Benzoylpropionic acid was prepared by the method of Somerville and Allen,¹⁴ m.p. 115–116°. 2-Benzoylbenzoic acid, m.p. 126–127° (from benzene), 4-benzoylbenzoic acid, m.p. 193–194° (from ethanol), benzoin, m.p. 136–137° (from ethanol), benzil, m.p. 94–95° (from ether), benzoic acid, m.p. 121–122° (from aqueous ethanol), and acetophenone, b.p. 73–74° at 7 Torr, were obtained commercially and recrystallized before use. *o*-Hydroxyacetophenone, b.p. 215°, and *o*-nitrobenzoic acid, m.p. 147–148°, were of analytical grade and were used without further purification.

Solvents.—Acetonitrile and carbon tetrachloride were refluxed over calcium hydride and distilled. Benzene was washed with concentrated sulphuric acid, dried with metallic sodium, and distilled. [²H₆]benzene (Merck; 99%) was used without further purification. Chloroform was washed with concentrated sulphuric acid, dried with phosphorus pentoxide, and distilled. 1,4-Dioxan was dried with calcium chloride and metallic sodium and distilled. Tetrahydrofuran was refluxed, distilled over potassium hydroxide, and then redistilled over lithium aluminum hydride. Alcohols were purified by refluxing over magnesium ribbon followed by distillation.

Apparatus.—Polarimetric measurements were made on a Perkin-Elmer 141 polarimeter and c.d. spectra were observed with a JASCO J-10 automatic spectrometer. I.r. spectra were recorded with a Hitachi 225 spectrometer using a 1 mm cell. U.v. spectra were taken with a Hitachi EPS-3 spectrophotometer.

Measurement of C.d. Spectra.—Prior to the measurement of c.d. the absorption band and absorptivity of the u.v. spectrum of the sample were determined in order to adjust the concentration to a value that made the absorbance less than unity. The molecular ellipticity $[\theta]$ was evaluated by the equation^{15,16} $[\theta] = 3300(\epsilon_l - \epsilon_d)$, where ϵ_l and ϵ_d are the molar absorptivities for left and right circularly polarized light, respectively. Usually $[\theta]$ was measured for the wavelength of maximum absorption $[\theta]_{\max}$, but $[\theta]$ for a wavelength approximating to the absorption maximum when this was uncertain. The measurement of c.d. was usually undertaken for an equimolar mixture of a keto-acid and an amine.

⁹ M. E. Smith, *J. Amer. Chem. Soc.*, 1921, **43**, 1921.

¹⁰ J. Gresly and F. Meyer, *Ber.*, 1882, **15**, 639.

¹¹ H. L. Yale, *J. Amer. Chem. Soc.*, 1947, **69**, 1547.

¹² H. Rupe, *Ber.*, 1900, **33**, 3407.

¹³ O. Crummitt, E. J. Becker, and C. Miese, *Org. Synth.*, Coll. Vol. III, 1955, p. 109.

¹⁴ L. F. Somerville and C. F. H. Allen, *Org. Synth.*, Coll. Vol. II, 1943, p. 81.

¹⁵ C. Djerassi and E. Bunnenberg, *Proc. Chem. Soc.*, 1963, 299.

¹⁶ L. Vellz, M. Legrand, and M. Grosjean, 'Optical Circular Dichroism, Principle, Measurements and Applications,' Verlag Chemie, Weinheim, 1965.

RESULTS

Induced C.d. of 2-Benzoylbenzoic Acid (I) by (-)-(R)-Amphetamine.—The u.v. absorption of 2-benzoylbenzoic acid (I) in benzene showed λ_{\max} 322 nm (ϵ 111) due to the $n \rightarrow \pi^*$ transition of the carbonyl group. In the presence of an approximately equimolar quantity of (-)-(R)-amphetamine strong c.d. was induced in the absorption of the $n \rightarrow \pi^*$ transition (Figure 1). The sign of the c.d. was

