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Induced optical activity in cyclodextrin complexes

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ABSTRACT. The phenomenon of induced optical activity (IOA) is briefly described. The IOA that occurs in complexes of cyclodextrins (CYDs) with achiral and chiral organic molecules is examined. The types of information obtained using chiroptical spectroscopic methods are described. It is shown how these methods in conjunction with the theoretical representation of this phenomenon can be used to obtain information about the fine structure of the complexes, including the orientation of the "guest" molecule in the cavity of the "host" molecule, the formation of two-guest complexes, and the selection of chiromers by complexation.

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I. Introduction

Rapid progress in the chemistry of cyclodextrins has occurred because of the unique ability of these compounds to react with a large number of organic and inorganic compounds to form complexes of the type "host–guest" (H–G),[7] which are classed as virtual topological isomers,[8] and it is very closely related to the development of a new topic–supramolecular organic chemistry.[9] As a result of this property CDXs can be used as models of enzymes,[3,10] catalysts of chemical reactions,[11] modifiers of pharmaceutical compounds,[12–14] and in a number of other areas of science and industry.[14]

One of the most important properties of CDXs that distinguishes them from the majority of synthetic hosts, such as podands, coronands, cryptands, etc.,[7] is their chirality, namely the property that distinguishes a compound from its mirror image.[15] It is true that the overall chirality of CDX molecules is regarded as insignificant because of their symmetrical structure,[16] but sufficient information has been collected for the chiral field of the CDX cavity to be considered capable of inducing optical activity in the electronic transitions of the guest molecule. In this review an attempt is made for the first time to correlate these data in order to demonstrate the potentialities of chiroptical methods, induced optical rotatory dispersion (IORD), and principally induced circular dichroism (ICD) for studying the fine structure of CDX complexes.

II. Induced optical activity

Induced optical activity (IOA) denotes[17] the induction of optical activity in the molecules of an achiral compound (the chromophore) when they are in contact with the molecules of a chiral compound (the inducer). The main consequence of this interaction is asymmetric perturbation of the electronic transitions of the chromophore by the chiral field of the inducer, with the result that the transitions become optically active and are exhibited in the optical rotatory dispersion (ORD) or induced optical rotatory dispersion (IORD) spectra and circular dichroism (CD) or induced circular dichroism (ICD) spectra. The asymmetric perturbation can be so intense that it stabilises certain chiral conformers of the chromophore, thus intensifying the parameters of the ICD spectra by many times. This occurs in many CDX complexes (see below). The phenomenon of ICD occurs for low-molecular-weight chromophores, such as saturated and aromatic ketones,[18–21] aliphatic nitrites,[20–21] azulenes,[22] and free-radical hydrazines[23] in the presence of the following inducers: 2,3-butanediol,[18] menthol,[19,27] diethyl tartrate,[20] nopinone,[22] 2-octanol,[23] and *N*-cetyl-α-phenylethylamine.[24] Metal complexes can also be subject to induced optical activity[18,25–29] from butanediols,[18,26] ethyl tartrates,[25] amino alcohols,[27,29] and amino acids.[28]

High-molecular-weight inducers, in particular biopolymers, have proved more effective than low-molecular-weight inducers. Thus, polypeptides give rise to strong IOA in dyes[30,31] and bile pigments,[32] while nucleic acids produce IOA in dyes.[33–35] Carbohydrates also give rise to IOA, with both monosaccharides (in ketones[36] and metal complexes[37]) and particularly polysaccharides being active. The IOA of pyrene and tetracyanonaphthodimethane in triacetylcellulose films,[38] azo dyes and bacterial polysaccharides.[39] and chitosan[40] can be given as an example. The IOA in the complexation of amylose with iodine[41] and in the complexation of anionic polysaccharides with cationic dyes[42,43] have been studied in particular detail. The IOA produced by the cyclic oligosaccharides—cyclodextrins—is discussed in the present review. Synthetic chiral polymers also give rise to IOA,[44–47] and the inducer and chromophore can be present in the same polymer molecule.[45] The induction of optical activity by supermolecular chiral structures such as liquid crystals[48,49] and micelles[50–52] is worthy of note.

The degree of IOA depends primarily on the structure of the inducer and chromophore. If the chirality of the inducer were the only condition for IOA to occur, there would be an infinite number of inducer–chromophore systems with IOA, which does not correspond to reality. It is evident that the chirality of the inducer is a necessary but incomplete condition for IOA to occur. However, for the present it is not possible to give comprehensive details of the precise conditions (they will be briefly reviewed in the concluding section). It may simply be stated that one of the sufficient

conditions for IOA to occur is an ordered supermolecular organisation in the system polymeric inducer–chromophore which restricts the number of rotational and translational degrees of freedom of the chromophore. In fact, the most intense IOA has occurred in systems with internally organised polymeric inducers that have sections of regular spiral conformation of the polymer chain, which evidently gives rise to a chiral configuration of the chromophore molecules (the formation of an internally asymmetric chromophore). This situation occurs, for example,[43] in the system sodium carboxymethylcellulose (anionic polysaccharide, inducer)–safranine T (cationic dye, chromophore), in which the value of the apparent molar ellipticity [θ] in the ICD spectrum is 10^5.

The nonspecific inducer–chromophore interactions that occur when chromophores are dissolved in chiral solvents[18,19,21–23,26,36] or in achiral solvents with chiral additives[19,20,24,25,27–29,36,37] constitute the opposite extreme for IOA. It is thought that the inducer–chromophore interaction is a dispersion interaction, which is expressed as dispersion-induced optical activity and hence dispersion-induced circular dichroism (DICD).[37]

Since information about the relative configuration of guest–host molecules in CDX complexes may be derived from the chiroptical properties of the complexes based on a correlation between the structure and the rotational properties (see below), a brief consideration of the general theory of IOA is worthwhile.

The central model of the quantum mechanical theory of optical activity (OA) is the Rosenfeld equation[53,54]

$$R_{0k} = I_m\left\{\left\langle\psi_0\left|\overline{\mu}\right|\psi_k\right\rangle\left\langle\psi_k\left|\overline{m}\right|\psi_0\right\rangle\right\},$$

where R_{0k}, the rotatory strength of the kth electronic transition of a molecule, is generated when electric ($\overline{\mu}$) and magnetic ($\overline{m}$) dipole transition moments occur in it. The rotatory strength of the transition corresponds to the strength of the oscillator in the theory of electronic spectra and is therefore determined as the area under the band of the corresponding Cotton effect in the CD spectrum. The Rosenfeld equation, like the Schrödinger equation, requires a knowledge of the exact form of the wave functions of the ground (ψ_0) and excited (ψ_k) states of the molecule, which is known to be impracticable. That is why the quantum mechanical theory of OA is essentially a combination of different approximated approaches to the solution of the Rosenfeld equation.

