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Internal and External Induced Circular Dichroism in Cyclodextrin Complexes: A Study of the Complexes of α-Cyclodextrin with (R)-3-Methylcyclopentanone and Cyclopentanone

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The circular dichroism (CD) of (R)-3-methylcyclopentanone *1* in the presence of α-cyclodextrin (αCx) in water has been measured. The formation constant ($K' = 24$ mol^{-1} litre) of a 1—1 complex, specific CD ($\delta_o = +1.74$) of *1* in water solution, and specific CD of this complex in water ($\Delta\varepsilon' = +1.45$) have been calculated. Similarly, the induced CD (ICD) of cyclopentanone *2* in the presence of αCx in water has been measured. The formation constant ($K = 25$ mol^{-1} litre) of a 1—1 complex and the specific CD ($\Delta\varepsilon' = -0.034$) of this complex have been calculated.

A model is presented for the interpretation of the ICD data. Various theoretical possibilities are discussed. A comparison with X-Ray and low-temperature neutron-diffraction data for the (*2*-αCx) complex is attempted. It seems reasonable to conclude that there is only a weak chiral discrimination in this complex in water solution at room temperature.

Some of us recently studied the complexation of cyclopentanone (P) by α-cyclodextrin (D) by circular dichroism (CD) and by X-ray and neutron diffraction[1]. In this note, we would like to present an analysis of the CD results and to compare them with the structural results. The circular dichroism induced by complexation (ICD) may be used to determine the association constant K of the complexation equilibrium in solution (water for instance):

$$D + M \rightleftharpoons DM$$

between a chiral host (D) and an achiral guest (M) molecule, and the specific molar circular dichroism $\Delta\varepsilon'$ of the (1—1) complex C. $\Delta\varepsilon'$ is a quantitative measure of ICD.

Theoretical treatments and physical models have been successfully applied to the analysis of ICD[2]. Here we shall present an empirical approach, concentrating mainly on possible complexation-induced conformational changes of the guest. In the complex, the equilibrium conformation M is not neces-

sarily identical with the equilibrium conformation M_o of M in water. We shall decompose the ICD $\Delta\varepsilon'$ in two terms: an »external« contribution E and an »internal« one I:

$$\Delta\varepsilon' = E + I$$

E is the CD due to the chiral host (D) acting as a perturbation on the chromophore of M (in its equilibrium conformation $\check{M}$ in the complex). I is the circular dichroism that would be shown by M in its $\check{M}$ conformation but in an achiral solvent S. S is a hypothetical solvent so that all the non-chiral properties induced by complexation with the guest would be the same for $\check{M}$ in the complex and for $\check{M}$ in solvent S. Several situations may occur, among which the following limiting cases may be considered (Figure 1):

A: $\check{M}$ is achiral because its equilibrium conformation $\check{M}_o$ (in nonchiral solvents) is achiral. In the complex, the equilibrium conformation is $\check{M}$:

Case AI: $\check{M}$ is achiral, identical to $\check{M}_o$ (a »rigid« molecule such as 2-adamantanone may be an example) or not. In this case, $I \rightleftharpoons 0$.

Case AII: $\check{M}$ is chiral: M may undergo chiral deformation(s) in the host, because some force constants for chiral normal vibrations are weak in the isolated molecule or in the presence of a functional group of the host (HDCO may be an example[3]). In this case, I cannot be measured but may be estimated from model studies.

B: M is optically inactive because it exists, in non-chiral solvents, as a racemic mixture of interconverting enantiomers M^+ and M^-. There are now two enantiomeric equilibrium-conformations $\check{M}_o^+$ and $\check{M}_o^-$ in achiral solution and two conformations $\check{M}^+$ and $\check{M}^-$ in the complex. In principle, the $C^+ (= D, \check{M}^+)$ and $C^- (= D, \check{M}^-)$ complexes will not be present at the same concentration. There will be a complexation-induced conformational chiral discrimination.

