Ion-pair Aggregation of a Long-chain Carboxylic Acid and an Amine in Benzene studied by Induced Circular Dichroism

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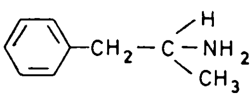
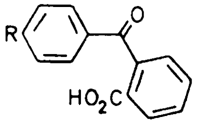
Association of the ion-pairs from 2-(4-alkylbenzoyl)benzoic acids and (−)-(*R*)-amphetamine or (+)-(*R*)-*N*-cetyl-α-phenylethylamine in benzene was investigated by i.c.d. In non-polar solvents, such as benzene and carbon tetrachloride, the ion-pairs of (−)-(*R*)-amphetamine and (+)-(*R*)-*N*-cetyl-α-phenylethylamine with 2-(4-alkylbenzoyl)benzoic acids where the alkyl group consists of a hydrocarbon chain with more than six carbon atoms, exhibited association phenomena in solutions of salt concentrations $<10^{-3}$M; these produced large increases in the magnitude of the i.c.d. effect. Aggregation did not occur in relatively polar solvents such as tetrahydrofuran, acetonitrile, and methanol. The aggregates are assumed to be spherical micelles with the polar groups in the core thus giving polar space. The core of the micelles containing (+)-(*R*)-*N*-cetyl-α-phenylethylamine is a large asymmetric space which results in the large i.c.d. on the chromophore of the guest molecule.

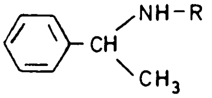
INDUCED circular dichroism (i.c.d.) is one of the most useful methods for the study of molecular interactions, since the sign and magnitude of the Cotton effect are very sensitive to the direction and distance between the chromophore of an achiral molecule and the asymmetric centre of a chiral molecule.[1-3] For example, the ion-pair equilibrium of 2-benzoylbenzoic acid and amphetamine in non-polar solvents was successfully investigated with this technique by which induced optical activity was observed in the region of the $n-\pi^*$ transition of the carbonyl group.[4,5]



(I)



(III) R = H
(IV) R = CH_3
(V) R = C_2H_5
(VI) R = $n-C_3H_7$
(VII) R = $n-C_4H_9$
(VIII) R = $n-C_8H_{17}$
(IX) R = $n-C_{12}H_{25}$
(X) R = $n-C_{16}H_{33}$



(II)
a; R = H
b; R = $n-C_{15}H_{31}$

In opposition to our conclusions on the ion-pair equilibrium of 2-benzoylbenzoic acid–amphetamine,[4,5] the ion-pairs from 2-benzoylbenzoic acids with a long aliphatic substituent at the 4-position of the benzoyl group and amphetamine and *N*-cetyl-α-phenylethylamine show pronounced aggregation phenomena, resulting in large increases in the magnitude of the i.c.d. effect. In this paper, we report the results for ion-pair aggregation of these compounds in benzene, and examine the utility of the i.c.d. technique for the study.

EXPERIMENTAL

Materials.—(−)-(*R*)-Amphetamine (I), $[\alpha]_D^{20}$ −33° (neat) and (+)-(*R*)-α-phenylethylamine (IIa), $[\alpha]_D^{20}$ +39° (neat), were purchased from Aldrich and redistilled *in vacuo* before use. (+)-(*R*)-N-*Cetyl-α-phenylethylamine* (IIb) was prepared by the method of Westphahl[6] (Found: C, 82.65; H, 12.75; N, 4.05. $C_{24}H_{24}N$ requires C, 83.4; H, 12.55; N, 4.05%), $[\alpha]_D^{25}$ +0.026° (in benzene). 2-Benzoylbenzoic acid and 4-alkylbenzoyl derivatives were prepared by the method of Friedel and Crafts[7] with phthalic anhydride and the corresponding alkylbenzene. 2-Benzoylbenzoic acid (III) had m.p. 126—127 °C, 2-(4-methylbenzoyl) benzoic acid (IV) 137.5—138°, 2-(4-ethylbenzoyl)benzoic acid (V) 127.5—128°, 2-(4-propylbenzoyl)benzoic acid (VI) 124—125°, 2-(4-butylbenzoyl)benzoic acid (VII) 96—97°, 2-(4-laurylbenzoyl)benzoic acid (VIII) 126—127°, 2-(4-dodecylbenzoyl)benzoic acid (IX) 99°, and 2-(4-pentadecylbenzoyl)-benzoic acid (X) 89—90°. Purity was checked by elemental analysis. Solvent benzene (Merck spectral grade) was used without further purification.

