Optical Rotation and Absolute Configuration of Chlorofluoroacetic Acid

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Chlorofluoroacetic acid, $[\alpha]_D^{25}$ − 55·8° (benzene), was shown to be of at least 98% optical purity by n.m.r. analysis of its adduct with (−)-1,2-epoxy-1-phenylcyclohexane. An *X*-ray diffraction study on the adduct of the (+)-acid with the (−)-epoxide has established that (+)-chlorofluoroacetic acid has the *S*-configuration, in contrast with expectation on the basis of the Brewster polarizability rule.

WE have previously reported[1] the optical resolution of chlorofluoroacetic acid (1) by use of its dehydroabietylamine salts. An approximate determination of the optical purities of the enantiomeric acids, carried out by a method involving g.l.c. of the amides formed by treatment with deoxyephedrine, had shown that the product of highest specific rotation {α_D −29·9° (neat); $[\alpha]_D$ −56·3° (benzene)} was at least 90% optically pure, but the determination was not very precise because of an uncertainty about the maximum rotation of deoxyephedrine.[2] Since the acid (1) is one of the simplest chiral molecules so far obtained with high optical purity,

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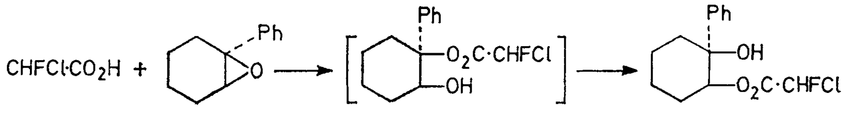
[1] G. Bellucci, G. Berti, A. Borraccini, and F. Macchia, *Tetrahedron*, 1969, **25**, 2979.

[2] J. Jacobus and T. B. Jones, *J. Amer. Chem. Soc.*, 1970, **92**, 4583.

we wished to obtain a more reliable value for its specific rotation, and, particularly, to determine its absolute configuration.

The most promising approach to the solution of both problems appeared to be in the reaction of the acid (1) with a molecule of known chirality in such a way that the product could be used both for the assessment of optical purity through a g.l.c. or n.m.r. method, and for deducing the chirality of the chlorofluoroacetyl group on the basis of its relative configuration with respect to the known chiral centre, as determined by *X*-ray diffraction.



(1) (2) (3)

The availability of the enantiomeric 1,2-epoxy-1-phenylcyclohexanes (2) of high optical purity, whose absolute configurations had been firmly established through chemical correlation with 2-phenyladipic acid and by the Horeau partial resolution method,[3] and the fact that the epoxides (2) reacted cleanly with the acid (1) to give crystalline products, provided a neat solution to the problem.

The n.m.r. spectrum of the crude product obtained from (±)-(1) and (±)-(2) (Figure 1) showed that it was an equimolar mixture of two diastereoisomeric pairs of enantiomers: two sets of closely spaced signals were observed for each of the C*H*FCl systems and for the protons α to the functional group in the cyclohexane ring. On the other hand when (—)-(1), $[\alpha]_D^{25}$ —55·8° (benzene) was treated with (—)-(2), $[\alpha]_D^{25}$ —119·0° (benzene; >98% optical purity), the resulting ester showed only one set of such signals in its n.m.r. spectrum (Figure 2).

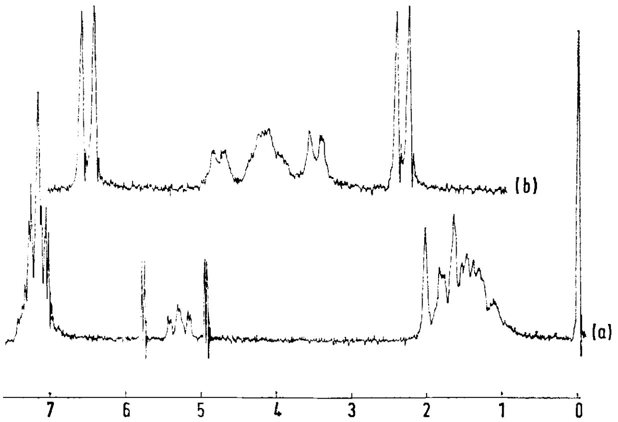


FIGURE 1 (a) N.m.r. spectrum of diastereoisomeric (3) obtained from (±)-1 and (±)-2; (b) expanded central portion of the same spectrum (solvent C_6D_6)

