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CIRCULAR DICHROISM OF α-DEUTERIOPHENYLETHANES[1]

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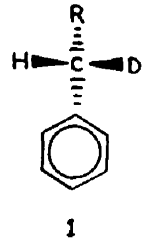
Abstract—CD measurements on a series of α-deuteriophenylethanes (1) which owe their chirality solely to deuterium substitution show that all compounds of related configuration display positive Cotton effects with pronounced fine structure for the ^1L_b band of benzene (240–270 nm), as do the configurationally related chiral 1-substituted phenylethanes (2) where the α-substituent is N, O or halogen. From a discussion of conformational preferences and a quadrant sector rule, the sign of the Cotton effects permits conclusions to be drawn regarding the conformational equilibrium in α-deuteriophenylethanes.

The first observation of a Cotton effect in a molecule which is chiral solely due to deuterium substitution, i.e. where the protio analogue is achiral, was reported in 1967 for (*R*)-(+)-1-butyl-1-*d* acetate.[2] Since then several compounds, especially ketones[3] and acids,[4] which owe their chirality to the isotopic difference between H and D have been shown to display Cotton effects in either optical rotatory dispersion (ORD) or circular dichroism (CD). Recent studies of D-substituted rigid cycloalkanones have been particularly fruitful and have proved to be useful in solving some conformational problems.[5]

Although some benzene derivatives **1** are known which are chiral due to incorporation of D at a benzylic carbon,[6] no Cotton effects of such compounds have been reported. The reason for this might be sought in the low rotational strength of the 260 nm (^1L_b) transition in **1** due to the fact that the transition is only weakly electric-dipole allowed.[7] Conformational flexibility about the phenyl carbon–benzylic carbon bond could be another reason for low optical activity.

We wish to report the CD spectra in the 220–280 nm region (measured in cyclohexane) of compounds **1a**–**1e**, which are configurationally related.



1

1a, R = CH_3
1b, R = CD_2H
1c, R = C_3H_7
1d, R = CH_2OH
1e, R = CH_2Br

RESULTS AND DISCUSSION

The CD measurements (Table 1) show that all compounds display positive ^1L_b bands with pronounced fine structure (Fig. 1), similar in appearance to those observed in the unpolarized absorption spectra of alkyl-substituted benzenes.[8] Below 250 nm considerable broadening of the CD bands permitted only an approximate determination of their positions. The hydrocarbon (*S*)-(+)-1-phenylethane-1-*d* (**1a**) and its closely related trideuterated analogue (**1b**) which were observed by Elsenbaumer and Mosher[9] to have the same optical rotation also show virtually identical CD spectra. The higher molar ellipticity of (*S*)-(+)-1-phenylbutane-1-*d* (**1c**) compared to that of **1a** is in agreement with earlier ORD measurements carried out down to 400 nm[10] and with their D-line rotations.[6] Increasing absorption did not allow measurements of the CD for the ^1L_a band.

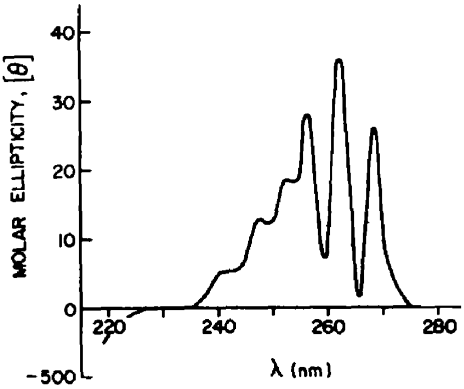
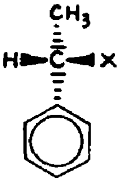


Fig. 1. Circular dichroism of (*R*)-(+)-2-phenylethanol-2-*d* (**1d**) in cyclohexane.

For an interpretation of the CD spectra of compounds **1a**–**1e** it is helpful to make a comparison with the closely related α-substituted phenylethanes (**2**), for which a large body of chiroptical data is available.

