Formation of Inclusion Complexes of Benzophenone Derivatives; β-Cyclodextrin studied by Induced Circular Dichroism

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Benzophenone derivatives form 1 : 1 inclusion complex with β-cyclodextrin, exhibiting an induced optical activity. The induced c.d. data arising from the n–π^* electric transition of the carbonyl group indicate that complex formation is enhanced by hydrophobic substituents and is prevented by hydrophilic ones on the aromatic rings, and that the substituents often exert an influence on the structure of the inclusion complex.

THE β-cyclodextrin molecule contains a cavity (diameter of 7.5, thickness 6, thickness of wall 3.5 Å), and is known to form non-covalently bonded complexes with various organic compounds in aqueous solution.[1-3] A molecule in the cavity exhibits an induced optical activity as a result of asymmetric interaction.[4-7] We have briefly reported that benzoylbenzoic acids form molecular complexes with β-cyclodextrin exhibiting a large induced c.d. effect on the n–π^* transition of the carbonyl group.[8] We now describe some further studies on the complex formation.

EXPERIMENTAL

The optical procedures are described in ref. 9. Benzophenone derivatives were prepared by Friedel–Crafts reactions,[10] and β-cyclodextrin (Nakarai Chemicals) was recrystallized from water. Compounds are referred to by number as shown in the Table.

RESULTS

In aqueous solutions of β-cyclodextrin (1), benzophenone derivatives exhibit induced circular dichroism (i.c.d.) arising from the n–π^* electronic transition of the carbonyl group in the 300—400 nm region; data are summarized in the Table. The molecular ellipticities were calculated from the equation, $\theta = 3\,300\ \Delta A/C$ where C is the total (initial) concentration of the substrate. The spectra of methoxy-, nitro-, and halogeno- (F, Cl, or Br) benzophenones also exhibit one positive Cotton effect, similar to those of the alkyl derivatives (2).

The ratio of substrate to (1) in the complexes was determined to be 1 : 1 by the continuous variation method.[11] The equilibrium constant K for complex formation was evaluated by applying the Benesi–Hildebrand equation[12] to the i.c.d. data, and the results are shown in the Table.

Temperature Dependence.—Both intensity and features of the i.c.d. spectra are strongly dependent on temperature, as shown in the Figure where the molecular ellipticities given are the values at 330 nm for (4d) and (5e) and at the maxima indicated in the Table for the others. The maximal intensities of the derivatives (2) decrease with increasing temperature without change in features, and the plots of log $|\theta|$ *vs.* T^{-1} give approximately straight lines. The chiroptical enthalpies for these derivatives are estimated

I.c.d. of benzophenone–β-cyclodextrin complexes in aqueous solution (pH 7.2), at 20 °C ([benzophenone derivative] 0.1—0.5 × 10^{-2} mol l^{-1}; [β-cyclodextrin] 0.3—1.5 × 10^{-2} mol l^{-1})

Compounds	$[\theta]_{max.}$	$\lambda_{max.}$	$10^{-2}K$/l mol^{-1}
Benzophenone (2a)	1 560	330	8.75
2-Methylbenzophenone (2b)	1 708	330	45.6
3-Methylbenzophenone (2c)	1 890	326	13.8
4-Methylbenzophenone (2d)	959	326	7.77
4-Ethylbenzophenone (2e)	481	328	
2,4,6-Trimethylbenzophenone (2f)	1 264	338	
2-Benzoylbenzoic acid (3a)	87	322	1.50
	405	322	6.70 (pH 4)
2-(2-Methylbenzoyl)benzoic acid (3b)	2 111	328	
2-(3-Methylbenzoyl)benzoic acid (3c)	297	335	
2-(4-Methylbenzoyl)benzoic acid (3d)	−182	324	
2-(4-Ethylbenzoyl)benzoic acid (3e)	−102	320	
2-(2,4,6-Trimethylbenzoyl)-benzoic acid (3f)	79	350	
	81	350 (pH 9)	
3-Benzoylbenzoic acid (4a)	360	330	5.78 (pH 9)
	1 146	330	19.7 (pH 4)
3-(2-Methylbenzoyl)benzoic acid (4b)	1 556	335	
3-(3-Methylbenzoyl)benzoic acid (4c)	965	332	
3-(4-Methylbenzoyl)benzoic acid (4d)	−144	355	5.00
	46	323	
3-(4-Ethylbenzoyl)benzoic acid (4e)	−3 618	334	13.2
3-(2,4,6-Trimethylbenzoyl)-acid (4f)	1 940	340 (pH 9)	
4-Benzoylbenzoic acid (5a)	4 092	334	6.25 (pH 9)
	3 158	332	18.3 (pH 4)
4-(2-Methylbenzoyl)benzoic acid (5b)	574	342	
4-(3-Methylbenzoyl)benzoic acid (5c)	1 358	342	
4-(4-Methylbenzoyl)benzoic acid (5d)	4 294	340	9.21
4-(4-Ethylbenzoyl)benzoic acid (5e)	−45	376	11.1
	2 421	330	
4-(2,4,6-Trimethylbenzoyl)-benzoic acid (5f)	771	348 (pH 9)	