Previous work on the reaction between the epoxide (2) and trichloroacetic acid had established that this reaction is entirely stereoselective, involving *syn*-opening of the epoxide ring, and that the initially formed tertiary ester is rapidly and quantitatively converted in the reaction medium into the less hindered secondary ester by an acyl group shift.[4] Since the reaction of the acid (1) with the epoxide (2) should take exactly the same course, the diastereoisomeric esters must have structure (3). This was confirmed by the n.m.r. spectra, in which the signal for the proton α to the functional group indicated that this proton was α to an acyloxy- rather than to a hydroxy-group (δ 5·32 p.p.m.), and axial (broad quartet, width 15·7 Hz). Chemical confirmation came from the hydrolysis of compound (3), which gave exclusively 1-phenylcyclohexane-*r*-1,*c*-2-diol, and from its resistance to Jones oxidation.

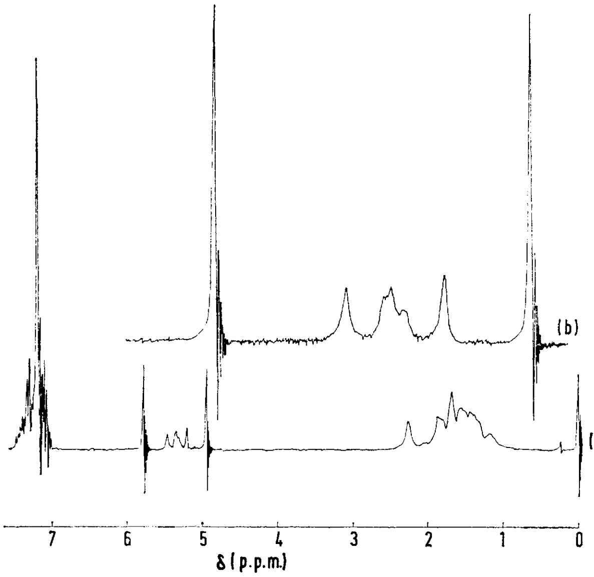


FIGURE 2 (a) N.m.r. spectrum of (1*S*,2*S*)-2-[(*R*)-chlorofluoroacetoxy]-1-phenylcyclohexanol; (b) expanded central portion of the same spectrum (solvent C_6D_6)

The determination of the optical purities of the esters (3) was possible by integration of the C*H*FCl signals (doublets, $^2J_{HF}$ 50·3 Hz). Although the difference in chemical shift for these diastereotopic protons was only 2 Hz (at 60 MHz), the sharpness of the signals allowed good integration, particularly with C_6D_6 as solvent; in $CDCl_3$ there was a partial overlap of the signal of the α proton of the cyclohexane ring with one of the doublet

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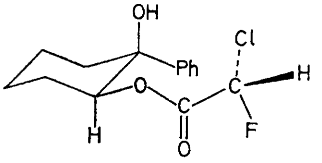
[3] G. Berti, B. Macchia, F. Macchia, and L. Monti, *J. Org. Chem.*, 1968, **33**, 4045.

[4] G. Berti, F. Bottari, B. Macchia, and F. Macchia, *Tetrahedron*, 1965, **21**, 3277.

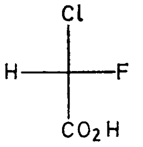
components. It was estimated that the method could detect 1% of one diastereoisomer in the presence of the other. Therefore the fact that the n.m.r. spectrum of the crude ester obtained from (−)-(1) did not show any evidence for the presence of the other isomer, indicated that the acid (1) of $[\alpha]_D^{25}$ −55·8° (benzene) is at least 98% optically pure. Further confirmation came from the reaction of (+)-(1), $[\alpha]_D^{25}$ +47·2° with the same (−)-(2), which gave a product (3), the n.m.r. spectrum of which showed that the diastereoisomers were present in a ratio of 92 : 8; this corresponds to an optical purity of 84% and to a maximum rotation of 56·2 ± 1·5° for (+)-(1), in good agreement with the value for (−)-(1). Repeated crystallization of this mixture gave the second diastereoisomer in pure form.

Structure determination of the ester (3) from (+)-(1) and (−)-(2) by *X*-ray diffraction is reported in the following paper.[5] The results gave the relative configuration shown in (3a), which, on the basis of the known (1*S*,2*S*) chirality of (−)-(2), also corresponds to the absolute configuration. Therefore (+)-chlorofluoroacetic acid has the *S*-configuration (1a). The *X*-ray analysis also indicated a high probability for the ester having the absolute configuration shown (3a), thus further confirming the absolute configuration of the epoxide (2) previously established by chemical means.