Method.—C.d. spectra were taken with a JASCO-J-10 automatic spectrometer using a quartz cell of 1 or 10 cm

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[1] A. D. Buckingham, *Accounts Chem. Res.*, 1974, 258.

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

[3] J. A. Schellman, *J. Chem. Phys.*, 1966, **44**, 55.

[4] N. Tokura, T. Nagai, S. Takenaka, and T. Oshima, *J.C.S. Perkin II*, 1974, 338.

[5] S. Takenaka, K. Kondo, and N. Tokura, *J.C.S. Perkin II*, 1974, 1749.

[6] O. Westphal and D. Jerchel, *Ber.*, 1940, **73**, 1002.

[7] C. Friedel and J. M. Crafts, *Compt. rend.*, 1878, **86**, 1368.

width. Temperature variation was within ±1°. The molecular ellipticity $(\theta)_{\text{max.}}$ was evaluated by equation (1),[8]

$$(\theta)_{\text{max.}} = 3330A_{\text{lr}}/cl \qquad (1)$$

where A_{lr} is a difference in absorbance between the left and right circularly polarized light, l is the path length of the light, and c the concentration of the 1 : 1 salt.

RESULTS

Solvation of (III)–(I) *and* (X)–(I) *Salts in Mixed Solvent.*—The i.c.d. effects of the salts were investigated in carbon tetrachloride–benzene where the latter is expected to interact strongly with the salts. The results are shown in Figure 1.

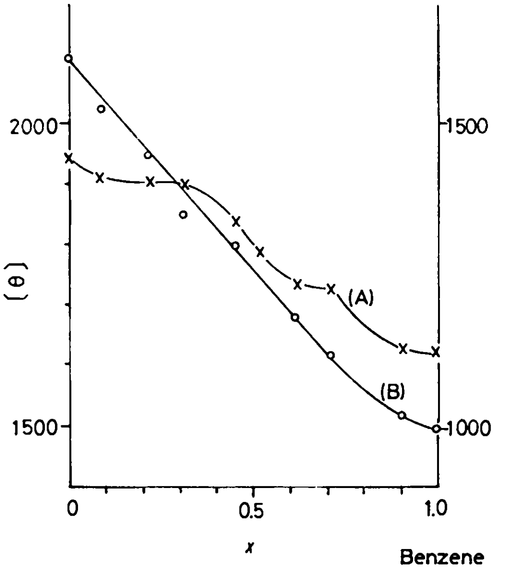

Figure 1 Solvent effects of the i.c.d. in carbon tetrachloride–benzene (x = mole fraction) at 17° of: (A) (III)–(I) (1.02×10^{-2}M) and (B) (X)–(I) (1.02×10^{-2}M)

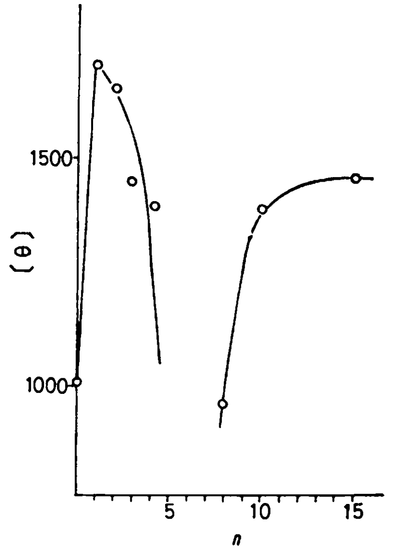

Figure 2 Effect of carbon chain length (n) on i.c.d.: [Acid] = [amphetamine] = 1.02×10^{-2}M; solvent benzene; 17°