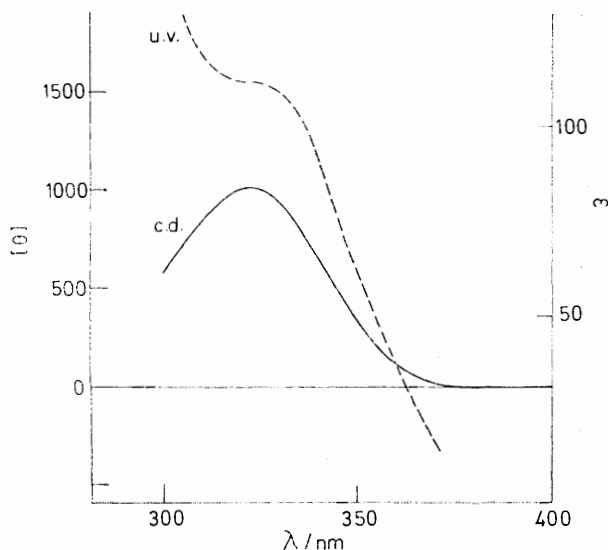


FIGURE 1 U.v. and c.d. spectra of 2-benzoylbenzoic acid ($7.05 \times 10^{-3}M$) with (-)-amphetamine ($6.80 \times 10^{-3}M$) in benzene at 25°

positive and the magnitude was largely influenced by the polarity of the solvent as indicated in Table 1. The

TABLE I

Solvent effects on the induced c.d. of the 2-benzoylbenzoic acid-amphetamine system *

Solvent	No.	λ_{\max}/nm	$[\theta]$
Carbon tetrachloride	1	324	+1320
Toluene	2	324	+1239
Benzene	3	322	+1010
Chlorobenzene	4	324	+830
Chloroform	5	322	+477
Dichloromethane	6	318	+434
t-Butyl alcohol	7	320	+329
1,4-Dioxan	8	326	+324
Acetonitrile	9	320	+229
Tetrahydrofuran	10	325	+224
Propan-2-ol	11	318	+191
Propan-1-ol	12	318	+124
Ethanol	13	318	+76
Methanol	14	318	0

* Approximately equimolar (ca. $6.9 \times 10^{-3}M$) quantities of (I) and amphetamine in a solvent at 25° .

polarity of the solvent has a relatively small influence on the wavelength of maximum absorption. On the other hand, the strength of the induced c.d. band is highly affected by the polarity of the solvent. An increase in the polarity of the solvent causes a marked reduction in the induced c.d. of the keto-acid. The largest value of the molecular ellipticity $[\theta]$ of (I) (+1320 in carbon tetrachloride) is ten times larger than those of the similar

¹⁷ K. Dimroth and C. Reichardt, *Z. Analyt. Chem.*, 1966, **215**, 344.

compounds hitherto reported.^{1,16} However, in polar solvents such as methanol and ethanol the $[\theta]$ values are extremely small compared with that in carbon tetrachloride.

A plot of $\log [\theta]$ against a measure of the polarity of the solvent, the E_T value of Dimroth and Reichardt¹⁷ (derived from the energy of an electronic transition of an *N*-phenolpyridinium betaine in a given solvent), is linear (Figure 2). In this plot the points for both dioxan 8, and tetrahydrofuran 10 lie off the line. Deviation in such ethereal solvents results^{18,19} from competitive hydrogen bonding of the solvent to the keto-acid.

Induced C.d. of Other Aroylarene-carboxylic Acids with Amphetamine.—The c.d. of the other keto-acids examined which was induced by amphetamine is listed in Table 2. Although acids (II)—(V) showed a significant effect, acids (VI)—(X) and the ester (XII) gave no recognizable c.d. band. In benzoyl- and acetyl-benzoic acids (I)—(V) the values were strongly affected by the position of the substituent on the benzene ring, indicating a pronounced decrease in the order *ortho* > *meta* > *para*. 2-(2,4,6-Tri-methylbenzoyl)benzoic acid (IV) shows a slight depression of the $[\theta]$ value compared with that of (I). Acids containing no keto carbonyl group [(X) and (XI)] were also examined, and no induced c.d. was observed.

