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A Circular Dichroism Study of Molecular Association of Cinchona Alkaloids and Carboxylic Acids

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Circular dichroism (CD) spectra of cinchona alkaloids and their salts with carboxylic acids have been investigated. A contribution of the exciton type Cotton effect to the 230 nm CD band of free bases in non-polar solvents is suggested to result from the association of alkaloid molecules. Strong association is observed in the case of dihydrocupreidine — an alkaloid with free phenolic group.

Comparison of the CD spectra of salts of alkaloids with mono- and dicarboxylic acids demonstrates that in the latter case the β-band Cotton effects originate from the exciton type interactions between the associated molecules.

The unusual rotations of salts of cinchona alkaloids with biphenyl 1,1'-dicarboxylic acids have been found to originate from the strong intermolecular exciton coupling, rather than from the »first-order asymmetric transformation«. The existence of the two low energy staggered conformations around the C(8)—C(9) bond in the alkaloid molecule has been confirmed by the MMP2 calculation on a model compound.

INTRODUCTION

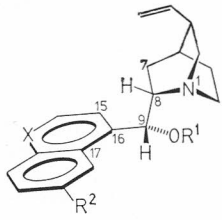
Quinine (*1*), cinchonidine (*3*), quinidine (*5*) and cinchonine (*7*) are the four major constituents of the cinchona alkaloid group. In addition to their pharmacological use they have found numerous chemical applications as chiral bases for resolution of racemates.[1] Owing to their unique stereostructure, these β-aminoalcohols are efficient chiral basic catalysts for the conjugate addition reactions[2,3], two-phase alkylation[4] and ring-opening reactions of prochiral cyclic acid anhydrides with alcohols[5]. Recently, it has been found that cinchona alkaloids induce strong Cotton effects within absorption bands of sulphonephthalein dyes[6] and bilirubin[7] due to the non-equal concentration of the diastereoisomeric complexes in solution (»first-order asymmetric transformation«[8]). The »anomalous« optical rotation of solutions of salts of cinchona alkaloids with biphenyl 1,1'-dicarboxylic acids was observed long time ago and interpreted as »asymmetric rearrangement of the first type«[9] or »asymmetric induction«[10], but later recognized as a phenomenon of a more complex character[11].

All the properties of cinchona alkaloids listed above are related to their structure and mode of complexation with other molecules in solution. Sur-

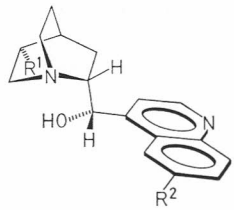
prisingly, circular dichroism studies of these alkaloids have not been reported,[12] although they could have been expected to reveal more details on conformation and complexation of cinchona alkaloids in solution. The results of our CD studies are discussed below, following the discussion of stereochemistry of cinchona alkaloids.

STEREOCHEMISTRY

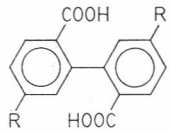
The pairs of diastereoisomeric erythro-alkaloids, quinine (*1*) and quinidine (*5*), as well cinchonidine (*3*) and cinchonine (*7*), can be considered for most practical applications as pairs of quasi-enantiomers of (8*S*,9*R*) and (8*R*,9*S*) absolute configuration, respectively.



	R^1	R^2	X
(1)	H	OMe	N
(2)	Ac	OMe	N
(3)	H	H	N
(4)	H	H	CH



	R^1	R^2
(5)	$CH=CH_2$	OMe
(6)	Et	OH
(7)	$CH=CH_2$	H



	R
(8)	H
(9)	NO_2

Despite the presence of the two single bonds, C(8)—C(9) and C(9)—C(16), connecting the two rigid quinuclidine and quinoline rings, the conformation of the cinchona alkaloid molecules seems to be well defined.[13] The X-ray structural studies on (*1*)[14], (*3*)[15], (*5*)[16] and (*7*)[17], as well as on salts of (*5*)[18] and (*7*)[19], clearly demonstrate that in the solid state the preferred conformation around the C(8)—C(9) bond is synclinal *(gauche), i. e.* the C(7)—C(8)—C(9)——C(16) bonds form acute dihedral angles.