Stepwise solvation by benzene of the (III)–(I) salt is apparent in the mixed solvent system and the Δθ values for the first, second, and third steps are 42, 172, and 99, respectively. This pattern is characteristic of aromatic sol-

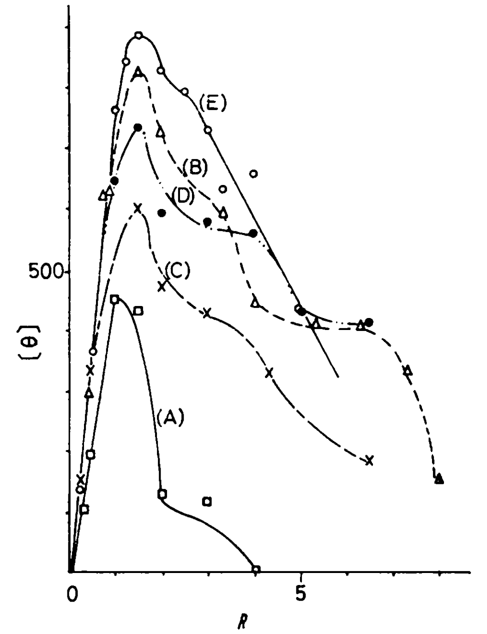

Figure 3 Variation of molecular ellipticity [θ] with [acid] : [amphetamine] molar ratio R: (A) (III)–(I); (B) (VII)–(I); (C) (VIII)–(I); (D) (IX)–(I); (E) (X)–(I). [Amphetamine] = 5×10^{-4}M; solvent benzene; 17°

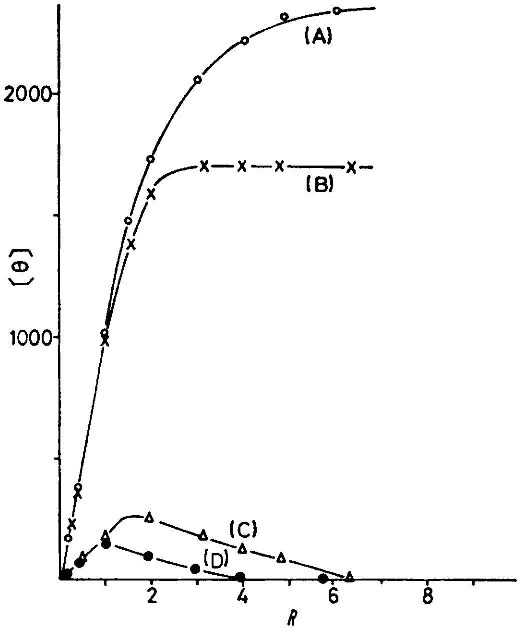

Figure 4 Variation of molecular ellipticity [θ] with [acid] : [amine] molar ratio R: (A) (III)–(IIb); (B) (X)–(IIb); (C) (X)–(IIa); (D) (III)–(IIa). [(IIa)] = [(IIb)] = 5×10^{-4}M; solvent benzene; 17°

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

vents. A simple curve was observed in the mixed systems carbon tetrachloride–dioxan,–tetrahydrofuran, –acetonitrile, and –n-butanol. On the other hand, the (X)–(I) salt did not show a characteristic pattern in any of these solvent systems.

Effect of Chain Length on I.c.d.—The 4-alkyl substituent of the benzoyl group has a large effect on the magnitude of the i.c.d. as shown in Figure 2. A plot of θ *versus* the number of carbon atoms in the chain indicate that the θ values go through two maxima with a minimum for a chain length of 6—7 carbon atoms. The effect of chain length is more apparent in Figures 3 and 4.