The *S*-configuration for (+)-(1) is the opposite of what one would expect on the basis of the Brewster model for deriving optical rotations at the D line on the basis of the polarizabilities of the atoms attached to the chiral centre:[6] since the reported order of polarizabilities is $F < H < CO_2H < Cl$, structure (1a) should be laevorotatory. The failure of Brewster's rule in this case indicates its limitations, since structure (1) would be expected to be highly suitable for a treatment on the basis of pure atomic asymmetry. The carboxy-group can often be treated in such a way, but the possibility of formation of intramolecular hydrogen bonds can lead to anomalous results.[6] However, the fact that on passing from the acid (1) to its ammonium salt, methyl ester, and acid chloride, and to the corresponding alcohol the sign of rotation remains the same [1] is evidence against this hypothesis.*



(3a)



(1a)
(+)—(*S*)

Caution should therefore be exercised in applying the Brewster rules to new classes of compound. Chiroptical data on fluorinated derivatives are so far very scarce, and, although a recent investigation of the 2-methylbutyl halides [7] gave results which were compatible with a modified form of the Brewster rules, a much more systematic study is required before it is possible to make any predictions about the absolute configurations of compounds having a fluorine atom directly attached to the chiral centre.

EXPERIMENTAL

M.p.s were taken with a Kofler hot-stage apparatus. I.r. spectra were recorded with a Perkin-Elmer Infracord 137 spectrophotometer for mineral oil mulls; optical rotations were determined with a Perkin-Elmer 141 photoelectric polarimeter; n.m.r. spectra were determined for 15% solutions with a JEOL C60HL spectrometer, with tetramethylsilane as internal standard. All comparisons bebetween compounds were made on the basis of i.r. and n.m.r. spectra. Light petroleum refers to the fraction b.p. 30—50°; benzene was washed with concentrated sulphuric acid, refluxed over sodium, and rectified. Magnesium sulphate was used as drying agent; evaporations were carried out *in vacuo* (rotary evaporator). Analyses of the mixtures of diastereoisomeric monoesters (3) were carried out by integration of the two doublets at δ 5·39 and 5·42 p.p.m. in the n.m.r. spectra of solutions in C_6D_6, and were accurate to ±1%.

(+)- *and* (−)-*Chlorofluoroacetic acid* (1).—The resolution of (±)-(1) [8] was carried out through the dehydroabietylamine salts as previously described.[1] Eleven crystallizations of the crude mixture of the diastereoisomeric salts from ethyl acetate gave a salt, m.p. 160—161° (sealed capillary), $[\alpha]_D^{25}$ +37·2° (*c* 0·72 in $CHCl_3$), from which (+)-(1), b.p. 72° at 17 mmHg, n_D^{20} 1·4138, $[\alpha]_D^{25}$ +47·2° (*c* 3·33 in C_6H_6), was obtained. Evaporation of the combined mother liquors from the first four crystallizations, followed by six crystallizations of the residue from chloroform, gave a salt, m.p. 164—165° (sealed capillary), $[\alpha]_D^{25}$ +18·4° (*c* 0·84 in MeOH), from which (−)-(1), b.p. 46—47° at 8 mmHg, n_D^{25} 1·4150, $[\alpha]_D^{25}$ −55·8° (*c* 2·89 in C_6H_6) was recovered.

(1S,2S)-1,2-*Epoxy*-1-*phenylcyclohexane* [(−)-(2)].—The epoxide, $[\alpha]_D^{25}$ −119·0° (*c* 0·81 in C_6H_6), optical purity 98·2%, was prepared by the previously described method.[3]

Reactions of 1,2-*Epoxy*-1-*phenylcyclohexane* (2) *with Chlorofluoroacetic Acid* (1).—(*a*) A solution of (±)-(2) (2·0 g, 11·5 mmol) in benzene (50 ml) was treated with a solution of (±)-(1) (1·3 g, 11·6 mmol) in the same solvent (50 ml), left at room temp. for 12 h, washed with water, saturated aqueous sodium hydrogen carbonate, dried, and evaporated. The solid residue (3·2 g) consisted of a 1 : 1 mixture of the two diastereoisomeric racemic monoesters (3), δ (C_6D_6) 5·32 (2H, m, *W* 17·5 Hz, >CHO–), and 5·39 and 5·42 (1H each, d, $^2J_{HF}$ 50·3 Hz, C*H*FCl) (Figure 1); δ ($CDCl_3$) 5·42 (2H, m, >C*H*O–), and 5·99 and 6·02 (1H each, d, $^2J_{HF}$ 50·5 Hz). A sample of the crude mixture was recovered unchanged after treatment of its solution in acetone with Jones reagent [9] for 30 min. A solution of the same mixture (0·300 g) in 2N-potassium hydroxide in

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* Preliminary measurements, carried out by Dr. J. Hudec, indicate that the c.d. curves of (−)-(1) and its sodium salt exhibit negative maxima around 210 nm, and that of the methyl ester of (+)-(1) shows a positive one; (−)-(1) has Δε −2·56 at 213 nm.