For a variety of substituents X, including amino,[11,12]



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2a, X = NH_2
2b, X = $N(CH_3)_2$
2c, X = $N(CH_3)_3^+$
2d, X = OH
2e, X = OCH_3
2f, X = Cl

Table 1. Circular dichroism of α-deuteriophenylethanes 1

Compound	CD maxima: λ_{nm} ([θ])^a					
	^1L_b band^b					^1L_a band
($\underline{S}$)-(+)-1-Phenylethane-1-$\underline{d}$ (1a)^c	268.5 (23)	262 (32)	256 (22)	252^d (14)	248 (13)	219^e (-400)
($\underline{S}$)-(+)-1-Phenylethane-1,2,2-$\underline{d}_3$ (1b)	268.5 (25)	262 (29)	256 (20)	253^d (14)	248 (12)	
($\underline{S}$)-(+)-1-Phenylbutane-1-$\underline{d}$ (1c)	268.5 (53)	262.5 (62)	256 (49)	251^d (31)	247 (25)	220^e (-650)
($\underline{R}$)-(+)-2-Phenylethanol-2-$\underline{d}$ (1d)	268.5 (26)	262 (36)	256 (28)	253 (19)	248 (13)	219^e (-240)
($\underline{R}$)-(-)-1-Bromo-2-phenylethane-2-$\underline{d}$ (1e)	269 (35)	262 (49)	256.5 (44)	252 (31)		

[a] In cyclohexane

[b] The rotational strength of the ^1L_b Cotton effects of 1a-1d was in the range of + 1.4 to 3 x 10^{-42} c.g.s.

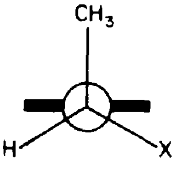
[c] UV spectrum in cyclohexane, λ_{max} nm (ϵ): 268 (160), 264 (147), 261 (203), 259 (193), 254.5 (166), 253 (160), 248 (113), 243 (70)^d.

[d] Shoulder

[e] Lowest wavelength reached

N,N-dimethylamino[11] and their hydrochlorides,[11,12] N,N,N-trimethylammonium,[11] hydroxy,[13,14] methoxy[14] and chloro,[15] the sign of the ^1L_b Cotton effect of 2 is positive for the *S*-configuration indicated. The positive Cotton effects observed for **1a** and **1b** (Table 1) show that D can also be included among these substituents. If the Me group in 2 is replaced by larger alkyl groups the sign of the ^1L_b Cotton effect remains positive as shown by the ORD and CD data on some 1-phenylalkylamines[16] and 1-phenyl-1-propanols.[17] The same holds true for the D-compounds 1 since **1c** displays a positive Cotton effect. Furthermore, introduction of an OH group at the α-C atom of **1a** and 2 does not affect the sign of the ^1L_b Cotton effect since both **1d** and (*R*)-1-phenylethane-1, 2-diol[14] exhibit positive Cotton effects.

The preferred conformation about the phenyl carbon–benzylic carbon bond of compounds **1a**–**1e** may be deduced from conformational data on ethylbenzene. MO calculations support a conformation for ethylbenzene in which the Me group is almost at right angles to the plane of the benzene ring,[18] while NMR[19] and Raman spectroscopic[20] observations as well as other calculations[21] suggest a slightly different conformation with a C–H bond more nearly eclipsing the plane of the benzene ring. On this basis the conformers 3, 4 and 5 may be depicted for **1a**–**1e**. Similar preferred conformations (6 and 7, X = OH) can be assumed for (*S*)-1-phenylethanol (**2d**) as Cervinka *et al.*[13] give the minimum nonbonded interaction in this alcohol when the C_α–C_β bond-phenyl ring plane dihedral angle is +75°, i.e. a conformation intermediate between 6 and 7. The conformation 7 (X = NH_2 or $\overset{+}{N}H_3$) was proposed for 1-phenyl-alkylamines **2a** and their hydrochlorides.[12] Other conformers were considered as being of higher energy due to the nonbonded