Induced C.d. of Ketones with Amphetamine.—The presence of a carboxy-group on the benzene ring was indispensable for the development of an induced c.d. band. The aromatic ketones (XIII)—(XVI) showed no detectable induced c.d. with amphetamine in non-polar solvents. It is noteworthy that benzophenone (XIII) and benzil (XV) were reported to give appreciable induced c.d. in (+)-L-butane-2,3-diol.¹²

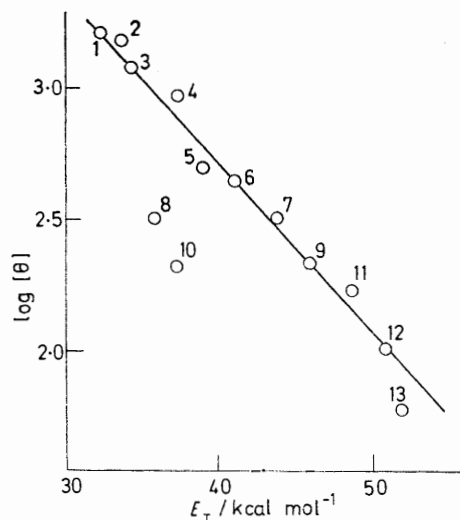


FIGURE 2 Plot of $\log [\theta]$ vs. the E_T values of the solvents used. Numbers refer to solvents listed in Table I

In the absence of solvent benzil (XV) exhibited strong c.d., $[\theta] +3400$ at λ_{\max} 356 nm, when dissolved in amphetamine [benzil-amphetamine 1 : 30 (w/w)].

Induced C.d. of Compound (I) with Other Optically Active Amines.—The c.d. induced in (I) in the presence of several other optically active amines was also examined (Table 3). The $[\theta]$ value of (I) in the presence of *N*-methylamphetamine

¹⁸ S. Nagakura and H. Baba, *J. Amer. Chem. Soc.*, 1952, **74**, 5693.

¹⁹ H. Hart, F. A. Cassis, and J. J. Bordeaux, *J. Amer. Chem. Soc.*, 1954, **76**, 1639.

TABLE 2

Induced c.d. of various ketones and carboxylic acids with amphetamine (AMP) in non-polar solvents

Ketone	Solvent	$10^3[\text{Substrate}]$ (M)	$10^3[\text{AMP}]$ (M)	λ_{max} (nm)	$[\theta]$
2-Benzoylbenzoic acid (I)	C_6H_6	7.05	6.80	322	1010
3-Benzoylbenzoic acid (II)	C_6H_6	6.14	5.89	345	140
	CHCl_3	6.50	22.6	346	132
4-Benzoylbenzoic acid (III)	CHCl_3	4.60	15.4	340	86
2-(2,4,6-trimethyl)benzoylbenzoic acid (IV)	C_6H_6	6.39	6.52	332	816
2-Acetylbenzoic acid (V)	CHCl_3	7.48	8.28	300*	172
	Dioxan	9.05	8.75	300*	62
3-Acetylbenzoic acid (VI)	Dioxan	10.7	11.2		0
β -Benzoylpropionic acid (VII)	CHCl_3	7.80	7.70		0
Benzoylacetic acid (VIII)	CHCl_3	6.30	8.28		0
β -Acetylacrylic acid (IX)	CHCl_3	10.6	15.4		0
2-Nitrobenzoic acid (X)	C_6H_6	1.29	1.29		0
Benzoic acid (XI)	C_6H_6	5.25	5.04		0
Methyl-2-benzoylbenzoate (XII)	C_6H_6	6.79	7.24		0
Benzophenone (XIII)	C_6H_6	6.50	7.06		0
Acetophenone (XIV)	Cyclohexane	14.3	94.8		0
Benzil (XV)	C_6H_6	12.7	12.1		0
Benzoin (XVI)	$\text{CH}_3\text{CN} \dagger$	2.9	3.4		0

* Absorption maximum uncertain. † The only solvent which is able to dissolve this compound.

