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The Significance of Induced Circular Dichroism

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ABSTRACT

Achiral molecules or ions can display induced circular dichroism (ICD) within their absorption bands on association with chiral inducing molecules. The reverse process is equally important, although less appreciated: chiral inducing molecules, such as tartrates, can show significantly differing CD bands in different achiral environments. Therefore true ICD due to achiral molecules can only be demonstrated in the spectral region outside the absorption bands of the chiral inducing molecules. The case of tartrate–trisimidazoline helical assembly in aqueous solvent is discussed.

The process of induction of optical activity in achiral solute molecules by chiral nonracemic molecules has been recognized very early[1] and received much attention, for example, as a method of either establishing absolute configuration of a transparent (nonchromophoric) chiral molecule with the use of an achiral or racemic chromophoric molecule or to study the orientation of the molecules within the complex between a chiral host and achiral guest.[2] Figure 1 represents the basic idea of induced optical activity, usually observed as induced circular dichroism (ICD).

On association of a chiral inducer (A) with the achiral molecule (B) ICD appears within the absorption bands of B, which were otherwise CD inactive. In general there are two different situations in which ICD can be generated, induction of a dominating chiral structure of the achiral molecule or induction of a chiral arrangement of the electric dipole transition moments between the relevant chromophores of the achiral (guest) and chiral (host) molecules. Although this process of induction of CD is generally accepted and quite obvious, less appreciated is the reverse effect: in the A−B complex formed, the CD of the chiral inducer A is also changed, as a result of the different environment in which the molecules are located. Both effects, i.e., the ICD of molecules B and modified CD of molecules A, can in principle be observed, providing that the electronic transitions of A and B are well separated. This condition usually cannot be met because in the short-wavelength spectral region transitions within A and B overlap. ICD of achiral molecules B can be readily detected when they absorb at longer wavelengths compared to chiral molecules A. Recent examples include the detection of the ICD due to the 1,8-naphthyridine derivative in the 300−350 nm range on binding to a single guanine bulge of duplex DNA[3] or detection of the ICD of the azo chromophore in a rigid

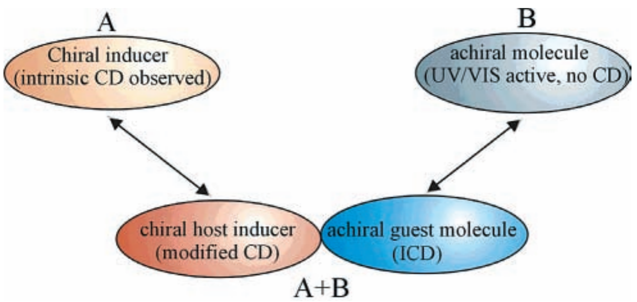

Figure 1. Changes in CD induced by the formation of complex A + B.

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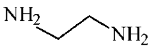
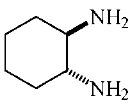
(1) (a) Bosnich, B. *J. Am. Chem. Soc.* **1966**, *88*, 2606. (b) Hayward, LD.; Totty RN. *Can. J. Chem.* **1971**, *49*, 624−631. (c) Norden, B. *Chem. Scr.* **1975**, *8*, 20−22.

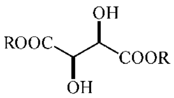
(2) For an excellent review, see: Allenmark, S. *Chirality* **2003**, *15*, 409−422.

10.1021/ol0352456 CCC: $25.00

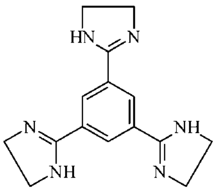
Table 1. Intrinsic Circular Dichroism of (*R*,*R*)-Tartaric Acid and Its Salts in Aqueous Solutions Measured at 295 K, $c = 5 \times 10^{-4}$ M dm^{-1}, $d = 1$ cm

compound	R	Δε (nm)	
1a	H, H	-4.6 (214)	-
1b	H, Na	-3.1 (211)	-2.7 (194)
1c	H, K	-3.4 (213)	-1.7 (199)
1d	H, NH_4	-3.8 (213)	-1.4 (193)
1e	H, NH_2Me_2	-2.7 (212)	-2.1 (194)
1f	H, $NHEt_3$	-3.2 (213)	-1.7 (199)
1g	Na, Na	-2.5 (210)	-4.2 (193)
1h	Na, K	-1.6 (211)	-2.9 (191)[7]
1i		-2.6 (210)	-4.2 (193)
1j		-3.0 (211)	-4.5 (193)
1k	NH_2Me_2, NH_2Me_2	-2.5 (213)	-3.3 (193)
1l	$CetNMe_3$, $CetNMe_3$	-1.7 (210)	-4.5 (193)[8]

symmetrical molecule due to the complexation with cyclodextrin molecules.[4]