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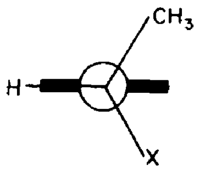

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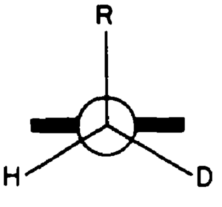

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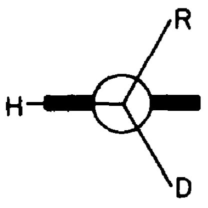

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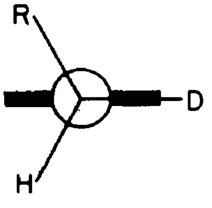

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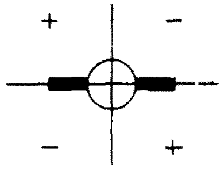

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interactions of the *ortho* hydrogens of the benzene ring with the amino group or with the alkyl group.[12] The conformity of the chiroptical behavior of all the α-substituted phenylethanes **2a–2f** suggests that conformations similar to **6** and **7** appear to be preferred for all the aforementioned substituents X in **2**.

The rotational strength of a monosubstituted benzene derivative of the types **1** and **2** is determined mainly by the one-electron mechanism.[22] The dipole–dipole contribution to the optical activity will be small since the electric transition moment of the ^1L_b band is small as is evident from the low molar absorptivities ($\epsilon \simeq 200$). Since the chromophoric units of **1** and **2** have C_{2v} symmetry the simplest sector rule applicable for the prediction of the one-electron contribution to the optical activity is a quadrant rule.[23] The sign of the CD contribution by groups in different sectors may then be assigned as shown in **8**. This assignment is in accord with the observed positive Cotton effects for the α-substituted phenylethanes **2** in the proposed conformations **6** and **7** and based on the assumption that the sector location of the heterosubstituent X takes precedence over the sector location of the methyl group. The latter assumption is reasonable since Brewster[24,25] showed that, when at a position α to a phenyl group, halogen, amino and OH substituents have a rotational rank higher than a Me group. The assignment of sector signs is supported by the theoretical study of Cervinka *et al.*[13] in which the one-electron contribution due to the OH group of (*S*)-1-phenylethanol **2d** in the conformation **7** (X = OH) was shown to be positive. This sign pattern is in agreement with sector rules proposed for chiral benzene derivatives[12,25,26] with transition moments for the ^1L_b band perpendicular to the C_2 axis of the chromophore.

Now consider the populations and rotational contributions of conformers in the equilibrium **3**⇄**4**⇄**5**. The actual conformers at energy minima need not be exactly these three forms but **3**, **4** and **5** can be used to approximate the most probable conformations. Using **8** to make rotational assignments, the R group in **3** is in a nodal plane and the hydrogen and deuterium atoms are situated in quadrants of opposite sign. Since, according to Brewster,[27] the relative atomic polarizability of D (1.004) is smaller than that of H (1.028), the H atom in **3** makes a slightly larger contribution to the Cotton effect than D atom. Lightner *et al.*[3] indeed have recently shown that in D-substituted cycloalkanones the rotational contribution from a C–D bond is smaller than that of its corresponding C–H bond. Accordingly, conformer **3** should make a negative contribution to the observed Cotton effect. Since compounds **1a–1e** give a positive Cotton effect, opposite to this prediction, we shall dimiss **3** as a major contributor to the observed optical activity. In conformations **4** and **5** the R group will be the major contributor to the rotation; thus **4** should make a negative, and **5** a positive contribution. If **4** and **5** were present in exactly equal amounts, their contributions *due to the R group* would exactly cancel. In that event the rotation based on the net contribution from H and D in **4** and **5** would be negative. We conclude that the observed positive Cotton effects for **1a–1e** are due to the greater population of the species represented by **5**.