TABLE 1

Miceller effects on the i.c.d. of benzophenone derivatives

System	(θ)	5×10^{-4}M-HOAc Added	$\lambda_{max.}$/nm
(III)[a] + (I)[b]	115	0	325
(X)[a] + (I)[b]	730	660	325
Benzophenone[c] + (IIb)[c]	296	296	340
9-Oxofluorene-1-carboxylic acid[d] + (IIb)[b]	315	315	(*ca.* 400)
(III)[a] + (IIa)[b]	198	0	325
(III)[a] + (IIb)[b]	1 596	1 580	325

[a] 1.5×10^{-3}M. [b] 5.0×10^{-4}M. [c] 1.5×10^{-2}M at 16°. [d] 7.5×10^{-4}M.

Other chain length effects due to micelle formation on the i.c.d. of benzophenone derivatives are summarized in Table 1.

Acetic acid was added to exclude i.c.d. effects arising from the ion-pair. The i.c.d. from ion-pairs such as (III)–(I) and (III)–(IIa), disappears readily on addition of small portions of acetic acid.

TABLE 2

Solvent effects on the i.c.d. of 1.5×10^{-3}M-(III)–5×10^{-4}M-(IIb)

Solvent	(θ)	$\lambda_{max.}$/nm
Carbon tetrachloride	1 800	327
Benzene	1 330	326
Acetonitrile	172	320
Tetrahydrofuran–methanol	0	

Solvent Effects on Aggregation of Salt (III)–(IIb).—The solvent effect on the i.c.d. of (III)–(IIb) is larger than that of (III)–(I) arising from the ion-pair.

DISCUSSION

The Cotton effect of optically inactive molecules is considered to be induced in two ways:[9] (a) an asymmetric perturbation of the electronic transition in the chromophore of an achiral molecule due to optically active substrate or solvent; (b) structural rearrangement by asymmetric interaction between the chiral and achiral molecules, leading to intrinsically optically active molecules, on time average. In our case, the optical activity originates from mechanism (b) for all 2-benzoylbenzoic acids and from mechanism (a) benzophenone and 9-oxofluorene-1-carboxylic acid.[10] The magnitude of the i.c.d. is in proportion to the magnitude of the molecular interaction between the chiral and achiral molecules. This correlation was applied qualitatively to this study.

The partial processes for carboxylate–ammonium ion equilibria are formulated as (2)—(6). The ionization

$$R^1CO_2H + R^2NH_2 \rightleftharpoons R^1CO_2^-, R^2NH_3^+ \rightleftharpoons R^1CO_2^-||R^2NH_3^+ \quad (2)$$

$$R^1CO_2H + R^1CO_2^-||R^2NH_3^+ \rightleftharpoons R^1CO_2\cdots H\cdots R^1CO_2^-||R^2NH_3^+ \quad (3)$$

$$R^1CO_2H + R^1CO_2^-||R^2NH_3^+ \rightleftharpoons R^1CO_2H + R^1CO_2 + R^2NH_3^+ \quad (4)$$

$$mR^1CO_2^-||R^2NH_3^+ \rightleftharpoons (R^1CO_2^-, R^2NH_3^+)_m \quad (5)$$

$$(R^1CO_2^-, R^2NH_3^+)_m + nR^1CO_2H \rightleftharpoons (R^1CO_2^-, R^2NH_3^+)_mR^1CO_2H_n \quad (6)$$

R^1CO_2H = 2-(4-alkylbenzoyl)benzoic acid
R^2NH_2 = amphetamine or α-phenylethylamine

equilibrium (2) involving contact and solvent separated ion-pairs is regarded as producing the i.c.d. effect.

The curious pattern developed by the (III)–(I) salt (Figure 1) is explained by the solvation model for an ammonium ion [process (2)] postulated by Armstrong *et al.*,[11] and Takenaka *et al.*[12] The plot in Figure 2 indicates that the magnitude of the i.c.d. depends on two factors. The change in the region of 1—4 carbon atoms coincides with the change of the spectroscopic moments[13] related to the i.c.d. mechanism and the steric hindrance to formation of the ion-pairs. The θ values in this region show a linear correlation with the σ^+ values of Sager *et al.*[14] Therefore, the i.c.d. in this region arises mainly from process (2).