The arbitrary division of a chiral molecule into achiral residues — oscillators or chromophores — forms the basis of all these approximations. At the same time it is thought that the optical activity of the electronic transitions of a given chromophore is induced by the nearest chiral centre, namely, it is induced optical activity.

One of the most widely used approximations for calculation is the Kirkwood–Tinoco theory of polarisabilities,[54–57] which is based on the rather broad assumption that it is possible to generate the rotatory strength R solely the interactions of the electric dipole transition moments of the chiral residue (inducer) and that of the chromophore. Since the electric dipole transition moment is proportional to the polarisability of the respective residue, it may be replaced experimentally by the more accessible polarisability of this residue. This theory is discussed in greater detail in Section III.

All the approaches to an approximate solution to the Rosenfeld equation essentially calculate the intramolecular IOA, so they can in principle also be used[58] to estimate intermolecularly induced optical activity, namely, IOA.

III. Information obtained from interpretation of the chiroptical properties of cyclodextrin complexes

The chiroptical properties of CDX complexes with various chromophores or guest molecules have been studied as follows:

Chromophore (guest)	Refs.
Carboaromatic compounds	59–119
benzene derivatives (including dyes)	59–88
napthalene derivatives (including dyes)	83, 85–87, 89–108
other carboaromatic derivatives	100, 109–119
Heteroaromatic compounds (including nucleic acids and their heteroaromatic components)	72, 73, 120–141
Organometallic compounds (ferrocence and its derivatives)	8, 101, 142–145
Metal complexes	81, 146–150
Carbonyl derivatives of alicyclic compounds (including prostaglandins)	151–155
Drugs	64, 65, 68, 72, 73, 128–131, 155–157

The vast majority of the above compounds fall into the category of carbo- and hetero-aromatic compounds, which is typical of COX complexes.[1,2]

Because of the symmetrical structure of CDX molecules as mentioned above,[17] their chiral cavities should not have a very marked ability to cause IOA. Another reason for this may be the generally low stability constants of these complexes,[1,2] which indicate that the chromophore is held insufficiently firmly in the CDX cavity. The experimentally determined values of [θ] lie in the region of 0.4–43 000 deg cm^2 dmol^{-1}, and in the majority of cases they gravitate to the upper end of this range, i.e., they are unexpectedly high. It is true that on the whole they are values of apparent molar ellipticity that are calculated assuming complete complexation of the guest. With the most frequently occurring guest–host molar ratio of 1:100 and stability constants of CDX complexes in the region of 30–3000 M^{-1} there is no doubt that complete complexation occurs.

In the vast majority of cases, studies have been made of the spectra of aqueous solutions of complexes, which are buffered in the case of proteolytic guest molecules. It has been shown, however,[142] that complexation is also possible in solutions of alcohols (ethylene glycol, diethylene glycol, triethylene glycol, etc.).

The information obtained from studies of the chiroptical properties of CDX complexes is analysed below in an order corresponding to the increase in its quantitative content.

1. Information similar to that obtained from electronic absorption spectra

The chiroptical spectra — ORD spectrum (Fig. 1*a*) (dependence of the molar rotation [M] on the wavelength λ) and CD spectrum (Fig. 1*b*) (dependence of the dichromic absorption ΔE or molar ellipticity [θ] on wavelength) — of a given chiral compound correspond to the electronic absorption spectrum of the same compound (Fig. 1*c*) in the form of a Cotton effect (positive Cotton effects are shown). If the compound is transparent in a given spectroscopic region, only a section of the electronic transition occurs in the ORD spectrum in the form of the so-called plain ORD curve (curve *AB* in Fig. 1*a*) and there is no Cotton effect in the CD spectrum or peak in the electronic absorption spectrum.

CDX complexes are particularly convenient for a study of their chiroptical properties, since CDXs as inducers (hosts) are transparent in the accessible spectroscopic region, while the chromophores (guests) listed above have at least one electronic transition in this region.

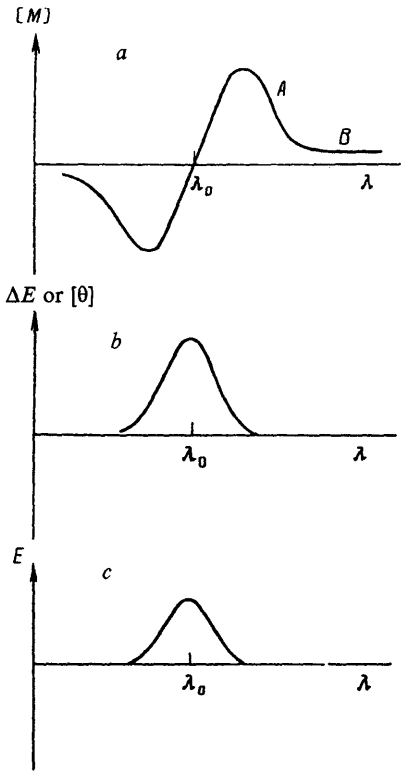
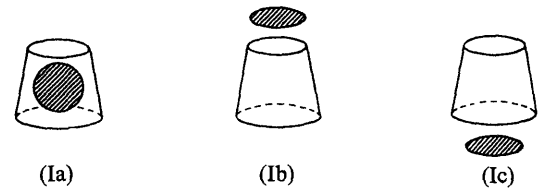


Figure 1. Cotton effects of a chiral compound with an electronic transition at λ_0 (*c*) in the ORD (*a*) and CD (*b*) spectra.

The ORD spectra of all CDXs comprise intense positive plain curves which mask possible induced Cotton effects (ICEs) of the chromophores in the ORD spectra of CDX complexes. Therefore, such spectra have little informative value. Thus, in the first study[108] on complexation with CDXs using chiroptical methods, ORD spectroscopy was used, with dyes serving as chromophores. In this case the Cotton effects appeared as weak deviations from a plain positive ORD curve on the sections of the spectrum corresponding to absorption of the dye in the UV spectrum. These deviations were largest for the dye Congo red and α-CDX. The assumption made from these observations that a complex is formed was, however, disrupted by Takeo and Kuge,[71] who used CD spectroscopy. It appeared that the deviations from the plain ORD curve discussed by Sensse and Kramer[108] were of the same order as the background noise of the instrument.

The ORD spectrum of a CDX complex contains additional rotatory contributions of the CDX molecule both through the slight change in conformation of the CDX on complexation and through induction of optical activity in the CDX molecule on the part of the guest molecule. The question concerning the methods of obtaining this information from the ORD spectra of CDX complexes still remains open.

In studies of the chiroptical properties of CDX complexes with azo dyes, much more accurate results in the form of several induced bands of the Cotton effect corresponding in wavelength to the electronic transitions of the dye were obtained.[106,107] It is true that the occurrence of an induced Cotton effect in the ICD spectra of a mixture of the guest and CDX in aqueous solution is merely an indication of complexation, which does not have to result in the formation of a G–H complex (1a) but may be restricted to conventional molecular complexes † of type (1b) or (1c).