Figure 1 shows this conformation (A) for the molecules (*1*) and (*3*) of (8*S*,9*R*) configuration, as well as the prefered conformation (C) around the C(9)—C(16) bond. The corresponding conformations for (*5*) and (*7*) are the mirror-images of those shown in Figure 1.

The synclinal conformation apparently facilitates formation of intermolecular hydrogen bonds in (*1*), (*3*), (*5*) and (*7*), between the hydroxy group

and the quinuclidine nitrogen atom in a chain of molecules, along the alternate screw axes in the crystal.

However, another staggered conformation around C(8)—C(9) was found in the derivative of *1*, in which acetylation of the hydroxy group does not allow for hydrogen bonding.[14] This antiperiplanar *(trans)* conformation (B) is shown in Figure 1.

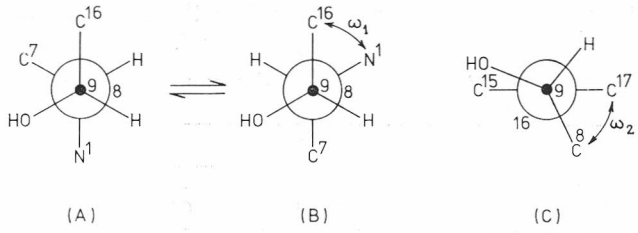


Figure 1. Newman projection of the synclinal (A) and antiperiplanar (B) conformation at C(8)—C(9) and conformation (C) at C(9)—C(16) in *1* and *3*.

The analysis of the coupling constants in the ^{1}H NMR spectrum of *1* led to the conclusion that in chloroform solution the most stable conformation was (A).[9] This conformation allows for intermolecular interactions in solution between alkaloid molecules at high concentrations.

The energy difference between conformations (A) and (B) in cinchona alkaloids was calculated using Motherwell's atom-atom potential approxi-

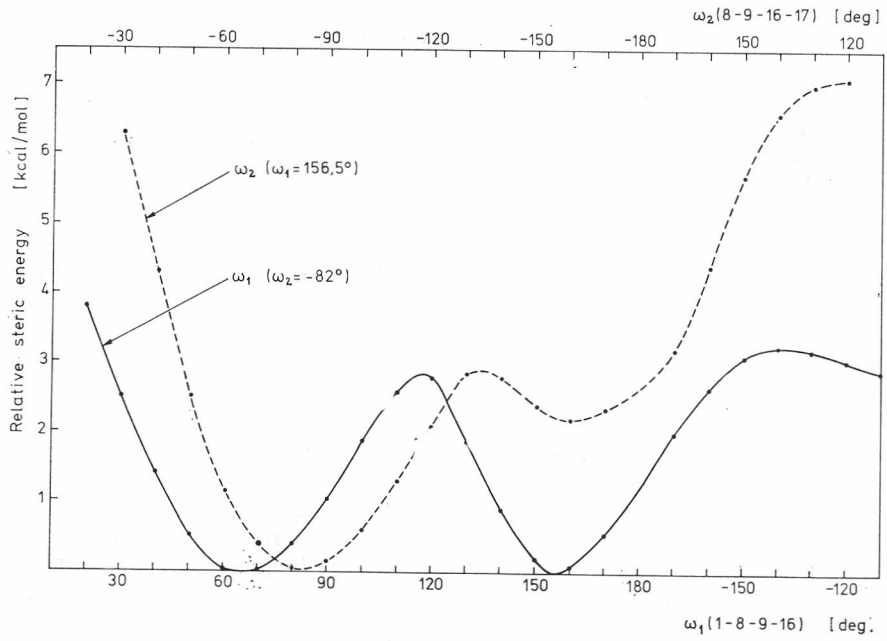


Figure 2. Calculated torsional energy profiles of *4* during rotation around the bonds specified in Figure 1.

mation, and the energy of the conformation (A) was found to be 6—12 kJ/mol (1.4—2.8 kcal/mol) higher.[14] This result prompted us to calculate the torsional energy profiles during rotation of the C(8)—C(9) and C(9)—C(16) bonds in the analogue (*4*) of cinchonidine (*3*). Using MMP2 force field[20] we have obtained quantitatively different results pertaining to the local minima of steric energy, for the rotation of each C(8)—C(9) and C(9)—C(16) bond (Figure 2).