On the other hand, the (X)–(I) salt in Figure 1 does not show a characteristic pattern in carbon tetrachloride–chloroform, –acetonitrile, and –tetrahydrofuran and also carbon tetrachloride–benzene, indicating that systematic solvation by benzene of the ammonium ion does not occur or that benzene is not present near the ammonium and carboxylate ions. Anyway, process (2) seems not to be important for the (X)–(I) salt. The i.c.d. in the region of 7—15 carbon atoms in Figure 2 increases markedly upon chain elongation and becomes constant independent of the chain length. As is evident from Figures 3 and 4, the magnitudes of the i.c.d. of the long-chain derivatives (X)–(I), (III)–(IIb), and (X)–(IIb) are larger than those of (III)–(I), (III)–(IIa), and (X)–(IIa) for low concentrations. These facts suggest that the benzophenone chromophore lies in a large asymmetric space. Consequently, the i.c.d. in this region must originate from the aggregation process (5). Though the i.c.d. of (III)–(I) which arises from process (2) depends on

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

[10] N. Tokura, unpublished results.

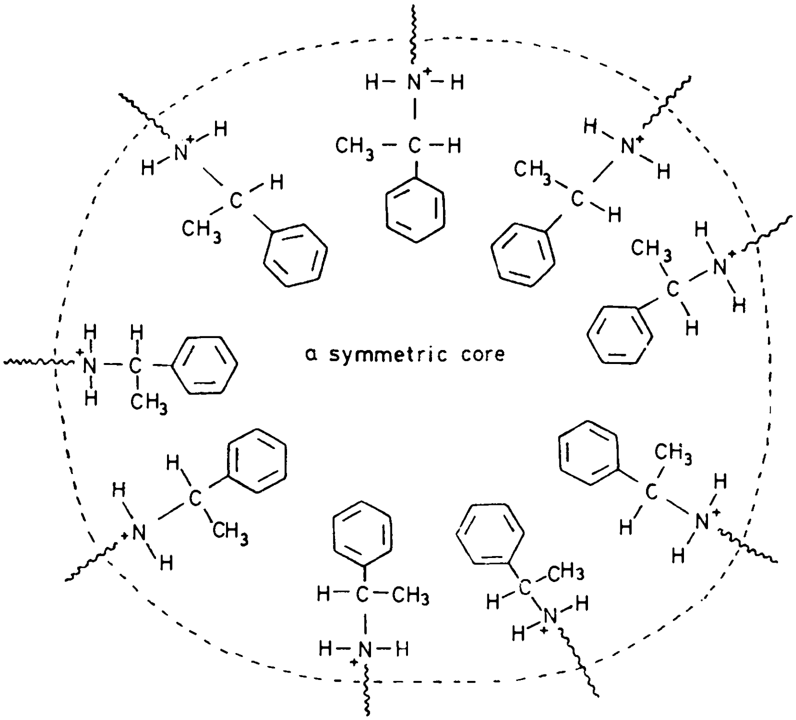
[11] R. S. Armstrong, M. J. Aroney, R. K. Duffin, H. J. S. Stootman, and R. J. W. LeFèvre, *J.C.S. Perkin II*, 1973, 1272, 1362.

[12] S. Takenaka, K. Kondo, and N. Tokura, *J.C.S. Perkin II*, in the press.

[13] J. R. Platt, *J. Chem. Phys.*, 1951, **19**, 263.

[14] C. D. Ritchie and W. F. Sager, *Progr. Phys. Org. Chem.*, 1964, **2**, 323.