Case BI: Conformations $\check{M}^\pm$ are identical with $\check{M}_o^\pm$, but the complexation of one of the enantiomers is favored (an example is bilirubin[4]). In this case, the following equilibria may be written (with their equilibrium constants)

$$M^+ \rightleftharpoons M^-, \quad (K_o = 1)$$

$$M^+ + D \rightleftharpoons C^+, \quad (K^+)$$

$$M^- + D \rightleftharpoons C^-, \quad (K^-)$$

or

$$C^+ \rightleftharpoons C^-, \quad (\chi = K^-/K^+)$$

C^+ and C^- are the diastereoisomeric complexes. This is equivalent to the single equilibrium:

$$M + D \rightleftharpoons C, \quad (K)$$

with

$$2K = K^+ + K^-,$$

where C represents the mixture of the two complexes C^+ and C^-. $\Delta\varepsilon'$ is the weighted average of $\Delta\varepsilon^+$ and $\Delta\varepsilon^-$, of each complex

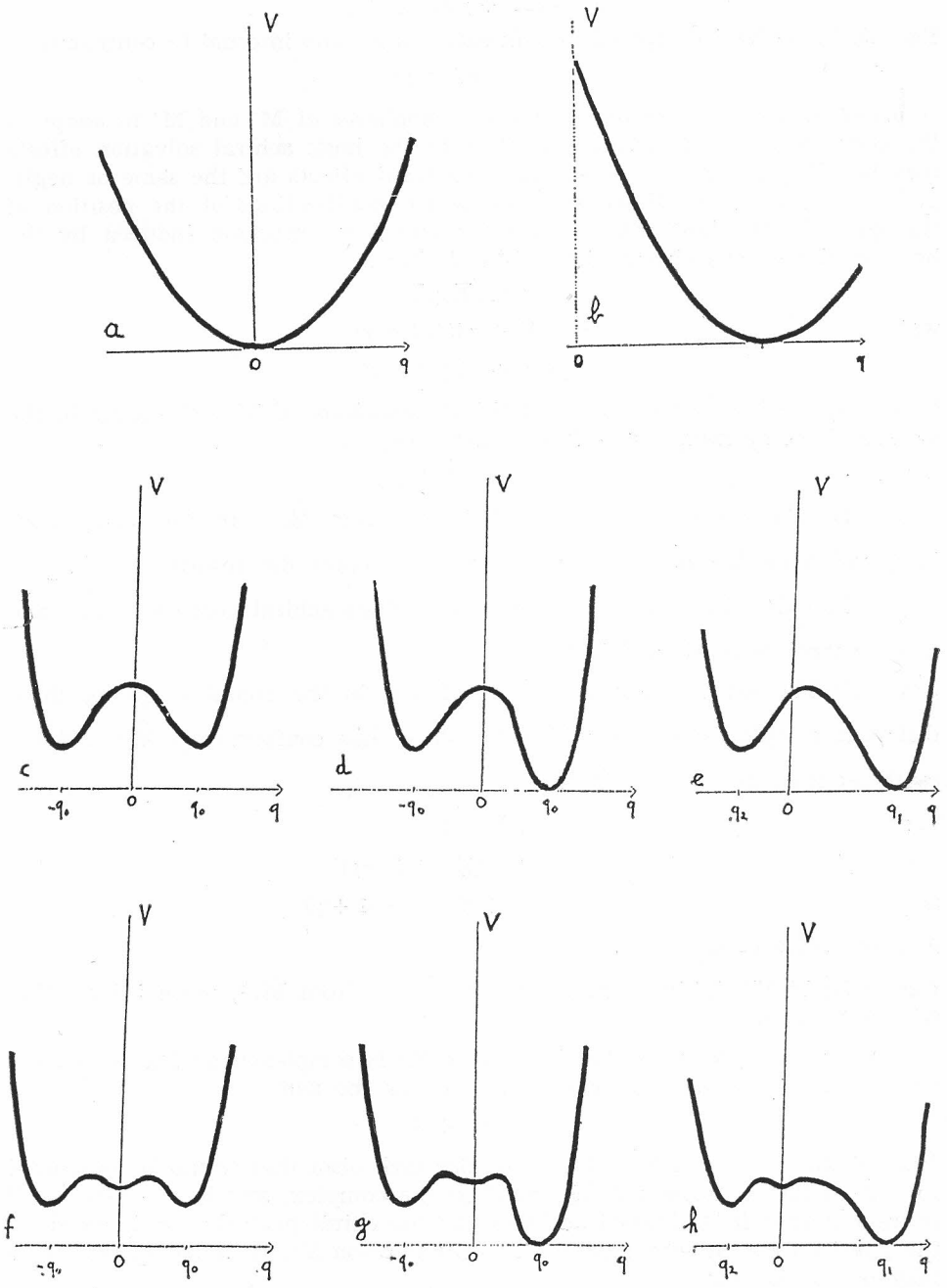

Figure 1. Schematic representation of case AI: (a) → (a); case AII: (a) → (b); case BI: (c) → (d); case BII: (c) → (e); case CI: (f) → (g); case CII: (f) → (h).