TABLE 3

Induced c.d. of acid (I) with various optically active amines in benzene at 25°

Amine	Optical purity (%)	$10^3[\text{Amine}]$ (M)	$10^3[\text{I}]$ (M)	$[\theta]$
(-)-(R)-Amphetamine	100	6.80	7.05	+1010.0
(-)-(R)-N-Methylamphetamine	100	5.92	6.21	+38.7
(+)-(R)- α -Phenylethylamine	86	8.99	8.78	-22.1
(-)-(S)- α -Phenylethylamine	62	8.18	7.54	+15.7
(+)-(S)-s-Butylamine	63	8.27	8.18	-31.0

is reduced to 1/25 of that in the presence of amphetamine perhaps owing to the bulky methyl group hindering a close association of the two compounds.

Concentration Dependence of C.d. of the 2-Benzoylbenzoic Acid-Amphetamine Systems: 1:1 Salt Formation.—The effect of variation of the molar ratio on the $[\theta]$ value was studied for benzene solutions, the results being shown in Figure 3. Increasing the proportion of amphetamine led to a rapid increase in the c.d. band strength which

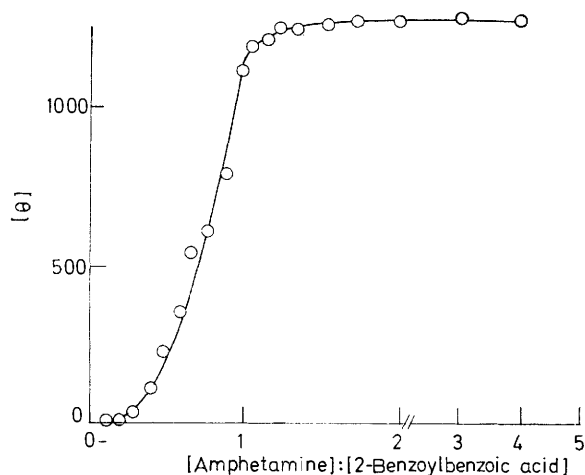


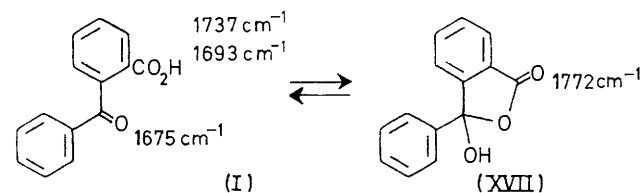
FIGURE 3 Variations of molecular ellipticity $[\theta]$ of 2-benzoylbenzoic acid ($7.36 \times 10^{-3}\text{M}$) with $[(-)\text{-Amphetamine}]:[\text{Acid}]$ in benzene at 25°

levelled off and became constant in the region $[(\text{I})]:[\text{Amphetamine}] 1:1$. These results indicate the formation of a

²⁰ G. M. Barrow and E. A. Yerger, *J. Amer. Chem. Soc.*, 1954, **76**, 5211; 1955, **77**, 4474.

1:1 salt which causes the induction of c.d. Potentiometric titration also suggests the formation of a 1:1 salt.

I.r. Spectrum of 2-Benzoylbenzoic Acid-Amphetamine.—Salt formation was also examined with the aid of i.r. spectroscopy. The i.r. spectrum of (I) in benzene showed



absorption maxima at 1772, 1737, 1693, and 1675 cm^{-1} due to $\nu_{\text{C=O}}$ of the ring tautomer (XVII), $\nu_{\text{C=O}}$ of the carboxy-group of dimeric (I), $\nu_{\text{C=O}}$ of the carboxy-group of monomeric (I), and $\nu_{\text{C=O}}$ of the oxo-group, respectively. The ratio of the peaks at 1772, 1737, and 1693 cm^{-1} was 1:9:7 at a concentration of $7.05 \times 10^{-3}\text{M}$. Addition of amphetamine to (I) in benzene caused the disappearance of the peaks at 1737 and 1675 cm^{-1} and the appearance of a new peak at 1370 cm^{-1} due to the carboxylate ion, and also a broad band between 2900 and 2700 cm^{-1} due to the ammonium ion.^{20,21}

The formation of carboxylate and ammonium ions was investigated by examining these peaks under the conditions for c.d. measurements, and the results were shown in Figures 4 and 5. For a constant concentration of (I) ($1.79 \times 10^{-3}\text{M}$), addition of amphetamine brought about a linear increase in the concentration of the carboxylate and ammonium ions which then remained constant for $[(\text{I})]:[\text{Amphetamine}]$ ratios ≥ 1 . This result agrees with that for the c.d. experiments and supports strongly the formation of a 1:1 salt from (I) and amphetamine (Figure 4).

