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Reassignment of the Chirality to a Series of 2,6-Disubstituted Spiro[3.3]heptanes by X-Ray Methods and Implications Thereof on Empirical Rules and Theoretical Models

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Abstract: The absolute configuration of a series of optically active 2,6-disubstituted spiro[3.3]heptane compounds has been elucidated. Application of Klyne's sector rule to spiro[3.3]heptane-2,6-dicarboxylic acid or Fecht acid (**1**) and of Lowe's rule to the spiro[3.3]heptane system suggested the *R* configuration for *d*-**1**. Use of the major theoretical models of optical activity also resulted in an assignment of the *R* configuration to *d*-**1**. This assignment supported the result obtained previously from an x-ray study of *d*-**1**, which on the basis of the (small) anomalous scattering of oxygen and carbon tended to the *R* configuration for *d*-**1**. Definite proof of the chirality could be obtained when a well-crystallized barium salt of *d*-**1** had been prepared. X-ray work on this compound showed beyond any doubt that *d*-Fecht acid (**1**) has the *S* configuration. Renewed x-ray work on the acid itself confirmed the *S* configuration of *d*-**1**. A discussion is given on the striking invalidity of empirical rules and theoretical models for establishing the chirality of these particular spiro systems.

Optically active spiro[3.3]heptane-2,6-dicarboxylic acid or Fecht acid (**1**) has been used by Wynberg and Houbiers[2] as starting material in the synthesis of a number of enantiomeric 2,6-disubstituted spiro[3.3]heptane derivatives. Our current interest[3] in this series of compounds encouraged us to solve the intriguing problem of configurational assignment to **1** and its derivatives. Knowledge of its chirality would establish the absolute configuration of this whole series of compounds.

Very recently we proposed the *R* configuration for dextrorotatory Fecht acid (see Figure 1) on the basis of three different types of experiments: (a) ORD and CD measurements including the application of Lowe's rule[5] to *d*-**1** and other configurationally related 2,6-disubstituted spiro[3.3]heptane derivatives,[2] (b) special solvent effects of *d*-Fecht acid (**1**),[6] and (c) x-ray diffraction of *d*-**1** using anomalous scattering.[7] In the present study we wish to report unambiguous evidence for establishing the absolute configuration of **1** and related compounds. The larger part of this study describes the assignment, along different lines, of the chirality to *d*-Fecht acid (**1**). After the Experimental Section, sections II–V deal with the conventional application of some empirical rules and theoretical models of optical activity. Section VI describes the determination of the absolute configuration by x-ray work. Section VII brings forward clear consequences for the applicability of the rules and models mentioned above.

I. Experimental Section

Boiling points are uncorrected. Melting points were determined on a Mettler FP_1 apparatus at a warm-up rate of 0.2 °C/min. Ultraviolet spectra were recorded on a Zeiss PMQ II apparatus. NMR spectra were obtained on a Varian A60 instrument using tetramethylsilane as an internal standard. Microanalyses were performed in the analytical section of our department under the supervision of Mr. W. M. Hazenberg. Optical activity was measured on a Zeiss Lichtelektrisches Präzisionspolarimeter 005 using 10-cm cells for compounds **2**, **4**, and **7**, and 5-cm cells for compounds **5** and **13**. Concentrations are given in grams/100 ml. The ORD spectrum was taken on a Bendix Ericsson Polarmetric 62, provided with a 150-W xenon lamp and a 1-cm cell. The measurements were taken at room temperature. Ellipticity was measured with a Roussel-Jouan Dichrograph II, provided with a deuterium lamp.

***l*-Spiro[3.3]heptane-2,6-diamine** (**2**) was prepared from *l*-spiro[3.3]heptane-2,6-diammonium chloride (**12**) with $[\Phi]_{578}$ $-6.0°$, $[\Phi]_{405}$ $-15.5°$ (*c* 2.8, water), in 50% yield according to the method of Lowry and Baldwin.[8] The obtained optical rotation of **2** was: $[\Phi]_{578}$ $-4.2°$, $[\Phi]_{405}$ $-10.4°$ (*c* 3.1, chloroform).