1a - 1l



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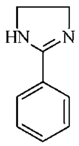

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To determine the effect of an achiral environment on the CD of a chiral inducer we have chosen (*R*,*R*)-tartaric acid and its salts (molecules A) with cations that are transparent in the UV absorption region studied. The counterions provide differing environment B while they do not produce ICD above 190 nm. Tartaric acid is a well-known chiral inducer, used as chiral reagent, chiral resolving agent, and chiral auxiliary in organic synthesis,[5] and it may induce CD in achiral molecules. The data collected in Table 1 and Figure 2 show that the CD spectrum of tartaric acid (**1a)** changes with the formation of various salts (**1b**−**l**) and that the salts give CD spectra differing not only in magnitude but also in the shape of the Cotton effects. Unlike tartaric acid (**1a**), which shows only a single negative Cotton effect at 214 nm due to the $n-\pi^*$ transition in the carboxylic group, the salts (**1b**−**l**) invariably give two negative Cotton effects (at 213−210 nm and at 199−191 nm) within the weak absorption region (ϵ below 500). The two Cotton effects differ in relative magnitudes: the monosalts **1b**−**f** show a more intense long-wavelength $n-\pi^*$ Cotton effect, whereas the disalts **1g**−**l** are characterized by a more intense short-wavelength $n-\pi^*$ Cotton effect. These differences apparently reflect the different electronic nature of the carboxy group in the free acid and in its salts. Less likely is the change of conformation of the tartrate carbon chain. It has been shown[6] that tartaric acid and its derivatives (with the exception of *N*,*N*,*N*′,*N*′-tetraalkyldiamides) exist preferentially in a planar *trans* conformation.

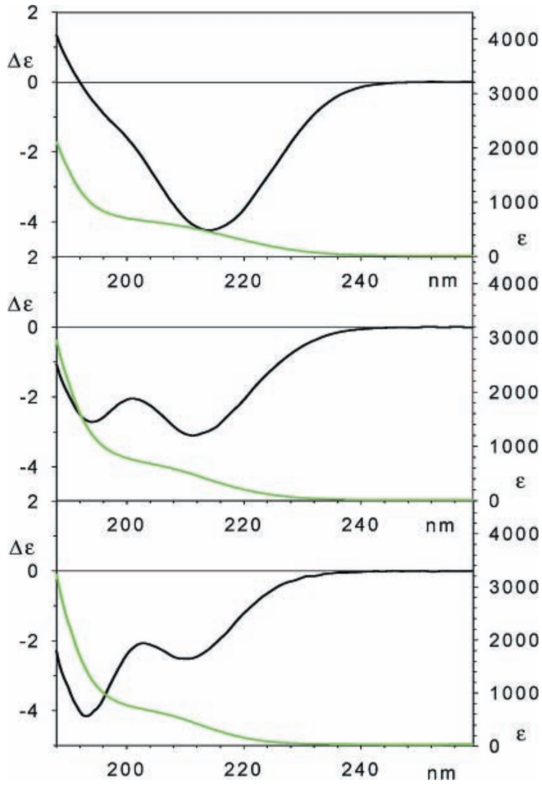

Figure 2. UV and CD spectra of (*R*,*R*)-tartaric acid (**1a**, upper panel), its monosodium salt (**1b**, middle panel), and its disodium salt (**1g**, lower panel) in aqueous solution.

As an example of the problems encountered in the interpretation of ICD measurements we quote a recent publication claiming the first observation of helicity induced in trisimidazoline molecule **2** by tartaric acid (**1a**) through the formation of a capsule-like supramolecule $[\mathbf{1a}_3\cdot\mathbf{2}_2]$ in aqueous solvent.[9] The authors have proven the stoichiometry of the $[\mathbf{1a}_3\cdot\mathbf{2}_2]$ complex by NMR, mass spectra (CSI,

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(3) Nakatami, K.; Sando, S.; Saito, I. *J. Am Chem. Soc.* **2000**, *122*, 2172−2177.