Interestingly, the two local minima corresponding to the ω_2 values (—82° and —160°) are separated by 2.2 kcal/mol, while the two minima for ω_1 (65.5° (conformer A) and 156.5° (conformer B)) differ by less than 0.1 kcal/mol. The X-ray and MMP2 geometries are compared below:

	ω_1 (A)	ω_1 (B)	ω_2 (C)
X-ray (3)[15]	158.0	—	—76.8
MMP2 (4)	156.5	65.5	—82.0

Thus, the two conformations (A) and (B) can be expected to participate in the equilibrium to the extent determined by the additional stabilizing interactions with other molecules in solution.

CIRCULAR DICHROISM

The chromophore of cinchona alkaloids is the substituted quinoline ring. Quinoline itself shows three ultraviolet bands at 313 nm (ε 2500), 268—275 nm (ε 3500) and 226 nm (ε 35500) in cyclohexane. The three absorption bands, designated after Clar as α, p and β bands, correspond to the ^1L_b, ^1L_a and ^1B_b bands, respectively, in naphthalene and dominate the UV spectra of quinoline and its derivatives. The position of the n—π^* transition has not been established. Although the positions and intensities of the corresponding bands of the substituted quinoline chromophore in cinchona alkaloids differ from those of quinoline, the basic features of the UV spectra remain unchanged. The UV spectra of cinchona alkaloids are similar for the pairs of (*1*), (*5*) and (*3*), (*7*). For the sake of brevity, we restrict the following discussion to the circular dichroism spectra of these cinchona alkaloids.

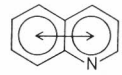
Table I contains the CD data for cinchona alkaloids (free bases) in various solvents. The three bands of the planar quinoline chromophore are optically active, due to the chiral substituents in positions α and β, *i. e.* at C(9) and at C(8). However, there are significant differences in the position, sign and magnitude of the Cotton effects belonging to the same band among the different alkaloids. Neither band α (around 330 nm) nor band p (around 270 nm) Cotton effects seems to reflect the absolute configuration of the alkaloid: band α Cotton effects are of opposite sign for quinine (*1*) and quinidine (*5*), but of the same sign for cinchonidine (*3*) and cinchonine (*7*). Band p Cotton effects are generally weak and frequently obscured by the neighbouring Cotton effects. This result is clearly different from the reported mirror-image band α and band p Cotton effects for (*3*) and (*7*) in aqueous buffer at pH 8.[21] On the other hand, the sign of band β Cotton effect in polar (methanol) solution seems to be related to the absolute configuration of the alkaloid: a negative Cotton effect is observed in the 225—235 nm range for alkaloids of (8*S*,9*R*)-configuration and a positive one for (8*R*,9*S*)-configuration, the

TABLE I

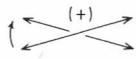
Circular dichroism of cinchona alkaloids in various solvents (conc. 4×10^{-4} M if not otherwise stated)