The preference of a C–D bond, (as in **5**), rather than a C–H bond (as in **4**), to eclipse the plane of the benzene ring is in agreement with the observation that D has a smaller effective bond length[3] and size than H[28] due to the smaller vibrational amplitudes of the C–D bond.[29] Therefore D, possessing a lower zero-point energy level than H, will prefer to be in the plane of the benzene ring, where its C–D bending motion will cause *less* interaction with, e.g. adjacent *ortho*-hydrogens of benzene than would an H atom in the same position.

These results, like those obtained with D-substituted cyclohexanones[5] where axially oriented D was shown to be energetically preferred over the corresponding equatorial orientation,[5] illustrate the potential usefulness of the CD technique in the conformational analysis of flexible systems.

EXPERIMENTAL

CD spectra were measured on a Jasco J-500A spectropolarimeter at 20° using cell lengths of 0.1–2 mm. Molar ellipticities were reproducible within ±10%.

The compounds **1b**, **1c** and **1d** were prepared as described.[9,30] **1b** and **1d**[9] were optically and isotopically pure. **1c** had $\alpha^{25}_D + 0.57°$ (neat, $l = 1$) and was 96% deuterated. The molar ellipticity was corrected to optical purity ($\alpha_D + 1.70°$)[30] and 100% d_1.

(S)-(+)-1-*Phenylethane*-1-*d*(**1a**). (*R*)-(+)-**1d**[9] (0.30 g, 2.4 mmol) was converted to the methanesulfonate according to a method described.[31] The crude methanesulfonate [0.43 g, IR (film) 1340 (asymm. SO_2 stretching), 1170 (symm. SO_2 stretching) cm^{-1}] was treated with LAH (0.12 g, 3.2 mmol) tetraglyme as described for the corresponding tosylate[9] and afforded (*S*)-(+)-1-phenylethane-1-*d* (0.15 g, 66% overall yield), $[\alpha]^{20}_{365} + 5.2°$ (*c* 2.8, cyclohexane), IR (film) 2175 cm^{-1} (C–D stretch); eims: *m/e* (rel. int.) M^+ 107 (27), 92 (100). Isotopic purity: 99% d_1.

(R)-(−)-1-*Bromo*-2-*phenylethane*-2-d (**1e**). The following procedure based on the method of Trippett[32] was superior in yield and lack of racemization over several tried. To a soln of triphenylphosphine (7.8 g, 30 mmol) in benzene (25 ml) at 0° under N_2 was added (*R*)-(+)-**1d** (3.69 g, 30 mmol, $\alpha^{20}_D + 1.58°$ (neat), $l = 1$, 99% deuterated) in benzene (5 ml). Over a 45 min period with mechanical stirring, N-bromosuccinimide (5.34 g, 30 mmol) was added in small portions at 0°. The mixture was stirred (1 hr at 0°, 1 hr at 20°). The salts were removed by filtration, washed with benzene and the product distilled to give 3.67 g, b.p. 51–55° (1 torr), 81% yield, $\alpha^{20}_D - 0.921$ (neat, $l = 1$). The product was homogeneous by gas chromotgraphy containing no starting alcohol (Carbowax 400 column, 170°); eims: *m/e* (rel. int.) M^+ 187 (22), 185 (22), 92 (100); isotopic purity 96 ± 2% d_1, 4 + 2% d_0. (Found: (hrms) M^+ 186.99300, 184.99344. Calc. for C_8H_8DBr: 186.99312, 184.99509.)

Enantiomeric purity of (R)-(−)-*bromo*-2-*phenylethane*-2-d. Another sample of this bromide made by the same method was converted to the Grignard reagent and oxidized by bubbling in O_2 at −78°. The usual workup gave (R)-(+)-**1d** which had the same rotation within experimental limits as the alcohol from which the bromide was prepared. Therefore no racemization had taken place during the bromide preparation.

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REFERENCES

[1] Paper No. 27 in the series, *Optical Rotatory Dispersion and Absolute Configuration.*

[2] L. Verbit, *J. Am. Chem. Soc.* **89**, 167 (1967).

[3] D. A. Lightner, J. K. Gawronski and T. D. Bouman, *Ibid.* **102**, 1983 (1980) and refs therein.