q is a coordinate for a chiral distortion ($q = 0$ for an achiral conformation). → means after complexation. V is the variation with q of the potential energy of molecule M in an achiral solvent (before complexation) or of molecule M in the chiral host (after complexation).

$$\Delta'\varepsilon = (\Delta\varepsilon^+ + \chi\,\Delta\varepsilon^-)/(1+\chi)$$

Each $\Delta\varepsilon^\pm$ may be decomposed into an external $E^\pm$ and internal $I^\pm$ contribution:

$$\Delta\varepsilon^\pm = E^\pm + I^\pm$$

A priori, there is no reason for the chromophores of M^+ and M^- to adopt in the complex the same position relative to the host: achiral solvation effects may be different, then $I^+ \neq -I^-$. If the solvent effects are the same or negligible[5], then $I^+ = -I^-$. However, since small modifications of the position of the guest in the host may change the chiral perturbation induced by the host on the guest's chromophore, $E^+ \neq E^-$ then

$$\Delta\varepsilon' = \overline{E} + \overline{I}$$

with

$$\overline{E} = (E^+ + \chi\,E^-)/(1+\chi)$$

$$\overline{I} = (I^+ + \chi\,I^-)/(1+\chi)$$

If we assume that the solvation of the chromophore of M is the same in the C^+ and C^- complexes, $I^+ = -I^-$ and therefore,

$$I = I^+(1-\chi)/(1+\chi)$$

Case BII: Conformations $\tilde{M}^\pm$ are distorted from $\tilde{M}_o^\pm$. In this case, more information on $\tilde{M}^\pm$ is needed in order to interpret the results.

C: M exists in solution as a mixture of an achiral conformer $\tilde{M}_o^a$ and chiral enantiomers $\tilde{M}_o$ and $\tilde{M}_o^-$.

Case CI: The same conformations are found in the complex, giving three different complexes: C^a (in which the guest has conformation $\tilde{M}_o^a$ and $C^\pm$ (with guest's conformation $\tilde{M}_o^\pm$).

Then

$$\Delta\varepsilon' = \overline{I} + \overline{E}$$

with

$$\overline{I} = (I^+ + I^-\chi)/(\varrho + 1 + \chi)$$

and

$$\overline{E} = (E^a + E^+ + E^-\chi)/(\varrho + 1 + \chi)$$

ρ is the ratio of C^a to C^+.

Case CII: If $\tilde{M}^\pm$ in the complex are different from $\tilde{M}_o^\pm$, more information will be needed.

D: Similarly, when a chiral molecule M* is complexed by D, the specific CD, $\Delta\varepsilon'$ of the complex may be expressed as the sum:

$$\Delta\varepsilon' = I + E$$

I is not the external ICD but the circular dichroism that would be measured for M* in the conformation M* found in the complex, and in »solvent S«. E is the external ICD, defined as before as the chiral perturbation induced by the guest on the M* chromophore in conformation M*. Here again, two cases may be considered:

Case DI: M* is rigid: I is the CD of M* in solvent S.

Case II: Conformation $\tilde{M}^*$ on the complex differs from the conformation in achiral solution and more information is needed to estimate I.

We shall apply these considerations to the complexation of (R)-3-methylcyclopentanone (P') and cyclopentanone (P) by α-cyclodextrin (D).

EXPERIMENTAL

(R)-3-Methylcyclopentanone and cyclopentanone were obtained from Fluka and Aldrich, respectively. α-Cyclodextrin was obtained from Aldrich and Sigma in anhydrous form and from Janssen as the hydrate with 6 H_2O. Solutions of the pure compounds in water were prepared at various concentrations and mixed to the appropriate concentration three hours before the measurements. The CD was recorded on a Jobin Yvon Dichograph V. Results are given in Table I for P' and Table II for P.