	Band α,Δε (nm)	Band p,Δε (nm)	Bands β,Δε (nm)	
Quinine (*1*) in:				
cyclohexane	—1.8 (333)	+0.9 (270)	+1.2 (251)	—8.8 (235)
dichloromethane	—1.0 (332)	+0.6 (272)	+0.9 (247)	—2.8 (235)
(conc. 4×10^{-5} M)	—1.2 (331)	—	+0.2 (247)	—2.5 (235)
(conc. 4×10^{-3} M)	—1.2 (331)	+0.7 (272)	+1.0 (247)	—3.4 (234)
dioxane	—1.4 (331)	+0.3 (272)		—6.0 (230)
methanol	—2.2 (332)	—		—8.3 (230)
Cinchonidine (*3*) in:				
dichloromethane	+0.4 (318)	+0.6 (278)	+0.8 (237)	—4.4! (229)
dioxane	+0.3 (318)	+0.6 (275)	+0.6 (237)	—10.8 (225)
methanol	+0.2 (315)	+0.6 (270)		—12.2 (226)
Quinidine (*5*) in:				
cyclohexane	+1.8 (332)	—1.0 (270)	—1.5 (254)	+9.8 (235)
dichloromethane	+1.7 (333)	—	—0.5 (254)	+5.6 (236)
dioxane	+1.4 (331)	—	—0.5 (259)	+9.0 (233)
methanol	+1.0 (332)	—		+2.7 (237)
Dihydrocupreidine (*6*) in:				
dichloromethane	+2.6 (342)	+1.0 (300)	+27.8 (244)	—8.0 (225)
methanol	+2.3 (333)	—1.2 (262)		+6.0 (238)
Cinchonine (*7*) in:				
dichloromethane	—0.4 (317)			
	+0.3 (290)	—		+8.0 (225)
dioxane	+0.6 (290)	—		+11.6 (226)
methanol	+1.1 (290)	—		+7.3 (228)

difference in the position of the Cotton effect being due to the presence or absence of the methoxy-substituent in the quinoline chromophore. Furthermore, in non-polar solvents all alkaloids except cinchonine (*7*) display an additional small Cotton effect at 237—251 nm of opposite sign to that at 225—235 nm. This small additional Cotton effect is attributed to the weak association of the alkaloid molecules in non-polar solvents *via* the N···HO hydrogen bonds. A small fraction of the molecules, present as dimers, produce exciton-type Cotton effects[22,23] due to the interaction of the electric transition moments of the allowed 230 nm transition, polarized along the long axis of the two quinoline chromophores[24] (Figure 3).



(a)



(b)

Figure 3. (a) Direction of the electric transition moment for the 230 nm transition (band β) in quinoline. (b) Positive exciton coupling in a dimer.

The exciton-type Cotton effects are superimposed on the band β Cotton effect of non-associated molecules. The magnitude of the exciton-type Cotton effect is concentration dependent: an increase of the long-wavelength part of the exciton couplet at 247 nm from +0.2 to +1.0 is observed upon 100-fold increase of quinine concentration (Table I). In methanol there is little association of the alkaloid molecules and simple band β Coton effects are observed. Similar effect of concentration on the ^{1}H NMR spectra of racemic and enantiomerically pure alkaloids has been observed and interpreted in terms of solute-solute interactions.[25]

The most evident effect of self-association of alkaloid molecules is observed in the CD spectra of dihydrocupreidine (*6*). In methanol this alkaloid gives a simple positive band β Cotton effect, as do the configurationally related *5* and *7*. However, in dichloromethane a strong bisignate Cotton effect is observed, with the sign in the 225—235 nm range opposite to that in methanol solution. The positive exciton Cotton effect of *6* in the 225—244 nm range in dichloromethane (estimated amplitude $A = +80$ for the dimer) is accounted for by the strong association of the dihydrocupreidine molecules *via* the phenolic OH — quinuclidine nitrogen hydrogen bonds.

Next, we examined the CD spectra of salts of cinchona alkaloids with carboxylic acids. The following discussion is limited to the band β Cotton effects, which show distinct changes upon association of the alkaloid molecules.

Protonation of the alkaloid molecule with monocarboxylic acid (or methanesulfonic acid) leads to a single band β Cotton effect (Table II), which

TABLE II

Short-wavelength Cotton effect of quinine (1) *and dihydrocupreidine* (6) *protonated with monoacids*[a]

	Solvent	Bands β, $\Delta\varepsilon$ (nm)
1 + methanesulfonic acid	CH_2Cl_2	—7.5 (235)
1 + acetic acid	CH_2Cl_2	—7.5 (237)
	dioxane	—6.5 (228)
	MeOH	—8.5 (230)
1 + benzoic acid	CH_2Cl_2	—11.2 (240)
1 + 3-nitrobenzoic acid	CH_2Cl_2	—12.7 (238)
1 + 4-nitrobenzoic acid	CH_2Cl_2	—11.6 (235)
1 + 3,5-dinitrobenzoic acid	CH_2Cl_2	—19.8 (239)
6 + methanesulfonic acid	CH_2Cl_2	+5.4 (238)
6 + acetic acid	CH_2Cl_2	+13.0 (240)