In the studies of Suzuki and Sasaki[106,107] structures of type (1a) were unequivocally chosen because of additional information obtained from ^{1}H NMR spectra. This choice can be made with sufficient assurance when the following arguments are applied:

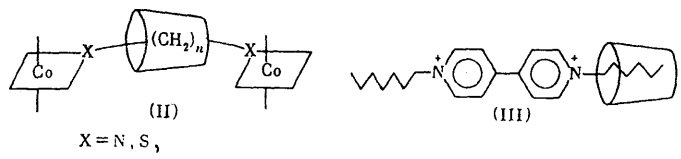
1. the cavity of the CDX molecule is hydrophobic[1–3] since it is formed by C–O–C and C–H bonds. Hence, the formation of complexes of type (1a) is assisted by guest molecules or their residues of a hydrophobic nature.

2. The size of the guest molecule must not exceed the diameter of the CDX molecule.[1–3]

3. The degree of IOA rises to a maximum in complexes of type (Ia), since contact between the inducer and chromophore is greatest in this case.

Thus, in a study of the ICD spectra of β-CDX complexes with hydrophobic uracil derivatives,[131] the choice was made in favour of structures of type (Ib) and (Ic) on the basis of the small values of [θ]. A similar choice was made by Blais et al.[134] in a study of the IORD spectra of β-CDX complexes with hydrophobic derivatives of isonicotinic acid.

Complexation of CDXs with a chromophore has only a slight effect on its chiroptical properties if a part of the chromophore contained in the cavity of the CDX is transparent in the spectroscopic region used. Thus, in the spectra of rotaxanes (II)[146–148]

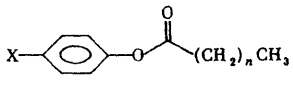


obtained as a mixture of diastereomers a very weak induced Cotton effect has been detected[146] in the visible region, which is probably

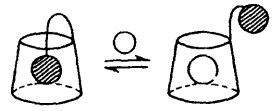
† Here and subsequently we shall use the standard notation[1–3] of a CDX molecule as a truncated cone on whose base are located the secondary hydroxyl groups and on the opposite side are located the primary hydroxyl groups of the CDX's α-*D*-glucopyranose residues.

caused because there is only a weak interaction between the chelate centres and hydroxyl groups in the CDX [contribution from complexation of type (Ib) and (Ic)]. At the same time pure diastereomers of (II) exhibit very strong Cotton effects[147,148] in this region of the spectrum, due to the chirality of these chelate centres. The even more intense induced Cotton effect in the case of the related heptylviologen complexes (III) is evidently caused by the large contribution from complexation of type (Ib) and (Ic).[122] It is interesting to note that in this case complexation cannot be detected in the Raman spectrum or ^{1}H NMR spectrum.

Competition between the aromatic and acyclic residues of *p*-substituted phenyl alkanoates (IV) for inclusion in the cavity of CDXs has been observed[76] in the ICD spectra as a progressive decrease in intensity of the aromatic induced Cotton effects with increase of n, while inclusion of the aromatic residue still occurs when $n = 6$ for α-CDX and at $n = 5$ for β-CDX. In all of these examples inclusion of the hydrophobic aliphatic residues is preferred, which clearly demonstrates the hydrophobic nature of the CDX cavities.



(IV)

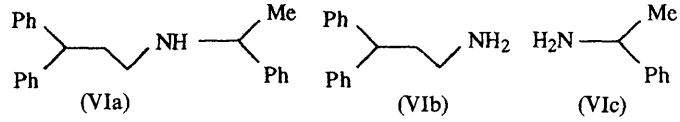


(Va) (Vb)

Complexation of CDX with a spectroscopically transparent guest can be detected in ICD spectra if at the same time a spectroscopically opaque guest is displaced from the CDX cavity. This situation occurs[81,92,136,138] in CDX complexes of type (Va) which are functionalised with an opaque chromophore (naphthyl,[92] a nucleic base,[136,138] nitrophenylacyl[81]). When a transparent chromophore (sodium 1-adamantanecarboxylate,[81,92,136,138] cyclododecanol,[92] 1-adamantylammonium chloride[81]) is added in increasing concentration to aqueous solutions of these complexes, the induced Cotton effect in the ICD spectrum gradually disappears as a result of the formation of complex (Vb). A more complex example of this type is provided by complex (Va) with an *N*-methylacetyl residue as a chromophore located in the cavity.[153] The induced Cotton effect of this complex in the region of amide absorption decreases with the addition of conjugated cyclohexanone derivatives, but an induced Cotton effect appears and then increases at the longer-wavelength region of conjugated carbonyl. Furthermore, this competing complexation can be used to determine the stability constants of CDX complexes with transparent chromophores (see below).

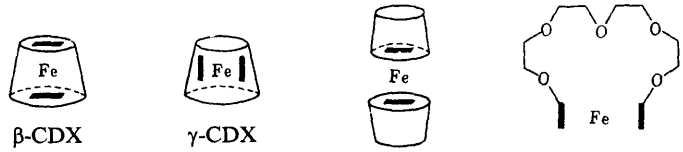
Qualitative information on complexation obtained from ICD spectra is by no means limited to these examples. This information is particularly useful for studying the complexation of CDXs with pharmacological compounds. Thus, the IOA which occurred in ORD[134] and CD[78,131,155] spectra constituted decisive evidence for the complexation of CDXs with derivatives of isonicotinic acid,[134] uracil,[131] indomethacin,[78] and prostaglandins.[155]

The fruitful approach of modelling in the interpretation of ICD spectra has been demonstrated[82] by a comparison of the ICD spectra of complexes of β-CDX with the drug fendiline (VIa) and models of its residues, 3,3-diphenylpropylamine (VIb) and 1-phenylethylamine (VIc). From the similarity between the ICD spectra of complexes of β-CDX with fendiline (VIa) and with 3,3-diphenylpropylamine (VIb) it was possible to conclude that the diphenyl residue of fendiline was included in the β-CDX cavity.



(VIa) (VIb) (VIc)

A semi-quantitative interpretation of ICD spectra using absolute values of the dichroic absorption ΔE or molar ellipticity [θ] may in certain cases provide a fairly reliable assessment of the stability of the respective complexes. In principle a direct correlation between the stability constants K and the corresponding values of ΔE or [θ] is not to be expected, since the latter incorporate the rotatory strength[53] (see the Rosenfeld equation), which is known not to depend on K but which is governed by the geometry of the G–H complex. Thus, in studies of the complexation of ferrocene with CDXs using ICD[8,142–144] it has been established that a strong induced Cotton effect occurs in the β-CDX complex, a weak effect occurs in the γ-CDX complex, while the α-CDX complex does not exhibit IOA, although according to other information complexes are formed in all cases. The proposed structures (VIIa–c) have geometries that are too diverse for comparison to be made from the magnitudes of the induced Cotton effects. Of these the structure (VIIa) has been demonstrated[145] by means of modelling. The ferrocene-containing crown ether (VIId),



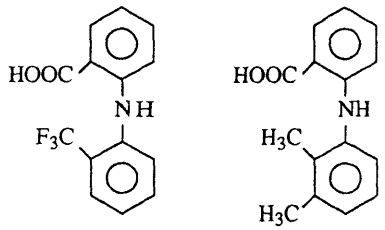
β-CDX (VIIa) γ-CDX (VIIb) α-CDX (VIIc) (VIId)

which can only be included equatorially, exhibited an induced Cotton effect when complexed with β-CDX that was opposite in sign to that of complex (VIIa). This correlation between the geometry of the complex and the sign of the corresponding induced Cotton effect will be discussed in detail below.