l-Spirane **12** was obtained from *d*-spiro[3.3]heptane-2,6-dicar-

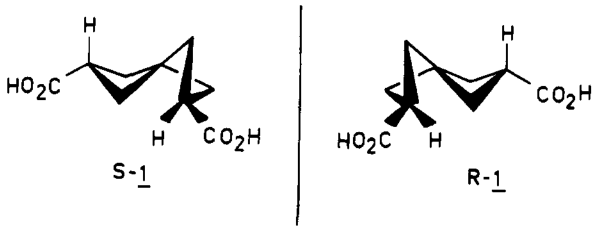


Figure 1. S and R Fecht acid with the notation of the Cahn, Ingold, Prelog convention (old method).[4]

boxylic acid (**1**) according to a modified procedure of Wynberg and Houbiers.[2,9]

***l*-Spiro[3.3]heptane-2,6-bis(dimethylamine)** (**6**) was prepared via a Leuckart reaction of the *d*-chloride or *d*-sulfate salt of **2.** The experimental details of this procedure have appeared in another study.[3]

***d*-Spiro[3.3]heptane-2,6-dicarboxamide** (**4**). Into a stirred solution of 0.8 g (3.6 mmol) of *d*-spiro[3.3]heptane-2,6-dicarbonyl chloride (**5**) with $[\Phi]_{578}$ +9.1°, $[\Phi]_{365}$ +21.8° (*c* 6.8, pentane) in 50 ml of pentane, ammonia was bubbled at a moderate rate. The introduction of ammonia was continued for 1 h. A white solid started to separate soon after the first addition of ammonia. After addition of water the pentane layer was separated. After one crystallization from water 0.55 g (3 mmol or 84%) of *d*-spiro[3.3]heptane-2,6-dicarboxamide (**4**) was obtained: mp 237–240 °C; uv end absorption (water and ethanol); $[\Phi]_{578}$ +5.9°, $[\Phi]_{546}$ +6.8°, $[\Phi]_{436}$ +10.4°, $[\Phi]_{405}$ +12.7°, $[\Phi]_{365}$ +16.8° (*c* 2.0, ca. 90% methanol); $[\Phi]_{578}$ +1.7°, $[\Phi]_{546}$ +2.9°, $[\Phi]_{436}$ +4.0°, $[\Phi]_{405}$ +5.2°, $[\Phi]_{365}$ +7.5° (*c* 1.6, water/methanol 1:1).

Anal. Calcd for $C_9H_{14}N_2O_2$: C, 59.32; H, 7.74; N, 15.37; mol wt, 182.22. Found: C, 59.3, 59.1; H, 7.7, 7.8; N, 15.1, 15.2.

***d*-Spiro[3.3]heptane-2,6-dicarbonyl Chloride** (**5**). A mixture of 2 g (0.011 mol) of *l*-spiro[3.3]heptane-2,6-dicarboxylic acid (**1**) with $[\Phi]_{578}$ −4.4°, $[\Phi]_{546}$ −4.8°, $[\Phi]_{365}$ −13.3° (*c* 5.0, acetone) and 3 ml of thionyl chloride was stirred for 2 h at 50 °C. Excess of thionyl chloride was removed at reduced pressure and distillation furnished 2.0 g (0.008 mol or 78%) of acid chloride **5**: bp 116–117 °C (1.2 mm); $[\Phi]_{578}$ +9.1°, $[\Phi]_{546}$ +10.1°, $[\Phi]_{436}$ +15.9°, $[\Phi]_{405}$ +18.5°, $[\Phi]_{365}$ +21.8° (*c* 6.8, pentane); $[\Phi]_{578}$ +5.5°, $[\Phi]_{546}$ +6.5°, $[\Phi]_{436}$ +9.8°, $[\Phi]_{405}$ +11.4°, $[\Phi]_{365}$ +13.0° (*c* 6.8, ether); $[\Phi]_{578}$ +5.7°, $[\Phi]_{546}$ +7.3°, $[\Phi]_{436}$ +10.4°, $[\Phi]_{405}$ +11.7°, $[\Phi]_{365}$ +13.1° (*c* 3.2, acetone); ^{1}H NMR (carbon tetrachloride) δ 2.37–2.75 (m, 8 H), 3.27–3.86 (quintet with fine splitting, 2 H); uv λ_{max} (pentane) 245 nm (ϵ 169);[10] ORD, negative Cotton effect near 245 nm, trough at 270 nm (pentane); CD, $[\theta]_{245}$ −352.0 (±11) (*c* 5.8 × 10^{-2} mol/l., pentane).