[a] Concentration of both the alkaloid and the acid was 4×10^{-4} M.

has the same sign and magnitude as the free base in methanol (Table I). Thus, for quinine (*1*) salts a negative band is obtained in the 228—240 nm range, and this is only slightly affected by solvent polarity. In salts with aromatic carboxylic monoacids the Cotton effects are stronger, probably due to superposition of Cotton effects induced within the absorption bands of the aromatic acids. However, as no exciton-type Cotton effects are seen to contribute to

the band β Cotton effects, it appears that there is no self-association of the alkaloid molecules. It is suggested that the structure of the alkaloid-monocarboxylic salt in solution in non-polar solvents is similar to that found in the solid state,[18] *i. e.* the alkaloid is in the synclinal (A) conformation, stabilized by the intermolecular hydrogen bonding $\overset{+}{N}H\cdots O=\overset{-}{C}=O\cdots HO$ within the 1 : 1 salt.

The CD spectra of the 2 : 1 salts of quinine (*1*) with the carboxylic di-acids, malonic, succinic, maleic, and fumaric acid in dichloromethane (Table III), show again a single negative band in the range 235—241 nm, with no sign of contribution of exciton coupling between the two quinoline residues.

TABLE III

Short wavelength Cotton effects of quinine (1) *and quinidine* (5) *as salts with diacids (in dichloromethane)*[a]

	Band β, $\Delta\varepsilon$ (nm)[b]	
(1) + sulfuric acid	+2.2 (251)	—22.0 (236)
(1) + oxalic acid	+5.0 (248)	—14.5 (236)
(1) + malonic acid		—12.0 (235)
(1) + succinic acid		—12.2 (235)
(1) + maleic acid		—17.0 (236)
(1) + fumaric acid		—29.0 (241)
(1) + phthalic acid	+3.0 (248)	—18.8 (237)
(1) + (*S*)-malic acid		—18.0 (236)
(5) + (*S*)-malic acid	—4.5 (248)	+18.0 (235)
(1) + (*R,R*)-tartaric acid	+16.0 (248)	—38.0 (233)
(5) + (*R,R*)-tartaric acid		+12.6 (236)
(1) + (*R,R*)-4-cyclohexene-1,2-dicarboxylic acid	+6.5 (249)	—24.0 (235)
(5) + (*R,R*)-4-cyclohexene-1,2-dicarboxylic acid	—14.4 (248)	+24.4 (235)

[a] Concentrations of the diacid and the alkaloid are 2×10^{-4} and 4×10^{-4} M, respectively.
[b] Calculated on the basis of the 2:1 salt concentration, *i. e.* 2×10^{-4} M.

However, salts of (*1*) with sulfuric acid, oxalic acid and phthalic acid, in which the quinine molecules are kept at a shorter distances, give the CD curves with characteristic contribution of the exciton bands. In these salts the long wavelength exciton Cotton effect is always positive. It appears that the preferred arrangement of the two quinine molecules in the complex is such that the two quinoline chromophores produce positive exciton Cotton effects *via* intermolecular coupling (Figure 3).

The CD spectra of the salts of quinine (*1*) and quinidine (*5*) with chiral carboxylic diacids provide an interesting insight into the mode of association in the diastereoisomeric salts. Thus, a single Cotton effect is observed in the CD spectra of quinine (*1*) with (*S*)-malic acid and quinidine (*5*) with (*R,R*)-tartaric acid, while contribution from the exciton coupling between the two quinoline residues is observed in the salts of *1* and *5* with (*R,R*)-4-cyclohexene-1,2-dicarboxylic acid as well as *1* with (*R,R*)-tartaric acid and *5* with (*S*)-malic acid. Thus, the CD spectra indicate a different arrangement of the alkaloid molecules in the diastereoisomeric salts with chiral diacids.