However, in certain systems (same chromophore—different CDXs, same CDX—structurally related chromophores) with similar fixed geometries a qualitative correlation between [θ] and the stability of the complex may occur. For example, in the complexation of α- and β-CDX with cyclohexanone[151] and cyclopentanone[154] the magnitudes of the induced Cotton effects of the α-CDX complexes proved to be greater than those for the β-CDX complexes. This result is consistent with the cavity sizes of the two CDXs.

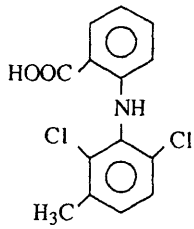
In a number of complexes of structurally related chromophores (VIIIa–c) with β-CDX a parallel decrease in intensity of the induced Cotton effect and stability of the complexes has been observed.[64] However, this pattern no longer occurs for the similar derivatives (VIIId), which are more extensively varied,[63] although [θ] increases with an increase in size of the CDX cavity, i.e., in the series α-CDX < β-CDX < γ-CDX. For *ortho* compounds [θ] is

considerably lower than for *meta* and *para* derivatives, which is apparently due to the nonplanar structure of the chromophore

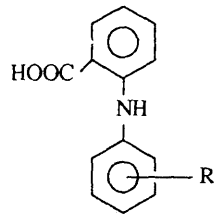


(VIIIa)

(VIIIb)

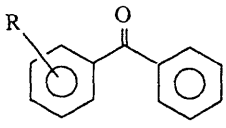


(VIIIc)

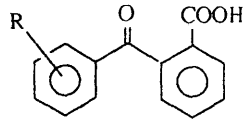


(VIIId)

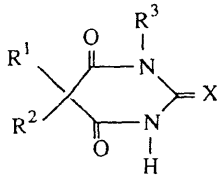
in the first case. There is also no correlation between [θ] and K in complexes of substituted benzophenone (IXa) and benzoic acids (IXb), barbiturates and thiobarbiturates (X),[128,129]



(IXa)



(IXb)



(X)

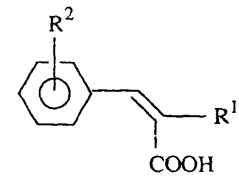
$R^1 = CH_3(CH_2)_n$ ($n = 0-6$), Ph;
R^2 = MeEt, R^3 = H, Me; X = O, S.

and probably in the majority of similar cases. Consequently, assumption of a correlation between [θ] and K should be treated with considerable caution, even if it is supported by matching the size of the chromophore and the radius of the CDX, the study of molecular molecules being particularly useful in this case.

According to the theory of optical activity, a more intense electronic transition corresponds to a lower rotatory strength and vice versa. Therefore, the anisotropy factor g—the ratio of the dichroic absorption ΔE to the extinction coefficient E or the equivalent ratio involving [θ]—may be regarded as a generalised characteristic of a chiral molecule:

$$g = \Delta E/E = \theta/3300E.$$

Cases where there is agreement between g and the stability of complexes are, however, fairly rare. They occurred in a number of phenylanthranylic acids (VIIIa–c)[64] and (VIIId)[65] and cinnamic acids (XI),[70]



(XI)

R^1 = H, Me;
R^2 = Me, Cl, OH, NO_2

but not in barbiturates (X).[129] A comparison of the values of g obtained at different CDX concentrations with the literature data was used[78] to estimate the stability of β-CDX complexes with the drug indomethacin. The use of g instead of [θ] evidently has no particular advantages.

The stability constant K—the most reliable criterion of the stability of a complex—may be determined by means of ICD using the same methods as for UV spectroscopy, since in essence the CD spectra represent a modification of the UV spectra (see Figs. 1*b* and 1*c*). The simplest method of Hildebrand and Benesei[158,159] used in several studies[60,67,69,85,143] has been applied quite extensively together with the modification of Scott[160] used by Otagiri et al.[124] and the modification of Rose and Drago[161] used by Harata.[75] The approximation of Mack[162] was used in three studies[87,98,101] while the approximation of Monk[163] was used by Formoso.[135,137]

The least squares method has become the most widely used of the calculation methods.[62,74,92,154] Individual cases are represented by the adjustment method[156] and nonlinear regression analysis.[130] Computational methods will probable find considerable application as a result of the computerisation of chemical calculations. In certain studies[63,136,138,153] no indication of the method of determination is given.

All these methods are applicable to complexes with an established or assumed 1 : 1 composition. In certain cases the composition was determined[60,67,70,120,142] using ICD with the method of continuous variations of the composition. Calculation of K from the ICD data at different temperatures made it possible[67,74,75,85] to determine the thermodynamic parameters of complexation. The phenomenon of displacement of an opaque chromophore by a transparent chromophore from the CDX cavity was used[81,92] to determine K for the complex of a transparent chromophore with CDX by means of ICD spectroscopy. The possibility of determining the composition of complexes polarimetrically was demonstrated by Giordano et al.[152]

2. Specific information

In this section an analysis is made of the specific information on CDX complexes which in principle cannot be obtained by methods other than chiroptical spectroscopy methods and which is based on the pseudoscalar property of the Cotton effect—its sign. The quality of such information is considerably improved by the applicaton of OA theory.

Interpretation of the CD spectra of CDX complexes with chiral chromophores[73,74,135–141,150–152,154–157] is frequently made difficult because the small induced Cotton effects are masked by the more intense inherent Cotton effects of the chromophore. In some cases[73] it is possible to limit this by recording the CD spectra of CDX complexes with both enantiomers of the chromophore, and the absence of mirror reflection properties suggests that complexation is occurring. A lack of change in the CD spectrum of one of the enantiomers of a chromophore when CDX is added to it may indicate[73] the absence of complexation. Otherwise[137] it may be a reliable indication of complexation, while the extent of change between the CD spectra of the initial enantiomer of the chromophore and its mixtures with different CDXs is proportional[155] to the degree of complexation. The changes in the CD spectra of a pure enantiomer on addition of CDX may be significant if the chromophore contains achiral residues that can undergo complexation and bulky chiral residues, such as in the case of *p*-nitrophenylglycoside.[74] Calculation of the stability constants in these cases[73,74,135–137,154] is complicated by the fact that the apparent values of [θ] include the inherent and induced ellipticity of the chromophore.

