Effect of fluorine on the circular dichroism of the benzene chromophore [1]

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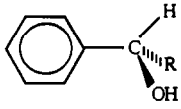
Abstract

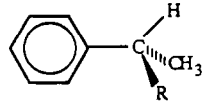
Examination of the electronic absorption and circular dichroism spectra of a number of chiral benzene compounds of known absolute configurations in which there is a fluorine atom at a chiral center contiguous to the benzene ring gives the rotatory contribution of a fluorine atom to the ^1L_b Cotton effects of the benzene chromophore in relation to other groups at the chiral center. These relative contributions may be used with the benzene sector rule to establish the absolute configurations of benzene compounds in which one substituent at a contiguous chiral center is a fluorine atom. Thus, the *R* absolute configuration was assigned to (−)-α-fluoro-α-phenylpropionic acid.

Introduction

In an earlier report [2], a sector rule was proposed by which for monosubstituted chiral benzene compounds **1** and **2** the absolute configuration at a chiral center contiguous to the benzene



(*S*)-**1a**: R = CH_3
(*R*)-**1b**: R = CO_2H



(*S*)-**2a**: R = Cl
(*S*)-**2b**: R = CO_2H

ring can be correlated with the observed Cotton effects (CEs) from about 255 to 270 nm in its circular dichroism (CD) spectrum (Fig. 1). These CEs are the result of transitions from the lowest energy totally symmetric vibrational mode in the electronic ground state to totally symmetric vibrational modes in the ^1L_b electronically excited state of the benzene chromophore [3], the lowest energy CE being associated with the ^1L_b band origin. For some benzene compounds, additional weak CD maxima are observed within the ^1L_b band

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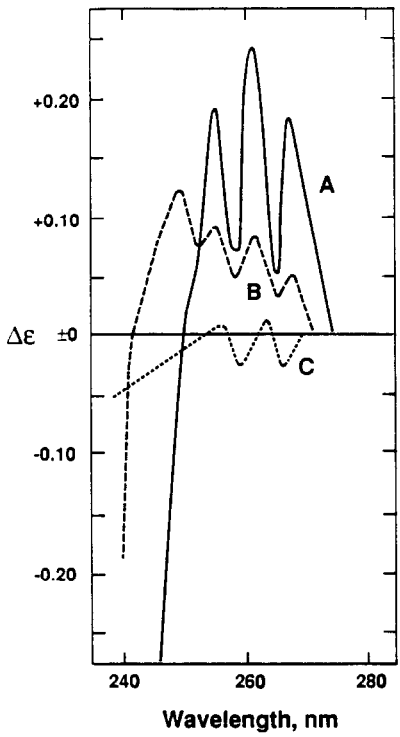
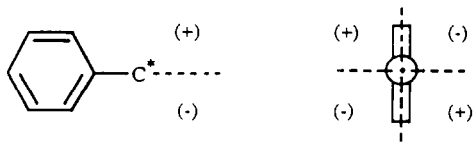


Fig. 1. Circular dichroism spectrum in methanol of (A) (*R*)-α-fluoro-α-phenylacetic acid [(*R*)-**3a**], (B) (*R*)-α-fluoro-α-phenylpropionic acid [(*R*)-**4**] and (C) potassium (*R*)-α-fluoro-α-phenylpropionate [(*R*)-**4** with added potassium hydroxide].

with a sign opposite to that of the ^1L_b band origin. These weak maxima are the result of transitions to nontotally symmetric vibrational modes in the electronically excited state [4].

For a particular configuration of the contiguous chiral center, the sign of the ^1L_b CEs associated with transitions to totally symmetric vibrational modes in the excited state can be predicted on the basis of the preferred conformation of the chiral group about its attachment bond to the benzene ring and quadrant projection I. The signs shown on projection I give the



near quadrants Ia

all quadrants Ib

CD contributions to the ^1L_b CEs by groups lying in the four quadrants, the sum of these contributions giving the sign to the CEs. For groups lying in sector boundaries, there is no contribution to the ^1L_b CEs.