the solvent polarity and shows a linear correlation with the E_T values of Dimroth,[15] the i.c.d. of long-chain derivatives arising from process (5) is very sensitive to solvent polarity (Table 2) and does not show a linear correlation with E_T, indicating that process (5) is important only in non-polar solvents. For (III)–(I) and (III)–(IIa) (Figure 4), the i.c.d. arising from process (2) is very weak and decreases upon addition of excess of carboxylic acid. Two reasons may be considered for the rapid reduction in the i.c.d. in this region. One is that the excess of acid binds to the ion-pairs by hydrogen bonding to give $R^1CO_2\cdots H\cdots R^1CO_2^-||R^2NH_3$, where the signs of the i.c.d. of the hydrogen-bonded part, R^1CO_2H, and the ionic part, $R^1CO_2^-$, are negative and positive, respectively. Thus formation of this complex by addition of an excess of acid is the cause of the reduction of i.c.d. [process (3)]. The other reason is that the dissociation process (4), accelerated by the assistance of an excess of carboxylic acid, occurs to form free ions resulting in the rapid reduction of the i.c.d. In such cases process (3) is preferred.[10] On the other hand, the aggregation process (5) followed by the inclusion process (6) must proceed preferentially to the addition of an excess of carboxylic acid, giving an increase in the i.c.d., as for (III)–(IIb) and (X)–(IIb) in Figure 4. The plots for (III)–(IIb) and (X)–(IIb) form plateaux at amine–acid ratios of 1 : 6–1 : 7 and 1 : 2 respectively.



possible model of the aggregate

The i.c.d. arising from process (2) for (III)–(I), (III)–(IIa) and 9-oxofluorene-1-carboxylic acid–(IIa) (Table 1) is very weak and disappears on addition of small portions of acetic acid, indicating that there are interactions between the carboxylate and ammonium ions. On the other hand, the i.c.d. arising from process (5) for (X)–(I), (III)–(IIb), and 9-oxofluorene-1-carboxylic acid–(IIb) is 'extremely' large and independent of the addition of acetic acid. These facts suggest that the aggregate is tight and stable in non-polar solvents. The 'extremely' means that the θ values of benzophenone and 9-oxofluorene-1-carboxylic acid in the presence of much lower concentrations of the chiral amine are of equal magnitude in chiral media.[9,16] That is to say, these molecules are in a large asymmetric space in the chiral media. Consequently, a spherical micelle model is assumed for the aggregates of long-chain derivatives of carboxylate and ammonium ions, where the polar head group must lie in the core of the micelle.[17-19] The core of the aggregate is large, polar, and asymmetric enough to include a small number of relatively polar compounds and induces the large Cotton effect on the chromophore of the achiral compounds in the core. Acid (X) of the (X)–(IIb) salt is too large to enter the core and it is not known whether the spherical model is applicable or not. Benzene is almost absent in the core, since specific solvation by benzene of (X)–(I) salt was not observed (Figure 1).

Self-association of the carboxylate and ammonium

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[15] K. Dimroth, C. Reichardt, T. Siepmann, and F. Bohlmann, *Annalen*, 1963, **661**, 1.

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

[17] P. H. Elworthy, A. T. Florence, and C. B. Macfarlane, 'Solubilization by Surface Active Agents,' Chapman and Hall, London, 1968.

[18] F. M. Fowkers, in 'Solvent Properties of Surfactant Solutions,' ed. K. Shinoda, Marcel Dekker, New York, 1967, p. 65.

[19] A. Kitahara, in 'Cationic Surfactants,' ed. E. Jungerman, Marcel Dekker, New York, 1970, p. 289 and references therein.

ions due to repulsion between the polar group and non-polar solvents seems to be the reason for the formation of the aggregate. The better solvating media for the ions, such as tetrahydrofuran, acetonitrile, and methanol, do not induce aggregation phenomena as shown in Table 2. Similar results were also obtained from alkylammonium propionate micelles.[20]

The aggregates from (X)–(I) and (IX)–(I) are essentially different from (III)–(IIb) in chiral nature, since the aggregates of the former have no asymmetry in themselves and the latter is inherently asymmetric. This is reflected in the differences in the magnitude of the i.c.d. (Figures 3 and 4).

We conclude that the carboxylate and ammonium ions of long-chain derivatives with a chain of more than six carbon atoms, readily form aggregates in non-polar solvents, and the core of the aggregates is polar space. When the long-chain carboxylic acids or amines are chiral the core turns into a large asymmetric space. Although we have no confirmation for this conclusion, similar results were also obtained from n.m.r. measurements.[20-22]

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[21] N. Muller, *J. Phys. Chem.*, 1975, **79**, 287.

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