The superior sensitivity of CD spectroscopy over UV spectroscopy is particularly evident in the case of CDX complexes with chiral chromophores. Thus, according to the data from differential UV spectroscopy,[164] β-CDX selectively complexes the monophosphates of adenosine and inosine, while according to the data of CD spectroscopy[135,137] this type of complexation occurs for all nucleotides. Thus the idea of using CDXs as probes for the structural analysis of nucleic acids can be rejected. From the CD spectra of CDX complexes with chiral guests it is possible to distinguish drugs qualitatively,[73] especially between chiral and achiral ones, while it is possible to identify cocaine quantitatively.[156] The complex of a chelated pyridoxal aldimine with γ-CDX has been successfully used[150] for studying the kinetics of the stereodifferentiating transamination of phenylpyruvic acid with pyridoxamine.

Let us now consider the correlation between the magnitude and sign of rotation of the Cotton effect, on the one hand, and the geometry of the inclusion of the guest, on the other hand. Specific definition of the Rosenfeld equation in terms of the geometric parameters of specific chiral molecules, based on the classical theory of interacting oscillators[165,166] and the principle of pairwise interactions,[167] led Kirkwood[168] to develop the first "practical" quantum-mechanical theory of optical activity that could be used to calculate the rotational parameters of simple chiral molecules. Starting from the concept of a molecule as a combination of arbitrarily discrete groups (chromophores) that are not exchanging electrons with each other (this concept was subsequently developed as the "discrete chromophore model"),[169] Kirkwood represented[56,168] the rotatory strength of such a molecule as the sum of several terms, one of which represents the interaction between electric dipole transition moments of different chromophores (which is true under certain conditions) and replaced these values with the polarisabilities of the respective groups, which are proportional to them, the latter being values that are more easily obtained experimentally. Kirkwood derived a relatively simple formula for calculating rotatory strength. Tinoco[55] subsequently developed the theory of Kirkwood in relation to polymers and put forward a more general equation for rotatory strength. Harata[62,90] used the Kirkwood–Tinoco equation in a form that was suitable for calculating the rotatory strengths of cyclodextrin complexes in the jth transition from the ground state 0 to an excited state a:

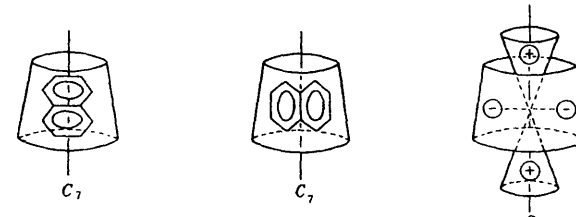
$$R_{0aj} = \frac{\pi \nu_a \nu_0^2 \mu_{0a}^2 \left(\alpha_{33} - \alpha_{11}\right)_j \left(GF\right)_j}{c\left(\nu_0^2 - \nu_a^2\right)},$$

$$\left(GF\right)_j = \left[\frac{1}{r_j^3}\vec{e}_{0a}\vec{e}_j - \frac{3\left(\vec{e}_{0a}\vec{r}_j\right)\left(\vec{e}_j\vec{r}_j\right)}{r_i^2}\right]\vec{e}_{0a}\vec{e}_j\vec{r}_j,$$

$\vec{e}_{0a}$ is the unit vector along the electric dipole transition $\vec{\mu}_{0a}$ of the guest chromophore; ν_a is the corresponding frequency; $\vec{e}_j$ is the unit vector along the axis of symmetry of the jth group; r_j is the distance from the chromophore to the jth group with frequency ν_0; α_{33} and α_{11} are the electric polarisabilities, corresponding to the parallel and perpendicular axes of symmetry of the jth group.

The origin of the system was located in the centre of the CDX molecule, while the z axis passed up along the C_7 axis (in the case of β-CDX). The C–O and C–C bonds in the α-*D*-glucopyranose residue of the β-CDX molecule were regarded as the jth groups with the corresponding tabular values of α_{11} and α_1. The frequency ν_0 of the host was taken from the absorption spectrum of cyclohexanol as a model compound while the values of μ_{0a} for the ^1L_a and ^1B_b transitions of the naphthalene ring for which r was calculated were taken from literature data. The details of the calculations are given in a study of Shimizu et al.[60] For the complexes of β-CDX with naphthalene derivatives that were studied, the calculated values of R differed from the experimental values by a factor of several times, which suggests that there was a small interaction in this case, but the predicted signs proved to be correct. As a result the following rule was developed (the rule of Harata):

If the electric dipole transition moment μ in the chromophore is aligned parallel to the C_7 axis of the symmetry of the β-CYD molecule, the corresponding induced Cotton effect is positive (+ICE). When μ is aligned perpendicular to this axis the induced Cotton effect is negative (−ICE). On the basis of this rule it was concluded that inclusion of the guest was axial (XIIa) rather than equatorial (XIIb), since the induced Cotton effect of the ^1L_a transition directed along the long axis of the naphthalene molecule proved to be positive. The rule of Harata is evidently valid for all CDXs.



(XIIa) (XIIb) (XIIc)

Shimizu et al. subsequently performed similar calculations of the rotatory strengths of β-CDX complexes with substituted benzenes[59,60] and azanaphthalenes.[120] Without starting the rule of Harata as such, the authors merely concluded that inclusion of these chromophores was axial. The rule of Harata was used to establish the form of inclusion of aromatic chromophores in CDX complexes,[77,79,93,119] and to postulate a "lid-type" complex (Ib) between 1,3,6,8-pyrenetetrasulphonate anion and β-CDX[111] with induced Cotton effects of the same sign as well as an axial complex between β-CDX and a nickel complex of a 14-membered macrocyclic

tetraamine.[149] In the latter case, because of the correspondence between the Cotton effect and the $d-d$ transitions, the method was considered to be useful in studying $d-d$ transitions.