²¹ D. F. DeTar and R. W. Novak, *J. Amer. Chem. Soc.*, 1970, **92**, 1361.

For a fixed concentration ($9.50 \times 10^{-3}M$) of amphetamine, the concentration of carboxylate and ammonium ions increased linearly on addition of (I), reached a limit when

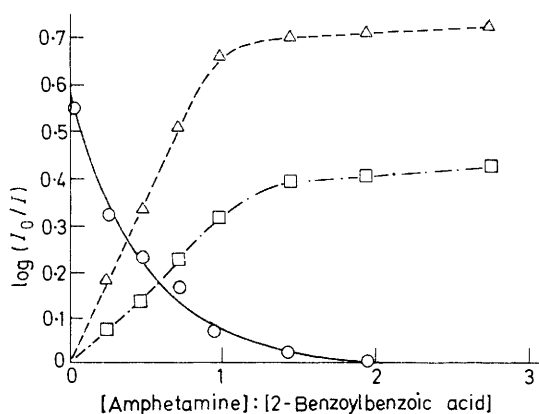


FIGURE 4 Optical densities of absorption bands in the system 2-benzoylbenzoic acid ($1.79 \times 10^{-2}M$)-(—)-amphetamine. \circ RCO_2H , ν 1737 cm^{-1} ; \square $R'NH_3^+$, ν 2840 cm^{-1} ; \triangle RCO_2^- , ν 1370 cm^{-1}

the ratio $[(I)]:[Amphetamine]$ was between 1:1 and 2:1, and then again increased gradually for $[(I)]:[Amphetamine] > 2$ (Figure 5). Moreover, the presence of the undissociated acid increased rapidly as $[(I)]:[Amphetamine]$ increased beyond unity. These results clearly suggest that 1:1 salt formation from the acid and the amine is responsible for the induced c.d.

The effect of temperature on the c.d. value of the 1:1 salt was compared with that on the value for *N*-(3-benzoylbenzoyl)amphetamine (Figure 6). The c.d. of *N*-(3-benzoylbenzoyl)amphetamine (+785 in benzene and +529 in ethanol at 10°) slowly decreased upon rise in temperature; this is attributable to intramolecular motion. The c.d. value of the 1:1 salt was very sensitive and decreased rapidly and linearly upon rise in temperature. A comparison suggests that dissociation of the 1:1 salt should

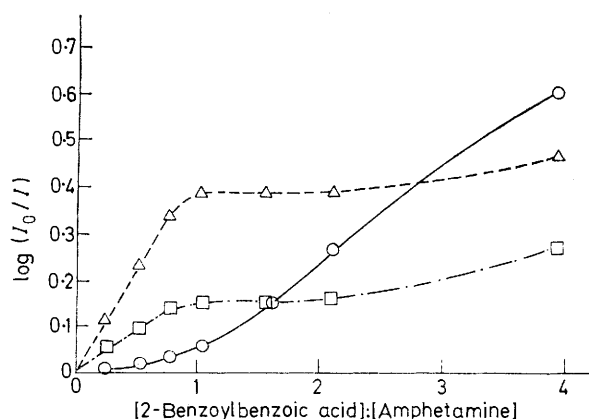


FIGURE 5 Optical densities of the absorption bands in the system (—)-amphetamine ($9.50 \times 10^{-3}M$)-2-benzoylbenzoic acid: \circ RCO_2H , ν 1737 cm^{-1} ; \square $R'NH_3^+$, ν 2840 cm^{-1} ; \triangle RCO_2^- , ν 1370 cm^{-1}

be taken into account in addition to intramolecular perturbation as the c.d. value is inversely proportional to the seventh power of the distance between the chromophore

and the asymmetric centre according to the model of Höhn and Weigang.²²

DISCUSSION

2-Oxobenzoic acid derivatives often exhibit ring-chain tautomerism and a small quantity of the ring tautomer (XVII) (6.5%) was found for 2-benzoylbenzoic acid dissolved in dioxan. A small contribution from the ring tautomer for benzene and methanol solutions has been revealed by i.r. spectral data.²³ It is not plausible