(4) (a) Zhang, X.; Nau, W. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 544−547. (b) Mayer, B.; Zhang, X.; Nau, W. M.; Marconi, G. *J. Am. Chem. Soc.* **2001**, *123*, 5240−5248.

(5) Gawronski, J.; Gawronska, K. *Tartaric and Malic Acids in Synthesis: A Source Book of Building Blocks, Ligands, Auxiliaries, and Resolving Agents*; Wiley-Interscience: New York, NY, 1999.

(6) (a) Gawronski, J.; Gawronska, K.; Rychlewska, U. *Tetrahedron Lett.* **1989**, *30*, 6071−6074. (b) Gawronski, J.; Gawronska, K.; Skowronek, P.; Rychlewska, U.; Warżajtis, B.; Rychlewski, J.; Hoffmann, M.; Szarecka, U. *Tetrahedron* **1997**, *53*, 6113−6144.

(7) Koralewski, M.; Mróz, M. *Acta Phys. Pol., A* **1983**, *63*, 507−517.

(8) Berthier, D.; Buffetean, T.; Leger, J.-M.; Oda, R.; Huc, I. *J. Am Chem. Soc.* **2002,** *124,* 13486−13494.

MALDI), and Job plot analysis. However, their claim of the induced helicity in the molecule **2** is exclusively based on the CD spectrum, which shows only one Cotton effect at 214−215 nm, conspicuously similar in the sign and magnitude to that of the chiral inducer **1a**, used in excess.[10] For example, the $\Delta\epsilon$ of [**1a**·**2**] with 22 molar excess of **1a** is −4.5 (214−215 nm) in water/ethanol (1:1, v/v) (compare the data for **1a** in Table 1). The differences observed in the n−π* absorption region of **1a** and its complex [**1a**·**2**] are insignificant as evidence of ICD due to helicity of **2**. Even more importantly, the authors failed to demonstrate any CD induced within the absorption bands of **2**, outside the CD bands of **1a**, i.e., above 250 nm.[11] Only such data could be regarded as an evidence for a defined helical conformation of **2** in the complex with **1a**. In water/ethanol (1:1) solution [$\mathbf{1a}_3$·$\mathbf{2}_2$] shows only a pair of Cotton effects, at 212 nm ($\Delta\epsilon$ −3.0) and at 201 nm ($\Delta\epsilon$ −2.1), similar to those of the monosalts of tartaric acid.

The experiment has been repeated with the complex [**1a**·$\mathbf{3}_2$] of monoimidazoline **3**.[12] The CD of the complex [**1a**·$\mathbf{3}_2$] in water solution is typical of the disalts of tartaric acid; it shows a pair of Cotton effects at 211 nm ($\Delta\epsilon$ −3.0) and at 195 nm ($\Delta\epsilon$ −4.0). No CD was observed at the wavelengths above 240 nm.[11]

In summary, ICD is a powerful method to study the stereostructures of molecular associates, if used judiciously. Small changes within the CD bands of the chiral inducer due to formation of a complex (salt) are not indicative of the chirality in the partner molecule. Unless the obligatory condition of detecting ICD within the absorption bands of the achiral component is fulfilled, the conclusions regarding the induction of helicity are speculative.

Supporting Information Available: CD spectra and ^{13}C NMR details. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Kim, H.-J.; Sakamoto, S.; Yamaguchi, K.; Hong, J.-I. *Org. Lett.* **2003**, *5*, 1051−1054.

(10) The data reported in ellipticity units θ in mdeg are readily converted: $\Delta\epsilon = 3.03 \times 10^{-5}\, \theta\, c^{-1}\, d^{-1}$ where c is concentration in mol dm^{-3} and d is path length in cm.

(11) The UV spectrum of **2** in the complex [$\mathbf{1a}_3$·$\mathbf{2}_2$] displays two features: a broad absorption between 330 and 250 nm (ϵ 5300 at 264 nm) and an intense maximum at 216 nm (ϵ 48 000). The UV maxima of **3** are at 197 nm (ϵ 52 000), 325 nm (ϵ 21 000), with a shoulder at ca. 270 nm.

(12) Oxley, P.; Short, W. F. *J. Chem. Soc.* **1950**, 859−862.