The case of (*R,R*)-4-cyclohexene-1,2-dicarboxylic acid is particulary striking. The two equatorial carboxylic groups in this diacid form a negative torsional angle. Despite that the salts with quinine (*1*) and quinidine (*5*) give exciton Cotton effects of opposite signs. It, thus, follows that the spatial arrangement of the two quinoline residues in the 2 : 1 salt is determined to a lesser extent by the chirality of the acid, but it is primarily related to the absolute configuration of the alkaloid (note positive exciton coupling in the case of quinine and negative in the case of quinidine — Table I).

In the case of biphenyl 1,1'-dicarboxylic acids (*8, 9*) strong exciton Cotton effects are observed for salts with the alkaloids *1, 2, 5* and *6* (Table IV).

TABLE IV

Short-wavelength Cotton effects of the alkaloids 1, 2, 5 *and* 6 *as salts with biphenyl 1,1'-dicarboxylic acids* 8 *and* 9[a]

	Solvent	Band β, Δε (nm)[b]	
1 + *8*	CH_2Cl_2	+107 (244)	—31 (222)
1[c] + *8*	CH_2Cl_2	+122 (244)	—36 (222)
1 + *8*	dioxane	+60 (243)	—23 (222)
1 + *8*	MeOH		—15 (230)
2 + *8*	CH_2Cl_2		+7 (235)
5 + *8*	CH_2Cl_2	—98 (244)	+21 (222)
6 + *8*	CH_2Cl_2	—74 (245)	+44 (226)
1 + *9*	CH_2Cl_2	+48 (245)	—47 (230)
5 + *9*	CH_2Cl_2	—54 (245)	+41 (230)

[a,b] See Table III. [c] Concentration of quinine 8×10^{-4} M.

The presence of these Cotton effects is apparently dependent on the formation of the intermolecular hydrogen bond of the diacid with the alkaloid hydroxy group, stabilizing the structure of the salt. Thus, no exciton Cotton effects are observed in methanol solution and in the salt of acetylquinine (*2*) with biphenyl 1,1'-dicarboxylic acid (*8*), the Cotton effects obtained in these cases resembling those of salts with monocarboxylic acids. An increase of the quinine concentration above the 2 : 1 ratio brings about only a slight increase of the exciton Cotton effect. Figure 4 presents the CD spectra of the salts of quinine (*1*) with biphenyl 1,1'-dicarboxylic and benzoic acids. From these spectra it follows that the optical rotation of the two salts at the sodium D-line is expected to be positive and negative respectively.

As expected, salts of (*1*) and (*5*) with biphenyl 1,1'-dicarboxylic acid give nearly mirror-image CD curves and quinine (*1*) gives positive exciton Cotton effects with both biphenyl 1,1'-dicarboxylic acid (*8*) and its 5,5'-dinitroderivative (*9*).

It can be concluded that strong exciton Cotton effects are induced in 2 : 1 salts with biphenyl 1,1'-dicarboxylic acid due to the coupling between the quinoline residues (or between the quinoline and biphenyl chromophores) in the rigid structure, formed by the interlocking hydrogen bonds between the alkaloid hydroxy-group and the carboxylate ions. By inspection of molecular models of the 2 : 1 salt it is difficult to indicate the preferred alkaloid molecular conformation, although conformation (B) seems to provide a less

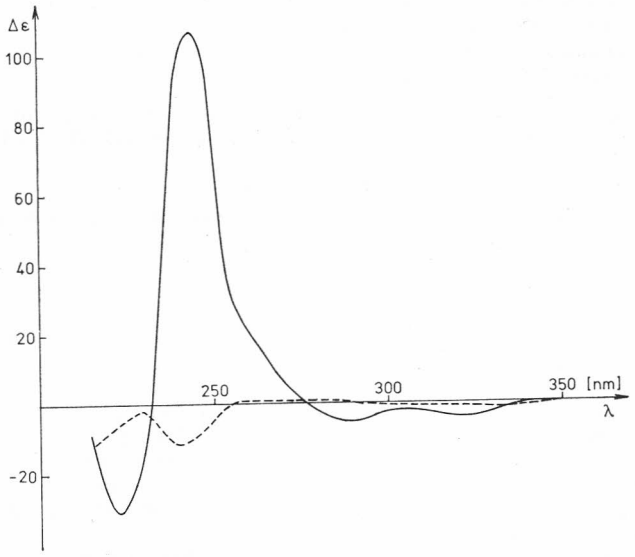


Figure 4. CD curves of quinine (*1*)/biphenyl 1,1'-dicarboxylic acid (*8*) (2:1, full line) and quinine (*1*)/benzoic acid (1:1, broken line) in dichloromethane.