TABLE I

CD of the Complex Between (R)-3-Methylcyclopentanone (P') and α-Cyclodextrin (D). ΔA: Observed CD for a 1 cm-Cell. The Concentration p_o' of P' was Fixed at 11.10^{-3} M. d_o is the Initial Concentration of α-Cyclodextrin

$10^3\, d_o$	40	28	11	0
$10^2\, \Delta A$	1.77	1.87	1.90	1.93

TABLE II

ICD of Cyclopentanone. ΔA: observed CD for a 1 cm-cell. p_o and d_o are the initial molar concentrations of cyclopentanone 5P) and α-cyclodextrin (D) in solution.

$10^3\, p_o$	28	31	34	38	42.3	48.3	52	14	19	38	40	45
$10^3\, d_o$	56.4 (a)	51.4 (a)	45 (a)	38 (a)	28 (a)	16 (a)	8.7 (a)	73.1 (b)	64.7 (b)	32 (b)	28.4 (b)	20 (b)
$10^4\, \Delta A$	—2.6	—2.5	—2.6	—2.5	—2.1	—1.5	—0.9	—1.4	—1.72	—2	—1.9	—1.5

(a) α-cyclodextrin from Sigma; (b) from Janssen.

RESULTS

I — (R)-3-Methylcyclopentanone (P')

From the complexation equilibrium,

$$D + P' \rightleftharpoons C', \qquad (K' = c'/dp')$$

with

$$d + c' = d_o \qquad \text{and} \qquad p' + c' = p'_o$$

(small letters refer to molar concentrations)

$$\Delta A = \delta_o p' + \Delta\varepsilon' \cdot c'$$

since where δ_o is the specific CD of P' in water, a little algebra gives:

$$(\Delta\varepsilon' - \delta_o)\ (\Delta A - p_o'\delta_o) = K'\ [\Delta\varepsilon' d_o + (p'_o - d_o)\ \delta_o - \Delta A]\ [\Delta\varepsilon' p'_o - \Delta A]$$

or

$$\Delta A = (\Delta\varepsilon' - \delta_o)\ [K\ (d_o + p'_o) + 1 - \sqrt{X}]/2K'$$

with

$$X = [K'\ (d_o + p_o) + 1]^2 - 4K'^2$$

$$\delta_0 = +1.74;$$

$$\Delta\varepsilon' = +1.45.$$

The single measurement in water without D, gives $\delta_0 = 1.73$.

II — Cyclopentanone (P)

From the complexation equilibrium,

$$D + P \rightleftharpoons C \qquad (K = c/dp)$$

with

$$d + c = d_0 \qquad \text{and} \qquad p + c = p_0$$

since $\Delta A = c \cdot \Delta\varepsilon'$, the treatment is similar to the previous one with $\delta_0 = 0$:

$$K(\Delta\varepsilon'^2 d_0 p_0 + \Delta A^2) = [(p_0 + d_0)K + 1]\Delta\varepsilon' \Delta A$$

or

$$\Delta A = [K(d_0 + p_0) + 1 - \sqrt{X}]\Delta\varepsilon'/2K$$

with

$$X = [K(d_0 + p_0) + 1]^2 - 2K^2 d_0 p_0$$

A least-square analysis gives

$$K = 25 \text{ Mole}^{-1} \text{ litre};$$

$$\Delta\varepsilon' = -0.034.$$

INTERPRETATION

The association constants K and K' are of the order of magnitude found for similar compounds in α-cyclodextrin[6]. They are almost identical, probably as a result of two conflicting factors; P′ is more hydrophobic than P, but the molecule is larger.

I — 3-Methylcyclopentanone

The CD of P′ in water, taken as 1.74, is of the order of magnitude of the value +2 measured in an ether-isopentane-ethanol mixture (EPA)[7] at 25 °C. (This value changes to +3.3 at —192 °C). It seems reasonable to assume that the average conformations of P′ in water and in EPA are close, so that the difference in $\Delta\varepsilon$ between water and EPA at 25° may be assigned to solvation effects only. With regard to its conformation in the complex, P′ is a flexible molecule: Temperature-induced conformational modifications may change the specific CD of P′ in EPA by ca 50%[7]. P′ is an example of case DII.

The first hypothesis is that the external ICD is negligible, the difference between +1.74 in water and +1.45 in the complex is assigned to conformational changes only: if $E = 0$, then $I = +1.45$.