For substituted benzene compounds such as **1** and **2**, molecular orbital calculations and various spectroscopic measurements indicate that the preferred conformation is such that a hydrogen atom at the contiguous chiral center eclipses or almost eclipses the benzene ring plane [2, 5]. With this conformational preference, the signs for the quadrants in projection I follow from the observed positive ^1L_b CEs for (*S*)-α-phenylethyl alcohol [(*S*)-**1a**] (Table 1) and the assumption of a larger positive rotatory contribution for a methyl group as compared to a smaller negative contribution by a hydroxy group. This latter assumption is based on a larger effective bond transition moment for a carbon–carbon bond as compared to that for a carbon–oxygen bond [8].

The relative rotatory contributions of the methyl, hydroxy and other groups for the prediction of the sign of the observed ^1L_b CEs may be shown as sequences: SH, CO_2^-, $C(CH_3)_3 > CH_3 > NH_2$, $^+NH_3$, $^+N(CH_3)_3$, OH, OCH_3, Cl; and $CH_3 > CO_2H > {}^+NH_3$, OH, OCH_3, the placement of groups within each sequence being the result of the sign of the observed ^1L_b CEs for chiral benzene compounds with appropriately substituted contiguous chiral centers [2]. Thus as seen in Table 1, the ^1L_b CEs for (*R*)-mandelic acid [(*R*)-**1b**] and its potassium salt are positive, and both the CO_2H and CO_2^- groups in a positive quadrant make greater positive contributions than the smaller negative contribution of the hydroxy group. Similarly, the positive ^1L_b CEs

TABLE 1

Spectral properties of chiral benzene compounds

Compound	^1L_b band origin maxima[a]			
	CH_3OH		CH_3OH–KOH[b]	
	λ (nm) (ε)[c]	λ (nm) (Δε)[d]	λ (nm) (ε)[c]	λ (nm) (Δε)[d]
(*S*)-**1a**[f]	267 (90)	268 (+0.17)[+][e]		
(*R*)-**1b**[g]	267 (79)	269 (+0.067)[+]	268 (75)	268 (+0.024)[+][e]
(*S*)-**2a**[h]	272 (110)	273 (+0.033)[+]		
(*S*)-**2b**	267 (79)	268 (+0.029)[+]	268 (120)	269 (−0.12)[−]
(*R*)-**3a**	268 (88)	268 (+0.18)[+]	267 (120)	268 (+0.12)[+]
(*R*)-**3b**	267 (120)	267 (+0.042)[+]	266 (88)	267 (+0.091)[+]
(1*R*,2*S*)-**3c**	266 (92)	266 (+0.091)[+]	266 (100)	268 (+0.29)[+]
(*R*)-**4**	268 (100)	268 (+0.045)[+]	267 (92)	267 (−0.028)[−]

[a]Complete electronic absorption and circular dichroism data are found as cited in a footnote or in the Experimental section.
[b]Carboxylate salt or free base.
[c]Molar absorptivity.
[d]Molar dichroic absorption; $\Delta\epsilon = [\theta]/3300$ where $[\theta]$ is the molecular ellipticity.
[e]Predicted sign for the ^1L_b CEs on application of the benzene sector rule.
[f]Complete spectral data in ref. 6.
[g]Complete spectral data in ref. 7.
[h]Complete spectra data in ref. 2.

TABLE 2

Fluorine-containing chiral benzene compounds

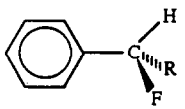
Compound	Name	$[\alpha]_D^{24-25}$(°)[a]
(*R*)-**3a**	(*R*)-α-fluoro-α-phenylacetic acid	−158[b] −122[c]
(*R*)-**3b**	(*R*)-β-fluoro-β-phenylethylamine hydrochloride	−39
(1*R*,2*S*)-**3c**	(1*R*,2*S*)-*N*,*N*-dimethyl-1-fluoro-1-phenyl-2-aminopropane hydrochloride	−7.6
(*R*)-**4**	(*R*)-α-fluoro-α-phenylpropionic acid	−28

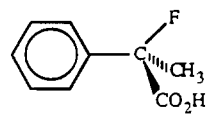
[a]*c* 1.00–1.58 g/100 ml of methanol or as noted otherwise.
[b]Solvent was acetone.
[c]Solvent was chloroform.

for (*S*)-α-phenylethyl chloride [(*S*)-**2a**] and (*S*)-α-phenylpropionic acid [(*S*)-**2b**] place a chlorine atom and the carboxy group lower in the sequences than a methyl group. On formation of the potassium salt of (*S*)-**2b**, there is no change in the preferred conformation of the chiral group about its attachment bond to the benzene ring, but the ^1L_b CEs change sign and are now negative. Thus the carboxylate group makes a greater contribution to the CEs than does a methyl group and is higher in the sequences of rotatory contributions.