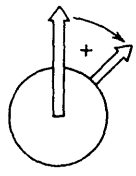
The reverse problem—to establish the direction (polarisation) of the electric of the electric dipole transition moment from the ICD spectra of CDX complexes of known structure—was resolved in four studies.[94,96,102,109] The method used for this was an improvement on those proposed previously which were technically more complex methods for determination of the direction of polarisation in oriented polymer films[170] or in cholesteric liquid crystals.[171] However, the new method is not suitable for chromophores of low symmetry or when there are strongly overlapping transitions of opposite sign.[120]

The rule of Harata has been stated more graphically[83] as a sector rule (XIIc) similar to the octant, quadrant, and sector rules in the quantitative theory of optical activity:[172–174] *if the electric dipole moment of a transition of an aromatic guest lies within a hypothetical double cone, the centre of which coincides with the centre of the CYD, and the generants form angles of 30° with the C_7 axis, the rotatory strength and the corresponding induced Cotton effect will be positive, while the same parameters that are induced by an electric dipole transition moment outside this cone will be negative. The maximum positive anisotropy factor g is approximately twice as high as the maximum negative g, corresponding to the maximum, negative induced Cotton effect of the electric dipole moment of the transition perpendicular to the C_7 axis.* This is in agreement both with the Kirkwood–Tinoco calculations[60] and with the experimental results.[83]

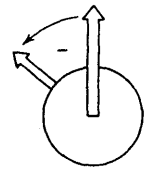
The eminent theoretician in the field of IOA, P E Schipper, having given the equation for the induced rotatory strength of a guest in a generalised form according to the model of interacting oscillators, demonstrated[175] that the correlation between the geometry of the complex and the sign of the induced Cotton effect, corresponding to the rule of Harata, is derived automatically from this equation on the basis of general selection rules for chromophores in perturbing fields.[176]

It was also possible to use the rule of Harata to assign the vibrational bands of aromatic chromophores in complexes of monosubstituted benzenes[61,66] and the 4,4-bipyridyl radical.[123]

The theory of interacting oscillators[17,177,178] represents the interaction of two chromophores that are identical or have a similar structure in terms of exciton theory[179] and it predicts the so-called Davydov splitting of the corresponding absorption band of the interacting chromophores. In the UV spectrum this splitting is insignificant and frequently does not occur, whereas in CD spectra the Davydov (exciton) splitting appears as a double Cotton effect of opposite sign, the so-called exciton couplet, which is positive (Fig. 2*a*) or negative (Fig. 2*b*) depending on whether the relative configuration of the electric dipole of the transition of these chromophores forms part of a right-handed (XIIIa) or left-handed (XIIIb) spiral respectively in the Newman projection.[17,177]



(XIIIa)



(XIIIb)

The electric dipoles of transitions approximate to the projections of planes of rings in the case of aromatic and heteroaromatic chromophores or to C=O bonds for carbonyl chromophores.

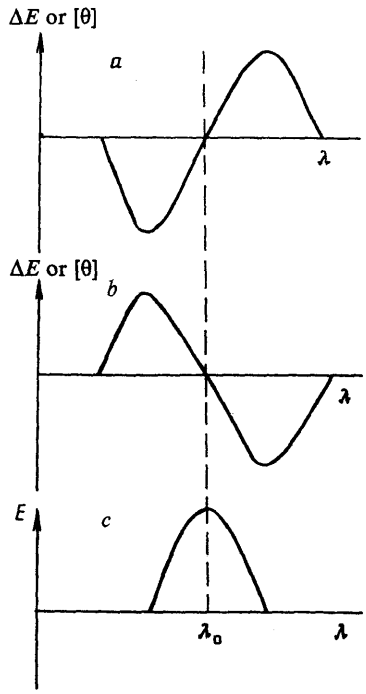
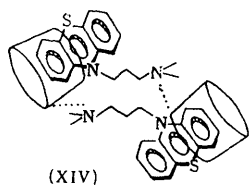


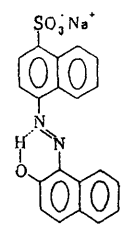
Figure 2. CD spectra with positive (*a*) and negative (*b*) exciton couplets by the absorption band at λ_0 in the UV spectrum (*c*).

The simple and graphic rule of exciton chirality has been extended to a determination of the absolute and relative configuration of natural compounds.[180] It has also recently successfully "started to work" in the field of CDX complexes, primarily in cases of the dimerisation of one-guest complexes or the formation of two-guest complexes.

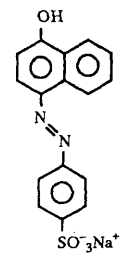
In a study of the complexation of β-CDX with phenothiazine tranquillisers it transpired[124] that 1:1 complexes with chlorpromazine and related derivatives with long alkyl substituents on the nitrogen atom have excited couplets in their ICD spectra, which may suggest that dimers (XIV) are formed through hydrogen bonding of the alkyl chains. An analogous dimeric structure was assigned[117] to a complex between β-CDX and benz[*b*]anthracene on the basis of similar arguments.



(XIV)

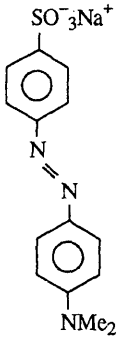


(XV)

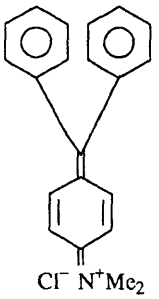


XVI

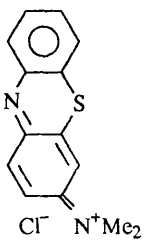
Reaction of chloropromazine with γ-CDX in aqueous solution gives a 2:1 complex (two-guest complex),[125] which was supported[115] by the observation of a negative exciton couplet in the ICD spectrum corresponding to a negative angle between the two chromophores as in structure (XIIIb), i.e., a laevospiral chirality of the guest dimer [(*S*)-chirality according to Cahn, Prelog, and Ingold]. Similar phenomena were observed in complexes of γ-CDX with a number of dyes such as roccellin (XV),[104] tropaeolin 000 (XVI),[103] methyl orange (XVII),[87,88] crystal violet (XVIII),[87] methylene blue (XIX),[87] and acridine orange (XX),[100] and the exciton couplets occurred in both the visible and ultraviolet regions of the spectrum.



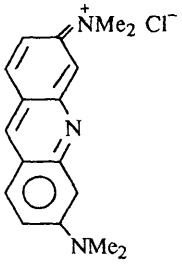
(XVII)



(XVIII)



(XIX)

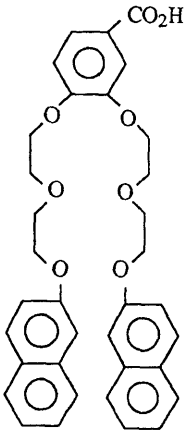


(XX)

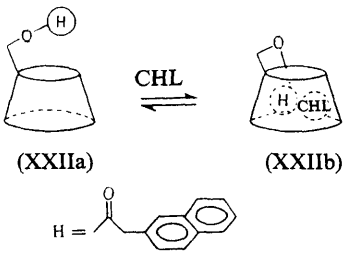
When β-CDX or γ-CDX is added to a mixture of a donor (naphthalene derivatives) and acceptor (nitrobenzene derivatives), a change in colour of the solution occurs and two Cotton effects of opposite sign (possibly an exciton couplet) appear in the charge-transfer region of the ICD spectrum, suggesting that a D^+A^- complex enters the CDX cavity.[85]

In the case of luminescent guests, the formation of two-guest complexes is also detected in the luminescence spectra. Thus, the formation of a (pyrene)$_2$-γ-CDX complex, detected by Kobayashi et al.[113] from its negative exciton couplet in the CD spectrum, was confirmed[114] by the presence of an excimer band in the luminescence spectra. The formation of an (anthracene-2-sulphonate)$_2$-γ-CDX complex with a positive exciton couplet was established in a similar manner,[16] but no excimer band was observed because of rapid photodimerisation of the dimer.