[4] B. Ringdahl, J. C. Craig, R. Keck and J. Retey, *Tetrahedron Letters* **21**, 3965 (1980), and refs therein.

[5] S.-F. Lee, G. Barth, K. Kieslich and C. Djerassi, *Ibid.* 3965 (1978); S.-F. Lee, G. Barth and C. Djerassi, *Ibid.* 8010 (1978).

[6] L. Verbit, *Prog. Phys. Org. Chem.* **7**, 51 (1970).

[7] C. W. Deutsche, D. A. Lightner, R. W. Woody and A. Moscowitz, *Ann. Rev. Phys. Chem.* **20**, 407 (1969).

[8] Sadtler Research Laboratories Inc., *Ultraviolet Spectra.* Spectrum No. 97, Philadelphia, Pa. 19104 (1966).

[9] R. L. Elsenbaumer and H. S. Mosher, *J. Org. Chem.* **44**, 600 (1979).

[10] A. Streitwieser, Jr., L. Verbit and S. Andreades, *Ibid.* **30**, 2078 (1965).

[11] J. C. Craig, R. P. K. Chan and S. K. Roy, *Tetrahedron* **23**, 3573 (1967).

[12] H. E. Smith and T. C. Willis, *J. Am. Chem. Soc.* **93**, 2282 (1971).

[13] O. Cervinka, M. Kral and P. Malon, *Coll. Czech. Chem. Commun.* **41**, 2406 (1976).

[14] R. W. Woodard, J. C. Craig and J. G. Bruhn, *Acta Chem. Scand. B* **32**, 619 (1978).

[15] J. C. Craig and W. E. Pereira, Jr., unpublished.

[16] H. E. Smith, M. E. Warren, Jr. and L. I. Katzin, *Tetrahedron* **24**, 1327 (1968); V. Ghislandi, A. La Manna and D. Vercesi, *Farmaco Ed. Sci.* **31**, 561 (1976).

[17] L. Angiolini and G. Gottarelli, *Tetrahedron* **26**, 421 (1970).

[18] W. J. Hehre, L. Radom and J. A. Pople, *J. Am. Chem. Soc.* **94**, 1496 (1972).

[19] R. J. Ouellette, B. K. Sinha, J. Stolfo, C. Levin and S. Williams, *Ibid.* **92**, 7145 (1970).

[20] L. Verdonck and G. P. Van Der Kelen, *Spectrochim. Acta A* **28**, 51 (1972).

[21] B. Maigret, B. Pullman and D. Perahia, *Biopolymers* **10**, 107 (1971); M. Camail, A. Proutiere and P. Verlaque, *J. Phys. Chem.* **79**, 1962 (1975).

[22] H. E. Smith, E. P. Burrows and F.-M. Chen, *J. Am. Chem. Soc.* **100**, 3714 (1978).

[23] J. A. Schellman, *J. Chem. Phys.* **44**, 55 (1966); H. Dickerson and F. S. Richardson, *Ibid.* **80**, 2686 (1976).

[24] J. H. Brewster, *Tetrahedron Letters* 23 (1959).

[25] J. H. Brewster and J. G. Buta, *J. Am. Chem. Soc.* **88**, 2233 (1966).

[26] J. H. Brewster and R. T. Prudence, *Ibid.* **95**, 1217 (1973).

[27] J. H. Brewster, *Ibid.* **81**, 5475 (1959).

[28] R. E. Carter and L. Melander, *Adv. Phys. Org. Chem.* **10**, 1 (1973).

[29] K. Kuchitsu and L. S. Bartell, *J. Chem. Phys.* **36**, 2470 (1962).

[30] V. E. Althouse, D. M. Feigl, W. A. Sanderson and H. S. Mosher, *J. Am. Chem. Soc.* **88**, 3595 (1966).

[31] R. K. Crossland and K. L. Servis, *J. Org. Chem.* **35**, 3195 (1970).

[32] S. Trippett, *J. Chem. Soc.* 233 (1962).