These sequences when used in connection with quadrant projection I have a general usefulness for the establishment of the absolute configuration of similar chiral benzene compounds in which one substituent at the contiguous center is a hydrogen atom and the other two groups or atoms at the chiral center are members of the sequences.

We have now examined the electronic absorption (EA) and CD spectra of a number of chiral benzene compounds of known absolute configurations in which there is a fluorine atom at a contiguous chiral center [**3a–c**] (Table 2) and have assessed the rotatory contribution of the





(*R*)-**3a**: R = CO_2H (*R*)-**4**
(*R*)-**3b**: R = $CH_2NH_2 \cdot HCl$
(1*R*,2*S*)-**3c**: R = $CH(CH_3)N(CH_3)_2 \cdot HCl$

fluorine atom to the ^1L_b CEs. A comparison of these CD data with those reported earlier for related compounds (Table 1) allows the *R* absolute configuration to be assigned to (−)-α-fluoro-α-phenylpropionic acid [(−)-**4**].

Results and discussion

The *R* absolute configuration was assigned earlier to (−)-α-fluorophenylacetic acid [9] [(*R*)-**3a**]. Since the preferred conformation of (*R*)-**3a** is such that the α-hydrogen atom eclipses the benzene ring plane and the fluorine atom is in a negative sector of projection I, the positive ^1L_b CEs for (*R*)-**3a** show that the carboxy group, in a positive sector, makes a greater rotatory contribution than does the fluorine atom. The potassium salt of (*R*)-**3a** also shows positive ^1L_b Cotton effects so that the rotatory contribution of a carboxylate group is still greater than that of a fluorine atom.

Similarly, the positive ^1L_b CEs of (*R*)-β-fluoro-β-phenylethylamine hydrochloride [10] [(*R*)-**3b**] and its free base show that the rotatory contribution to the ^1L_b CEs of methylammonium group, an aminomethyl group, and probably a methyl group [2] is larger than that of a fluorine atom. Since for (1*R*,2*S*)-*N*,*N*-dimethyl-1-fluoro-1-phenyl-2-aminopropane hydrochloride [11] [(1*R*,2*S*)-**3c**] and its free base, the sign of the ^1L_b CEs depends only on the chirality of the chiral center attached directly to the benzene ring [2], the positive signs for their CEs show that the rotatory contribution of a fluorine atom makes a smaller contribution than does the carbon substituent.

These experimental results then allow the fluorine atom to be put into the sequences at the same position as the chlorine atom, and the sequences may be used to predict the sign of the ^1L_b Cotton effect of a particular enantiomer of chiral benzene compounds in which both a hydrogen atom and a fluorine atom are at the contiguous chiral center.

For the assignment of the absolute configuration to (−)-α-fluoro-α-phenylpropionic acid [12][(−)-**4**], it may be assumed that, since the fluorine atom has been found experimentally to be substantially smaller in effective bulk size than either the carboxy or methyl groups [13], the preferred conformation of **4** is such that the fluorine atom eclipses the plane of the benzene ring. Assuming that it is this conformation which then gives the sign to the ^1L_b CEs, and since (−)-**4** shows positive ^1L_b CEs (Table 1 and Fig. 1), this enantiomer is assigned the *R* absolute configuration. For this configuration, the methyl group is in a positive sector and makes a greater rotatory contribution than does the carboxy group.

Supporting the assignment of the *R* configuration to (−)-**4** is the observation that on conversion of (−)-**4** to its potassium salt, the CEs associated with transitions to the totally symmetric vibrational modes in the ^1L_b excited state are now negative (Fig. 1). This change in sign is similar to that observed for (*S*)-α-phenylpropionic acid [(*S*)-**2b**] which displays positive ^1L_b CEs, whereas for its potassium salt the CEs are negative (Table 1). In the potassium salts of both (−)-**4** and (*S*)-**2b**, the negative sign results from the circumstance that a carboxylate group makes a larger rotatory contribution to the ^1L_b CEs than does a methyl group.

The small positive CEs in the CD spectrum of the salt of (−)-**4** are assigned to the transitions to nontotally symmetrical vibrational modes of the ^1L_b transition.