It was shown[100] that naphthalene and also the bis(naphthyl) derivative (XXI) form two-guest complexes with γ-CDX that can be readily detected from the excimer emission in their luminescence spectra. There are no exciton couplets, however, in the corresponding ICD spectra. Such a situation is possible when the naphthalene rings are situated parallel to each other in the CDX cavity, corresponding to the configuration of an achiral dimer.



(XXI)



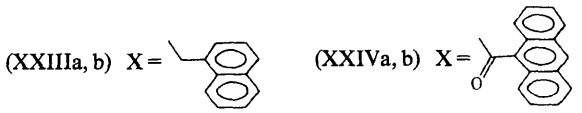
(XXIIa) (XXIIb)

Interesting results were obtained with functionalised γ-CDX. Contrary to expectation, the addition of the transparent chromophore cyclohexanol (CHL) to an aqueous solution of the derivative (XXIIa) increases[91,101] the intensity of the induced Cotton effect in the ICD spectrum, apparently because of the formation of a two-guest complex (XXIIb). A similar result was obtained[101] when the naphthalene residue in the host molecule (XXIIa) was replaced by an azobenzene or ferrocene residue.

In the ICD spectrum of a modified γ-CDX (XXIIIa) with two naphthalene residues there is a positive exciton couplet with its centre at 270 nm which corresponds to the ^1L_a absorption band of naphthalene and an excimer emission in the fluorescence spectrum, which is consistent with structure (XXIIIa). When transparent guests (adamantanecarboxylic acid, cyclohexanol, borneol) are added, the exciton couplet disappears but the excimer emission remains, suggesting that there is a conversion to structure (XXIIIb).[92,98,99] The similar conversion (XXIVa) → (XXIVb) was detected[115] by the same methods for a dianthracene derivative of γ-CDX (XXIVa).



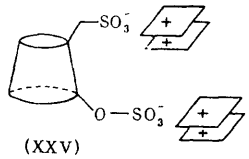
(XXIIIa) (XXIIIb)
(XXIVa) (XXIVb)



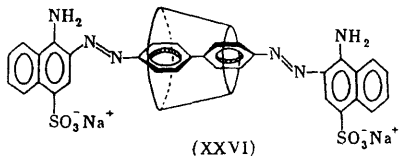
(XXIIIa, b) X = (XXIVa, b) X =

A special case occurs for the complex of acridine orange (XX) with the disulphate of β-CDX,[133] in whose spectrum a strong exciton couplet has been detected in the visible region of absorption of the dye. However, the intensity of this couplet is sensitive to pH and the ionic strength of solution, which is inconsistent with the occurrence of two dye molecules in the β-CDX cavity. It follows from the fact that such a couplet is absent from the ICD spectrum of a complex of acridine orange (XX) with glucose sulphate[181] while it is present in complexes of spiral conformations of sodium carboxymethylcellulose

with acridine orange[185] and safranine T[43,183] that the complex of β-CDX disulphate with acridine orange should be assigned structure (XXV) (the rectangles correspond to planar dye molecules).



(XXV)



(XXVI)

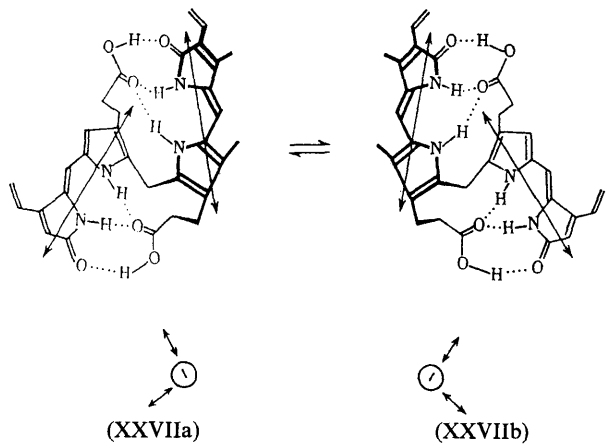
The presence of a chiral excimer can be recorded using circularly polarised luminescence spectroscopy (CPL spectroscopy),[184,185] which measures the emission anisotropy factor g_{em}.

$$g_{em} = 2(I_L - I_R)/(I_L + I_R),$$

where I_L and I_R are the intensities of emission of left- and right-handed circularly polarised light respectively. The method has so far not been widely developed mainly because of the elaborate recording equipment, and in the area of interest to use it has been used in two instances—for recording the chiral excimers of pyrene in the cavities of γ-CDX[110,112] and modified γ-CDX[110] and also for 1,3-dinaphthylpropanes in the cavity of modified γ-CDX.[110]

The dimeric guest in two-guest complexes is essentially a chromophore with its own internal[172,173] chirality (if, of course, the monomers are not parallel to each other) and therefore the components of exciton couplets are characterised by high [θ] values ($10^3 - 10^4$). With regard to the direction of chirality of the guest, it would appear that it should always be the same because of the uniform chirality of the CDX cavity. However, this is not so. While, for example, dimers of pyrene and acridine orange with γ-CDX have (*S*)-spiral chirality, the dimer of naphthalene is achiral, whereas in complex (XXIIIa) with covalently bonded naphthalene residues (*R*)-spiral chirality occurs, as in complex (XXIVa). The dimer of tropaeolin 000 (XVI) in the cavity of γ-CDX has (*S*)-chirality while in the cavity of β-CDX it has (*R*)-chirality. It is evident that the direction of this form of induced chirality is determined not only by the direction of spiral chirality of the cavity but also by the translational and rotational degrees of freedom of the guest in the host cavity.

However, ICD spectra of one-guest CDX complexes with exciton couplets have been recorded. Thus, the dye Congo red forms a one-guest complex with γ-CDX that exhibits a positive exciton couplet in its ICD spectrum.[87] This can be explained by the formation of the complex (XXVI) with one of several chiral conformers of the guest molecule located in the chiral cavity. The most studied[139–141] example of this type is complexation of CDX with the bile pigment bilirubin, which exists in aqueous solution as a mixture of interconvertible enantiomeric conformers—laevospiral (XXVIIa) and dextrospiral (XXVIIb).

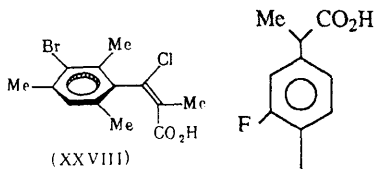


(XXVIIa) (XXVIIb)

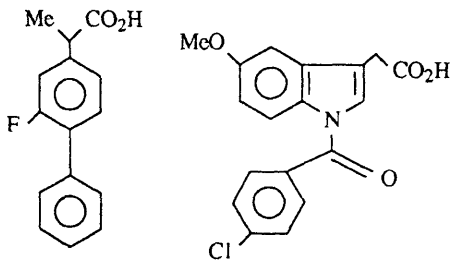
(The arrows denote the calculated directions of the electric dipole transition moments of the pyrromethene chromophores, the relative configuration of which corresponds to sections of a left- and right-handed spiral).