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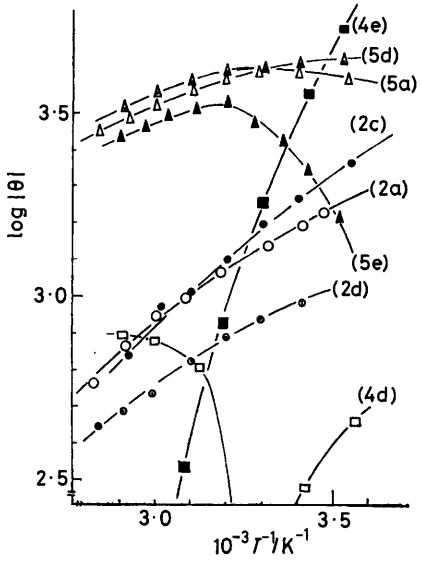
as −1.5 to −3 kcal mol^{-1}. On the other hand, the spectra of (4d and e), (3d and e), and (5e) exhibit a negative Cotton effect which is far more sensitive to temperature change, and becomes positive as the temperature rises, *e.g.* θ = −5 976 (334) at 10 °C, −1 729 (333) at 30 °C, −346 (334) at 50 °C, and 109 (330 nm) at 70 °C for (4e). These characteristic changes are observed in the low temperature region; the positive Cotton effect in the high temperature



Dependence of the logarithm of absolute molar i.c.d. for the complexes of β-cyclodextrin with the benzophenones (2a), (2c), (2d), (4d), (4e), (5a), (5d), and (5e) on temperature (in aqueous solution, pH *ca.* 7.2; [benzophenone] 0.5 × 10^{-2}; [β-cyclodextrin] 1.5 × 10^{-2} mol l^{-1})

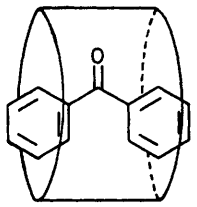
region shows similar behaviour to that of the derivatives (2) *e.g.* (5a, d, and e) in the Figure. The temperature dependence is completely reversible.

pH *Dependence.*—The i.c.d. effects of the derivatives (2) are almost independent of pH in the range 2—5. The i.c.d. intensities of (3a) and (4a) become large on increasing the acidity, *e.g.* θ = 0 at pH 8.15 and 694 (322 nm) at pH 2.99 for (3a); θ = 360 (330) at pH 8.83 and 2 292 (330 nm) at pH 2.62 for (4a). The inverse tendency is observed with (5a) [θ = 4 113 (334) at pH 9.49 and 521 (334 nm) at pH 2.71]. The θ values plotted as a function of pH give pK values 4.08, 3.97, and 3.85 for (2a), (4a), and (5a), respectively (at 20 °C). The variations are completely reversible.

DISCUSSION

It is apparent that benzophenone derivatives and β-cyclodextrin (1) in aqueous solution form 1 : 1 molecular complexes which exhibit induced optical activity in the region 300—400 nm. We are confident that the substrates are incorporated into the cavity of (1) to form an inclusion complex from the following indirect evidence. (i) Large substrates such as 2-(1-naphthyl)-benzoic acid, 2-(2,4,6-tri-isopropylbenzoyl)benzoic acid, dimesityl ketone, and (3f) exhibit no i.c.d. or only a very weak effect. (ii) Although (3a), (4a), and (5a) in aqueous solutions of D-glucose exhibit weak i.c.d.,* the intensities are almost independent of temperature and pH. Moreover, D-glucose in aqueous solution does not induce optical activity in the derivatives (2) ([substrate] 0.3 × 10^{-2}; [D-glucose] 5 × 10^{-2} mol l^{-1}). (iii) The pK values for the complexes of (3a), (4a), and (5a) do not agree with those in aqueous solution.[13] A possible model for the inclusion complex of (2a) is depicted (A). The substrate in the cavity is presumably rigid since the size of the substrate is nearly equal to that of the cavity. A major source of the large induced optical activity may be the preferential formation of an optically active isomer (P or M helix) of the substrate in the cavity by freezing of rotation of both phenyl rings on a time-averaged basis; rigid homologues of (2a) (fluorenone and anthrone) exhibit only weak i.c.d. under the same conditions.