Experimental

Melting points were taken in open capillary tubes and are corrected. Rotatory powers at the sodium D line were measured with a Rudoph Research Autopol III automatic polarimeter with a 1-dm sample tube. Electronic absorption (EA) spectra were measured with a Cary 2390 spectrometer in auto gain mode with matched 1-cm cells. Circular dichroism (CD) spectra were obtained at 25–28 °C with a Cary model 60 spectropolarimeter with a CD model 6001 accessory. The sample cell length was 1 cm, and the slit was programmed for a spectral band width of 1.5 nm. Spectral measurements began at 300 nm. The EA and CD spectra of the salt of the carboxylic acids and the free bases were determined after their formation *in situ*. Thus, 10% aqueous potassium hydroxide (2 drops) was added to the sample cell (3 ml) containing the solution of carboxylic acid or amine hydrochloride. For some of the solutions used for the measurement of the CD spectra, the pH is reported both before and after the 10% aqueous potassium hydroxide was added.

(*S*)-α-Phenylpropionic acid [(*S*)-**2b**]: $[\alpha]^{23}_D$ +70.4° (*c* 3.02, $CHCl_3$) [lit. [14] $[\alpha]_{589.3}$ +74.8° (*c* 3.060, $CHCl_3$)]. EA_{max} (CH_3OH) 267 nm (ε 79) 264 (140); 257 (190); 252 (150); 247 (120). EA_{max} (CH_3OH–KOH) 268 nm (ε 120): 265 (150) (sh); 261 (180) (sh); 259 (210); 253 (170); 248 (130); 242 (90). CD (CH_3OH, *c* 0.138): $[\theta]_{273}$ ±0; $[\theta]_{268}$ +96; $[\theta]_{266}$ +52; $[\theta]_{261}$ +150; $[\theta]_{259}$ +130; $[\theta]_{255}$ +170 (sh); $[\theta]_{250}$ +300. CD (CH_3OH–KOH, *c* 0.173): $[\theta]_{275}$ ±0; $[\theta]_{269}$ −400; $[\theta]_{266}$ −140; $[\theta]_{263}$ −470; $[\theta]_{259}$ −210; $[\theta]_{257}$ −280; $[\theta]_{252}$ −110; $[\theta]_{251}$ −120; $[\theta]_{246}$ ±0; $[\theta]_{238}$ +400.

(*R*)-α-Fluoro-α-phenylacetic acid [(*R*)-**3a**]: m.p. 100–102 °C; $[\alpha]^{25}_D$ −158° (*c* 1.53, CH_3COCH_3), $[\alpha]^{24}_D$ −122° (*c* 1.00, $CHCl_3$) [lit. [9] m.p. 103 °C, $[\alpha]^{20}_D$ −142° (*c* 1.25, CH_3COCH_3), $[\alpha]^{20}_D$ −153° (*c* 1.25, $CHCl_3$)]. EA_{max} (CH_3OH) 268 nm (ε 88): 262 (130); 257 (150); 251 (130); 247 (110). EA_{max} (CH_3OH–KOH) 267 nm (ε 120): 264 (190); 261 (180); 257 (240); 251 (240). CD (CH_3OH, pH 3.9, *c* 0.0314): $[\theta]_{275}$ ±0; $[\theta]_{268}$ +610; $[\theta]_{266}$ +180; $[\theta]_{262}$ +790; $[\theta]_{259}$ +290; $[\theta]_{256}$ +590; $[\theta]_{252}$ +120; $[\theta]_{250}$ ±0; $[\theta]_{246}$ −960 (*c* 0.0314): $[\theta]_{245}$ ±0; $[\theta]_{220}$ −35,000; $[\theta]_{217}$ −31,000. CD (CH_3OH–KOH, pH 13.6, *c* 0.0409): $[\theta]_{274}$ ±0; $[\theta]_{268}$ +390; $[\theta]_{266}$ +110; $[\theta]_{263}$ +470; $[\theta]_{258}$ +170; $[\theta]_{256}$ +300; $[\theta]_{253}$ +75 (sh); $[\theta]_{248}$ ±0; $[\theta]_{240}$ −770.