congested structure than (A). An X-ray determination of the molecular structure of 2 : 1 salts of alkaloids with biphenyl 1,1'-dicarboxylic acids is now under way.[26]

The above discussion does not imply that there is highly enantioselective complexation of biphenyl 1,1'-dicarboxylic acid with alkaloid molecules in solution. Due to the hydrogen donor-acceptor character of the carboxylic group, the interlocking hydrogen bond system with the alkaloid molecule can apparently be provided by biphenyl 1,1'-dicarboxylic acid of either (*R*) or (*S*) chirality. Thus, »anomalous« optical rotation of salts of biphenyl 1,1'-dicarboxylic acids with cinchona alkaloids cannot be unequivocally interpreted as resulting from enantioselective complexation of one of the enantiomeric interconverting conformations of the diacid with the alkaloid molecules (first-order asymmetric transformation).[8,9] In view of our CD results with salts of biphenyl and other carboxylic diacids, the anomalous rotation is mainly due to the exciton coupling mechanism involving the electrical transition moment of the quinoline chromophore in the alkaloid molecule.

EXPERIMENTAL

The CD spectra were recorded with a Jobin-Yvon Mark III dichrograph. The concentrations of the solutions are shown in Tables I—IV. The cell length was 0.1 cm.

Sources of compounds: alkaloids (*1*) (Fluka), (*3*) and (*5*) (BDH) and (*7*) (Koch-Light) as well as biphenyl 1,1-dicarboxylic (*8*), (*S*)-malic and (*R,R*)-tartaric acids (Aldrich) were all used without further purification.

Acetylquinine (*2*), *m. p.* 118—120 °C and dihydrocupreidine hydrochloride (6 × HCl), *m. p.* 264—8 °C (dec.), were kindly provided by Dr. J. Thiel of this Department. The unstable free base (*6*) was obtained from its hydrochloride by sodium bicarbonate extraction followed by silicagel filtration with chloroform as solvent, *m. p.* 161—5 °C.

5,5'-Dinitrobiphenyl-1,1'-dicarboxylic acid (*9*), *m.p.* 277—280 °C was synthesized from 4-nitroanthranilic acid.[27]

(*R*,*R*)-(4)-cyclohexene-1,2-dicarboxylic acid, $[\alpha]_D$ — 161° (c = 1,EtOH), *m.p.* 146—148.5 °C, was obtained from its racemate by resolution.[28]

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SAŽETAK

Studij cirkularnim dikroizmom molekulskih asocijata cinkona-alkaloida i karboksilnih kiselina

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Istraženi su spektri cirkularnog dikroizma cinkona-alkaloida i njihovih soli s karboksilnim kiselinama. Sugerira se da doprinos Cottonom efektu ekscitonskog tipa za CD vrpcu kod 230 nm slobodnih baza u nepolarnim otapalima potječe od asocijacije molekula alkaloida. Snažna asocijacija opažen je u slučaju dihidrokupreidina-alkaloida koji posjeduje slobodne fenolne skupine.

Usporedba CD spektra soli alkaloida s mono- i dikarboksilnim kiselinama pokazuje da u posljednjem slučaju Cottonov efekt za β-vrpcu potječe od interakcije ekscitonskog tipa između asociranih molekula.

Za neuobičajeno zakretanje soli cinkona-alkaloida za difenil-1,1'-dikarboksilnim kiselinama nađeno je da potječu od snažnog intermolekulskog ekscitonskog sprezanja, a ne od »asimetrične transformacije prvog reda«. Postojanje dviju energijski niskih, prekrivenih konformacija oko veze C(8)—C(9) u molekuli alkaloida potvrđeno je MMP2 računima na modelnom spoju.