The second hypothesis is that, in the complex, the (average) conformation is similar to the conformation in solution, (assumed to be the same in water and in EPA). Then the solvent effects on the CD may be (a) the same as in water if the carbonyl group is directed towards the outside of the cyclodextrin, where it is solvated by water, (b) the same as in EPA if the carbonyl group is inside the cyclodextrin cavity, where the polarity close to that of dioxane[8],

may be close to that of EPA. In these cases, the order of magnitude of I is the same: (a) $I = +1.74$ and $E = -0.29$ or (b) $I = +2$ and $E = -0.55$.

A third hypothesis would give a much larger (negative) value for E: If P′ is constrained in D in its low-temperature conformation, then $I = +3.3$ and $E = -1.85$. It seems reasonable to exclude this hypothesis and the external ICD is probably such that $|E| < 0.55$.

II — Cyclopentanone

The ICD (—0.034) is small. In order to get more information from this value, we shall examine two different models:

Model a: (Case IIA): In solution, cyclopentanone is interconverting between two chiral conformations $\overset{\smile}{P}_o^+$ and $\overset{\frown}{P}_o^-$ of C_2 symmetry.[9] The molecule has the same conformations in the corresponding C^+ and C^- complexes. The internal contribution to ICD is then the value ± 6 found in 16-oxosteroids[10] or for 2-hydrindanone[11]. Then $I^* = -I^- = +6$ and this gives $\chi = 1.011 + E/6$. It is impossible to determine the value E. However, for the order of magnitude found for P′, $|E| < 0.55$ gives $0.9 < \chi < 1.1$.

Model b (case CI): We now take into account the achiral C_s conformation ($\overset{\frown}{P}_o^a$) of cyclopentanone[9]. There are three interconverting conformations, P_o^a, $\overset{\smile}{P}_o^+$ and $\overset{\frown}{P}_o^-$, to be found in the corresponding C^a, C^+ and C^- complexes. Here

$$\chi = 1.011 + \frac{E}{6} + 0.006\ \varrho$$

(where $\varrho = c_a/c_+$). The influence of ϱ, (i. e. of conformation P_o^a) on χ is small and for $|E| < 0.6\ \chi > 1$ for $\varrho > 16$ only.

Thus, if there are only chiral conformations P^+ and P^- in the complex, there may be a weak chiral discrimination at room temperature, but from the measure of ICD only it is not possible to deduce which conformation is favored. If chiral and achiral conformations are found in the complex, chiral discrimination may be larger, but only if most of the complexed cyclopentanone is in its achiral conformation.

Comparison With Solid-State Results for the Cyclopentanone-α Cyclodextrin Complex

In the crystal, (space groups P6, Z = 3), there are two independent host molecules in the asymmetric unit, one on the 3-fold axis (position a), the other on the 6 fold axis (position b), thus in a 2 to 1 ratio. There is a symmetry-related orientational desorder for the position of the guest molecule P. Its CO bond is almost parallel to the symmetry axis[1].

Low-temperature X-ray and neutron diffraction data have been interpreted with different models: at 20K, the best fit is obtained for cyclopentanone in the C_2^- (16-oxosteroid-like) conformation at position *a*, while the fit is not sensitive to the choice of conformation at position *b* (C_2^+, C_2^- or C_s). There is a strong organization of hydrogen bonds in the host, the guest molecule being not totally inside the α-cyclodextrin cavity.

The complexation of P may be quite different in solution where water is present and where symmetry-related packing forces are absent. Thus, although the ICD results do not exclude the possibility of conformational chiral-discrimination in solution, they do not prove that the conformations of P in the complex are similar in solution at 300 °K and in solid state at 20 °K.

CONCLUSION

In principle, ICD gives information on the conformation of the guest molecule in a complex. We studied a case where we had precise low temperature neutron and X-ray data, but which is certainly not the easiest to analyze. For future studies, it would be necessary to have complementary information on the complex in solution by other physical methods.