On complexation of bilirubin with α-, β-, and γ-CDX, negative exciton couplets were recorded with a centre at 460 nm corresponding to the absorption of bilirubin, which indicates that in the CDX cavity the specific chiral conformer (XXVIIa) has been selected from the racemate (XXVIIa, b) in aqueous solution. On similar complexation benzil and diacetyl have no exciton couplets in their ICD spectra but the high intensities of the recorded single Cotton effects ([θ] values up to 40 000 deg cm^2 dmol^{-1}) have led to the assumption[139–141] that in these cases also selection of one of the chiral conformers occurs during complexation.

Intense Cotton effects ([θ] of the order of 2600–11 900 deg cm^2 dmol^{-1}) also occurred in the complexation of cinnamic acids (XI) with α- and β-CDX. Since all the recorded intense Cotton effects were positive and the optically active (*R*)-β-(3-bromo-2,4,6-trimethyl-β-chloromethylacrylic acid (XXVIII) had a positive Cotton effect in its CD spectrum, the authors came to the fairly plausible conclusion that the guests (XI) were held in the CDX cavities as (*R*)-conformational enantiomers.



(XXVIII)



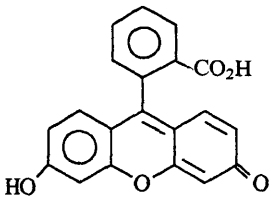
(XXIX) (XXX)

The same configuration is also selected[140] in the complexation of biphenyl derivatives with β-CDX.

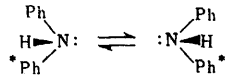
An analysis of the literature data given in the present review in relation to the possible selection of chiral conformers of guest molecules when they are included in CDX cavities as indicated by high-intensity Cotton effects showed that this situation is highly probable for flurbiprofen (XXIX),[68] indomethacin (XXX),[78] and

substituted barbiturates (X).[132] In the case of flurbiprofen (XXIX) this selection may occur with respect not only to the conformational enantiomer but also the configurational enantiomer (see below) because it has a chiral centre. The presence of a maximum in the region of 530 nm in the CPL spectrum of the complex of fluorescein (XXXI) with β-CDX has also been interpreted[126] as the selection of one of the chiral conformer of fluorescein during complexation.

Thus, the following conclusion is suggested: any sufficiently complex molecule having even one residue with restricted rotation can undergo complexation with CDXs as one of its rotational enantiomers. This phenomenon has been called[154] chiral conformational discrimination induced by complexation.



(XXXI)

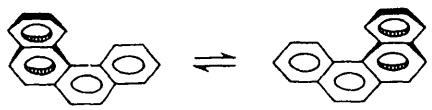


(XXXIIa) (XXXIIb)

We should also note the ability of CDXs to select one of the two enantiomorphic pyramidal conformations (XXXIIa, b) of substituted diphenylamines.[65] Because of this property there is reason to expect the selection of configurational enantiomers of the type $R_1R_2R_3N$ when they are complexed with CDXs.

The selection of configurational enantiomers has been demonstrated[151] using ICD in the complexation of racemates of 2- and 3-methylcyclohexanol with α- and β-CDX. The resolution of racemic esters[186] and sulphinyl compounds[187] using CDXs provides indirect evidence for the ability of CDXs to select configurational enantiomers of guest molecules, although the low optical yields (1–15%) indicate the limited enantiodifferentiating ability of CDX molecules with respect to small guest molecules. This conclusion has been supported[154] in the case of the complexation of α-CDX with cyclopentanol derivatives.

The enantiodifferentiating ability of CDXs probably increases for large guest molecules. At least one example of this kind is known, which relates, admittedly, to chiral conformational discrimination induced by complexation[140]—the appearance of a very intense Cotton effect ($[\theta] \simeq 40\,000$ deg cm^2 dmol^{-1}) in the ICD spectrum of the complex between γ-CDX and the racemate of 4-helicene, both enantiomers of which (XXXIIIa, b) are interconverted in solution.



(XXXIIIa) (XXXIIIb)

When the enantiodifferentiating ability of the CDX is weak, the observed ICD spectrum of the complex between CDX and racemate evidently represents the sum of the ICD spectra of the corresponding diastereomers provided that complete complexation occurs. With absolute enantiodifferentiation the opposite enantiomer is present in solution while the observed ICD spectrum essentially represents the optical activity induced by the CDX cavity in complexation of the guest enantiomer through additional hydrophobic interactions and/or hydrogen bonding of the guest with the hydroxyl groups of the host.[151] The high values of [θ] that occur for 4-helicene (XXXIIIa, b) may be due to the additional chiral distortion of the flexible conformational changes of a guest in the form of achiral and chiral molecules and a racemate in complexation with CDXs are discussed in detail by Boiswin et al.[154]

Thus, the data presented here provide a sufficiently convincing illustration of the ability of CDXs to distinguish between chiromers (conformational and configurational isomers).

IV. Conclusion

The material presented here shows that progress in the chemistry of CDXs is impossible without chiroptical spectroscopic methods[188] (ORD, CD, and CPL spectroscopy as well as infrared CD spectroscopy in the future). The most widely used method is ICD, with which it is possible to derive a variety of information about CDX complexes. Thus, an induced Cotton effect provides an indication of the complexation of a given chromophore with given CDXs, while small values of [θ] (less than 1000 deg cm^2 dmol^{-1}) most likely suggest the formation of conventional molecular complexes of type (Ib) and (Ic) and large values of [θ] (1000–10 000 deg cm^2 dmol^{-1}) indicate the presence of guest–host complexes (Ia). The shift in [θ] values to the upper end of this range may signify an increase in stability of the complex and/or a restriction of the rotational and translational degrees of freedom of the guest molecule in the CDX cavity. Even higher values of [θ] or the appearance of an exciton couplet may signify chiral conformational discrimination induced by complexation. This relates to complexes with a 1:1 composition which can be determined from the ICD spectra in the same way as the stability constants of the complexes.

If the directions of the electric dipole transition moments of an asymmetric chromophore are known, the nature of inclusion of the chromophore (axial or equatorial) in the CDX cavity can be established from the rule of Harata. If the nature of inclusion of the complex is known, the reverse problem—to establish the directions of the electric dipole transition moments of a chromophore—can be solved using the same rule.

Exciton couplets in the ICD spectra may also suggest that dimerisation of one-guest complexes is occurring or two-guest complexes are being formed.

Some of the information derived from ICD spectra (the complexation, composition, and stability constant of the complex) may also be obtained by other methods. However, the information (the geometry of the complex, dimerisation of complexes, chiral conformation discrimination induced by complexation) obtained from the pseudoscalar property of the Cotton effect—its sign—is unique, since it is impossible (or extremely difficult) to obtain it by other methods.

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