As shown in the Table, substituents influence both the formation of the inclusion complex and the structure, as reflected in changes in the i.c.d. spectrum. In general, the equilibrium lies well over to the side of complex formation, and hydrophobic substituents such as methyl and ethyl groups enhance this in the order H < Me < Et. In the typical example (2b) the methyl group at the *ortho*-position shields the hydrophilic carbonyl group and increases the hydrophobicity of the whole molecule. However, the effects of these groups at the *para*-position are comparatively weak. On the other hand, the



(A)

carboxy-group inhibits complex formation, and its hydrophilic effect becomes weaker in the order *ortho* > *meta* > *para*. The remarkable example (3a) is explicable by the inverse argument to that for (2b). Consequently, the formation of a hydrophobic bond is an important driving force for the inclusion complex formation. Comparison of the K values of (4a) and (5a) under acidic conditions with that of (2a) reveals that hydrogen bonds between the carboxy-groups of the substrates and hydroxy-groups of β-cyclodextrin (1) also aid inclusion complex formation.

Substituents in the phenyl rings perturb the n–π* transition and may contribute to geometrical changes in the inclusion complex, though the resulting effects on the i.c.d. spectra are not easy to distinguish. Nevertheless, it is certain that the temperature dependence of the i.c.d. arises mainly from the latter origin. The linear decrease (Figure) in i.c.d. intensities of the derivatives (2) and halogeno-, nitro-, and methoxy-derivatives of

* θ = −33(330), −220(335), and −170(335 nm) for (3a), (4a), and (5a), respectively (substrates; 1 × 10^{-2}, D-glucose; 3.6 × 10^{-2} mol l^{-1} at 20 °C) (results from our laboratory).

[13] I. Heibron, 'Dictionary of Organic Compounds,' Maruzen, Tokyo, 1965, vol. 1, p. 357.

(2a) with increasing temperature could be ascribed to a decrease in concentration of the complex rather than to a structural change. Taking into account the symmetry of the substrate, the structure of the complex is assumed to be similar to the depicted model (A) where the substrate in the cavity is held by hydrophobic bonds alone. On the other hand, the spectra of the derivatives (3) and (4) exhibit complicating features comprising both negative and positive Cotton effects. The resulting plots of log $|\theta|$ *vs.* T^{-1} deviate from linearity, especially in the low temperature region. The chiroptical enthalpy for (4e) estimated from the negative Cotton effect is *ca.* −15 kcal mol^{-1}. The non-linearity must be attributed to geometrical changes in the complex rather than to a decrease in its concentration. The geometry of the complexes which is stable only in the low temperature region is assumed to be slightly different from the depicted model, and the substrate in the cavity to be held by more than one type of force. The most likely binding force other than a hydrophobic interaction is hydrogen bonding between the carboxy-group of the substrate and the hydroxy-groups of (1).* The temperature dependence of the i.c.d. intensities of the derivatives (5) except for (5d and e) resembles that of the derivatives (2), indicating a geometrical similarity between the inclusion complexes. Methyl and ethyl groups at the *para*-position complicate both the spectral features and the temperature dependence [*e.g.* (4e) and (5d and e)]. In these cases, a displacement of the hydrophobicity centre of the whole molecule must be the cause of the structural change. It is not known whether inversion of the i.c.d. sign represents an inversion of the absolute configuration of the substrate in the cavity. Thus the geometry of the complex is strongly affected by hydrophobic substituents at terminal positions and by hydrophilic substituents near the centre of the molecule.

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* However, the i.c.d. spectra of (3a), (4a), (4e), and (5a) are completely independent of added urea concentration ([substrate] 0.5×10^{-2}; [β-cyclodextrin] 1.5×10^{-2}; [urea] $0.5—5.0 \times 10^{-2}$ mol l^{-1}, at 20 °C).