(*R*)-β-Fluoro-β-phenylethylamine hydrochloride [(*R*)-**3b**]: m.p. 198–200 °C; $[\alpha]^{24}_D$ −39° (*c* 1.29, CH_3OH) [lit. [10] m.p. 210 °C; $[\alpha]^{20}_D$ −41.5° (*c* 3.0, CH_3OH)] EA_{max} (CH_3OH) 267 nm (ε 120): 262 (210); 256 (230); 250 (170); 246 (110) (sh). EA_{max} (CH_3OH–KOH): 266 (88); 262 (170); 260 (140) (sh); 256 (210); 250 (160); 246 (110) (sh); 241 (74) (sh). CD (CH_3OH, pH 5.2, *c* 0.140): $[\theta]_{270}$ ±0; $[\theta]_{267}$ +140; $[\theta]_{264}$ +30; $[\theta]_{261}$ +150; $[\theta]_{257}$ +55; $[\theta]_{255}$ +110; $[\theta]_{243}$ ±0; $[\theta]_{223}$ −95. CD (CH_3OH–KOH, pH 13.8, *c* 0.0472): $[\theta]_{271}$ ±0; $[\theta]_{267}$ +300; $[\theta]_{265}$ +110; $[\theta]_{261}$ +330; $[\theta]_{257}$ +180; $[\theta]_{256}$ +220; $[\theta]_{251}$ +110; $[\theta]_{249}$ +130; $[\theta]_{240}$ ±0.

(1*R*,2*S*)-*N*,*N*-Dimethyl-1-fluoro-1-phenyl-2-aminopropane hydrochloride [(1*R*,2*S*)-**3c**]: m.p. 187–188 °C; $[\alpha]^{25}_D$ −7.6° (*c* 1.58, CH_3OH) [lit. [11] m.p.

220 °C; $[\alpha]^{20}_D$ −8.7° (*c* 2.6, CH_3OH)]. EA_{max} (CH_3OH) 266 nm (ϵ 92): 262 (180); 260 (150); 256 (220); 251 (170); 247 (120) (sh); 241 (92) (sh). EA_{max} (CH_3OH–KOH) 266 nm (ϵ 100) (sh): 263 (180); 257 (230); 251 (230). CD (CH_3OH), pH 4.2, *c* 0.147): $[\theta]_{270}$ ±0; $[\theta]_{266}$ +300; $[\theta]_{264}$ +100; $[\theta]_{261}$ +340; $[\theta]_{257}$ +150; $[\theta]_{255}$ +220; $[\theta]_{250}$ +100 (sh); $[\theta]_{233}$ ±0. CD (CH_3OH–KOH, pH 13.9, *c* 0.0613): $[\theta]_{273}$ ±0; $[\theta]_{268}$ +950; $[\theta]_{265}$ +350; $[\theta]_{261}$ +1000; $[\theta]_{258}$ +440; $[\theta]_{256}$ +650; $[\theta]_{250}$ +180 (sh); $[\theta]_{247}$ ±0.

(*R*)-α-Fluoro-α-phenylpropionic acid [(*R*)-**4**]: m.p. 62–70 °C; $[\alpha]^{25}_D$ −28° (*c* 1.05, CH_3OH) [lit.[12] $[\alpha]^{20}_D$ −28.5 (*c* 1.5, C_2H_5OH)]. EA_{max} (CH_3OH) 268 nm (ϵ 100): 263 (190); 256 (230); 251 (200). EA_{max} (CH_3OH–KOH) 267 nm (ϵ 92) (sh): 264 (180); 257 (230); 251 (200); 247 (160). CD (CH_3OH, *c* 0.0420): $[\theta]_{272}$ ±0; $[\theta]_{268}$ +150; $[\theta]_{266}$ +100; $[\theta]_{262}$ +250; $[\theta]_{259}$ +140; $[\theta]_{256}$ +270; $[\theta]_{253}$ +220; $[\theta]_{248}$ +360; $[\theta]_{242}$ ±0; $[\theta]_{240}$ −610. CD (CH_3OH–KOH, *c* 0.103): $[\theta]_{270}$ ±0; $[\theta]_{267}$ −92; $[\theta]_{265}$ ±0; $[\theta]_{264}$ +32; $[\theta]_{263}$ ±0; $[\theta]_{260}$ −96; $[\theta]_{258}$ ±0; $[\theta]_{257}$ +24; $[\theta]_{256}$ ±0; $[\theta]_{254}$ −72; $[\theta]_{252}$ −12; $[\theta]_{248}$ −36; $[\theta]_{247}$ −24; $[\theta]_{238}$ −180.

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