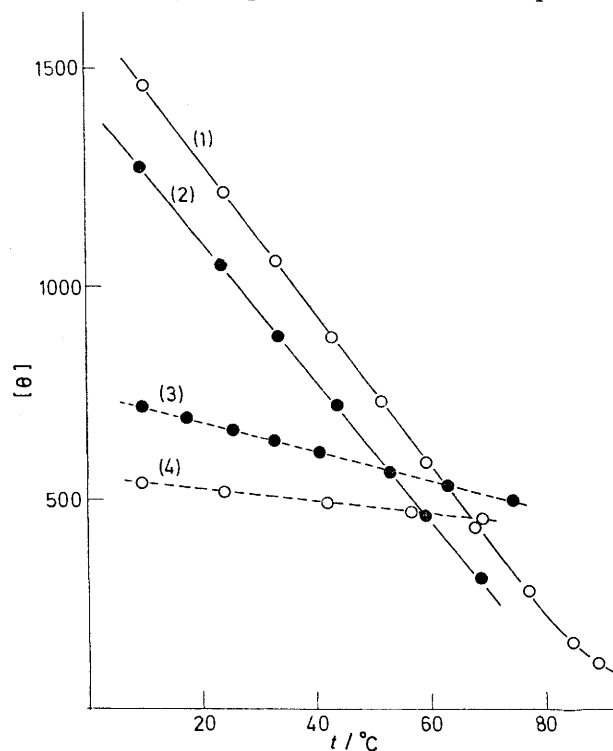


FIGURE 6 Temperature dependence of $[\theta]$ of the 2-benzoylbenzoic acid-(—)-amphetamine and *N*-(3-benzoylbenzoyl)amphetamine: (1) 2-benzoylbenzoic acid ($7.41 \times 10^{-3}M$) and (—)-amphetamine ($7.35 \times 10^{-3}M$) in toluene; (2) 2-benzoylbenzoic acid ($7.34 \times 10^{-3}M$) and (—)-amphetamine ($7.26 \times 10^{-3}M$) in benzene; (3) *N*-(3-benzoyl)amphetamine ($4.58 \times 10^{-3}M$) in benzene; (4) *N*-(3-benzoyl)amphetamine ($4.37 \times 10^{-3}M$) in ethanol

that an asymmetric carbon atom formed from ring tautomerism will cause the c.d. effect, since the strength of the band is not proportional to the amount of the ring tautomer present. The formation of an amide or a keto-imine may be ruled out since we could not detect such compounds by g.l.c., or by i.r. and n.m.r. spectroscopy. From our results, it appears likely that (I) forms a 1:1 hydrogen-bonded complex with amphetamine which immediately changes to a salt and the proximity of the counter ions of the salt is the origin of the induced c.d. band. The presence of a peak at 1370 cm^{-1} in the i.r. spectrum due to carboxylate ion suggests that the product of the interaction between (I) and amphetamine is not a hydrogen-bonded complex but a

²² E. G. Höhn and O. E. Weigang, jun., *J. Chem. Phys.*, 1968, **48**, 1127.

²³ K. Bowden and G. R. Taylor, *J. Chem. Soc. (B)*, 1971, 1390.

salt, a contact ion pair, a solvent separated ion pair, and/or free ions. The relative strength of the c.d. band of the (I)-amphetamine system in various solvents shows a strict inverse linear relationship with the polarity of the solvent except in the case of the two ethers, dioxan and tetrahydrofuran. On the other hand, Hayward *et al.*³ reported that the induced c.d. of the (+)-D-isosorbide-benzophenone and -3-methylcyclohexanone systems, in which specific bonding was not involved, did

not show any solvent effects, suggesting that solvent polarity does not essentially affect the induction of c.d. Therefore, the solvent dependence of c.d. in our case may be connected with the dissociation of the tight contact ion pair to the solvent separated ion pair or free ions.

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