[5] M. Colapietro, R. Spagna, and L. Zambonelli, following paper.

[6] J. H. Brewster, *J. Amer. Chem. Soc.*, 1959, **81**, 5475.

[7] D. D. Davis and F. R. Jensen, *J. Org. Chem.*, 1970, **35**, 3410.

[8] J. A. Young and P. Tarrant, *J. Amer. Chem. Soc.*, 1949, **71**, 2432.

[9] R. G. Curtis, I. Heilbron, E. H. R. Jones, and G. F. Woods, *J. Chem. Soc.*, 1953, 457.

ethanol (5 ml) was refluxed for 30 min, diluted with water, and extracted with ether. Evaporation of the dried solution yielded pure (g.l.c.) 1-phenylcyclohexane-*r*-1,*c*-2-diol[4] (0·160 g). Four crystallizations of the crude mixture of (3) (1·6 g) from light petroleum gave pure diastereoisomer (±)-(3a) (0·060 g), m.p. 94—95°; δ (C_6D_6) 5·31 (1H, m, *W* 15·7 Hz, >CHO–), 5·42 (1H, d, $^2J_{HF}$ 50·3 Hz, C*H*FCl) (Found: C, 58·5; H, 5·7; Cl, 12·4. Calc. for $C_{14}H_{16}ClFO_3$: C, 58·65; H, 5·65; Cl, 12·35%).

(*b*) A solution of (−)-(2), $[\alpha]_D^{25}$ −119·0° (0·317 g, 1·8 mmol), in benzene (5 ml) was treated with (−)-(1), $[\alpha]_D^{25}$ −55·8° (0·204 g, 1·8 mmol) in benzene (5 ml). After 12 h at room temp. the mixture was worked up as in (*a*) to give a crude monoester (3) (0·504 g), whose n.m.r. spectrum (Figure 2) did not show any evidence for the presence of (3a). Crystallization from light petroleum afforded pure (1*S*,2*S*)-2-[(*R*)-chlorofluoroacetoxy]-1-phenylcyclohexanol containing one molecule of water of crystallization, m.p. 50—74° (during this interval the water is lost); $\nu_{max.}$ 3600 (OH), 3370 (H_2O), and 1770 cm^{-1} (CO); δ (C_6D_6) 5·33 (1H, m, *W* 15·7 Hz, >CHO–) and 5·39 (1H, d, $^2J_{HF}$ 50·3 Hz, C*H*FCl); $[\alpha]_D^{25}$ −25·5° (*c* 3·00 in $CHCl_3$) (Found: C, 55·3; H, 5·8; Cl, 11·6. Calc. for $C_{14}H_{16}ClFO_3,H_2O$: C, 55·15; H, 5·95; Cl, 11·65%).

(*c*) Treatment of (−)-(2), $[\alpha]_D^{25}$ −119·0° (0·465 g, 2·7 mmol), with (+)-(1), $[\alpha]_D^{25}$ +47·2° (0·300 g, 2·7 mmol) as in (*b*) afforded a crude solid mixture (0·685 g), whose n.m.r. spectrum showed the presence of the two diastereoisomeric monoesters (3) in the ratio 92 : 8. Three crystallizations of this mixture from light petroleum gave pure (1*S*,2*S*)-2-[(*S*)-chlorofluoroacetoxy]-1-phenylcyclohexanol (3a), m.p. 71—72·5°; $\nu_{max.}$ 3545 (OH) and 1755 cm^{-1} (CO); δ (C_6D_6) 5·31 (1H, m, *W* 15·7 Hz, >CHO–) and 5·42 (1H, d, $^2J_{HF}$ 50·3 Hz, C*H*FCl); $[\alpha]_D^{25}$ −16·8° (*c* 3·12 in $CHCl_3$) (Found: C, 58·55; H, 5·7; Cl, 12·55%).

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