REFERENCES

1. G. Le Bas, G. Tsoucaris, *Mol. Cryst. Liq. Cryst.* **137** (1986) 287; G. Tsoucaris, G. Le Bas, N. Rysanek, F. Villain, *J. Inclus. Phenom.* **5** (1987) 77; G. Le Bas, N. Rysanek, F. Royer, G. Tsoucaris, *Mol. Cryst. Liq. Cryst.* (1988), in press; G. Le Bas, M. A. Mason, to be published (1989).
2. K. Harata, H. Uedaira, *Bull. Chem. Soc.* **48** (1975) 375; P. E. Schipter, and A. Rodger, *J. Am. Chem. Soc.* **105** (1983) 4541; for recent work see: N. Kobayashi, *J. Chem. Soc., Chem. Commun.* (1988), 918; K. Kano, H. Matsumoto, Y. Yoshimura, S. Hashimoto, *J. Am. Chem. Soc.* **110** (1988) 204; N. Kobayashi, X. Zao, T. Osa, K. Kato, K. Hanabusa, T. Imoto, H. Shirai, *J. Chem. Soc. Dalton Trans.* (1987) 1801; M. Hatano, *Stud. Phys. Theor. Chem.* **36** (1985) (Bio) 181, and references therein.
3. G. H. B. Bürgi and J. D. Dunitz, *Acc. Chem. Res.* **16** (1983) 153 and references therein.
4. G. Le Bas, A. Allegret, Y. Mauguen, C. De Rango, and M. Bailly, *Acta Cryst.* **B36** (1980) 3007; D. A. Lightner, *J. Am. Chem. Soc.* **107** (1985) 2456.
5. C. Coulombeau and A. Rassat, *Bull. Soc. Chim. Fr.* (1966) 3752; A. Rassat in *Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry,* G. Snatzke, Ed., Heyden, London 1967, p. 314.
6. E. Saint-Aman, D. Serve, *New J. Chem.* **111** (1989) and references therein, in press.
7. C. Djerassi, R. Records, C. Ouannes, and J. Jacques, *Bull. Soc. Chim. France* (1966) 2378.
8. R. L. Van Etten, J. F. Sebastian, G. A. Cloves, and M. L. Bender, *J. Am. Chem. Soc.* **89** (1967) 3242; J. Martinie, J. Michon, and A. Rassat, *J. Am. Chem. Soc.* **97** (1975) 1818.
9. T. B. Malloy, L. R. Bauman, and L. A. Carreira, *Topics in Stereochemistry* **11** (1979) 97; B. Fuchs, *Topics in Stereochemistry* **10** (1978) 1; C. Altona, in *Conformational Analysis,* G. Chiurdoglu Ed., Academic Press (N. Y.) 1971, p. 1.
10. L. Velluz, M. Legrand, and M. Grosjean, *Optical Circular Dichroism, Principles, Measurements and Applications,* Verlag Chemie, Weinheim (1965) p. 99.
11. P. Crabbé, *Application de la Dispersion Rotatoire Optique et du Dichroisme Circulaire Optique en Chimie Organique,* Gauthier-Villars, Paris (1968), p. 172; P. Crabbé, *Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry,* Holden Day, San Francisco, (1965), p. 89.

SAŽETAK

Interno i eksterno inducirani cirkularni dikroizam u ciklodektrinskim kompleksima: studij kompleksa α-ciklodekstrina s (R)-3-metilciklopentanonom i ciklopentanonom

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Izmjeren je cirkularni dikroizam (CD) (R)-3-metilciklopentanona *1* u prisutnosti α-ciklodekstrina (αCx) u vodi. Izračunane su konstanta nastajanja ($K = 24$ mol^{-1} L) 1 : 1 kompleksa, specifični CD ($\sigma_o = +1.74$) spoja *1* u vodenoj otopini, i specifični CD njegovog kompleksa u vodi ($\Delta\varepsilon' = +1.45$). Također je izmjeren inducirani CD (ICD) ciklopentanona *2* u prisutnosti αCx u vodi. Izračunana je konstanta nastajanja ($K = 25$ mol^{-1} L) 1 : 1 kompleksa, kao i specifični CD ($\Delta\varepsilon' = -0.034$) njegova kompleksa u vodi.

Prikazan je model za interpretaciju podataka o ICD. Diskutiraju se različite teorijske mogućnosti. Pokušana je usporedba podataka rentgenske strukturne analize i niskotemperaturne neutronske difrakcije za (2-αCx) kompleks. Čini se razložnim zaključiti da postoji samo slaba kiralna diskriminacija u ovom kompleksu u vodenoj otopini pri sobnoj temperaturi.