***d*-Spiro[3.3]heptane-2,6-bis(dimethylamine) *N*-oxide** (**3**) was prepared from *l*-**6** in a simple oxidation reaction. The details have been given in other work.[3]

***l*-2,6-Dicyanospiro[3.3]heptane** (**7**). A refluxing suspension of 0.3 g (1.8 mmol) of *d*-spiro[3.3]heptane-2,6-dicarboxamide (**4**) with $[\Phi]_{578}$ +1.7°, $[\Phi]_{365}$ +7.5° (*c* 1.6, water/methanol 1:1) in 10 ml of dry benzene and 0.8 g of thionyl chloride was stirred for 4 h. After addition of 2 ml of water and potassium hydroxide solution until the mixture was alkaline, the benzene layer was separated and dried over magnesium sulfate. Removal of the solvent furnished a crude product from which after distillation 0.2 g (1.4 mmol or 78%) of *l*-2,6-dicyanospiro[3.3]heptane (**7**) was obtained: bp 180 °C (1 mm), mp 48–53 °C; $[\Phi]_{578}$ −23.9°, $[\Phi]_{546}$ −26.7°, $[\Phi]_{436}$ −47.8°, $[\Phi]_{405}$ −58.4°, $[\Phi]_{365}$ −79.5° (*c* 1.3, benzene); $[\Phi]_{578}$ −7.0°, $[\Phi]_{546}$ −8.1°, $[\Phi]_{436}$ −15.1°, $[\Phi]_{405}$ −18.6°, $[\Phi]_{365}$ −25.0° (*c* 1.3, acetone).

Anal. Calcd for $C_9H_{10}N_2$: C, 73.94; H, 6.89; N, 19.16; mol wt, 146.19. Found: C, 73.6, 73.5; H, 6.9, 6.8; N, 19.1, 19.2.

***d*-Barium Salt of *d*-Fecht Acid** (**13**). *d*-Spiro[3.3]heptane-2,6-dicarboxylic acid or *d*-Fecht acid (**1**) (0.39 g, 2.1 mmol) with $[\Phi]_{578}$ +8.3°, $[\Phi]_{365}$ +24.6° (c 5.3, acetone), optical purity 95%, and 0.37 g (1.2 mmol) of barium hydroxide octahydrate were dissolved in a mixture of 10 ml of acetone and 10 ml of water under stirring for 4 h. After slow evaporation of the solvent for 2 weeks, followed by storing in a desiccator charged with concentrated sulfuric acid for 3 to 4 days, large colorless crystals of **13** were obtained: $[\alpha]_{578}$ +2.7°, $[\alpha]_{546}$ +3.5°, $[\alpha]_{436}$ +4.9°, $[\alpha]_{405}$ +6.2°, $[\alpha]_{365}$ +7.1° (*c* 1.13, water). Although barium hydroxide and *d*-Fecht acid (**1**) had been dissolved in a ratio of about 1:2, chemical analysis of the crystals indicated a ratio of one barium atom per three molecules of the acid. The subsequent structural analysis showed that a barium hydrogen salt had been obtained with one neutral acid molecule and a water molecule of crystallization, $Ba(C_9H_{11}O_4)_2 \cdot C_9H_{12}O_4 \cdot H_2O$.

Anal. Calcd for $BaC_{27}H_{36}O_{13}$: Ba, 19.46; C, 45.94; H, 5.14; mol wt, 705.92. Found: Ba, 19.4, 18.8; C, 45.1, 45.6; H, 5.1, 5.3.

X-Ray Analysis of the Barium Salt 13. Crystal Data and Intensity Measurements. Weissenberg photographs indicated monoclinic symmetry, and from the systematic absences ($0k0$, $k \neq 2n$) and the fact that the compound exhibits optical activity the space group was unequivocally found to be $P2_1$.[11] A fragment of a large crystal was shaped into a regular form with approximate dimensions 0.4 × 0.4 × 0.3 mm, and mounted along the *b* axis on a Nonius AD-3 diffractometer, which was equipped with a Mo tube and a Zr filter at the x-ray source (λ(Mo Kα) = 0.710 69 Å). The crystal was cooled to about −160 °C using a cold nitrogen gas stream.[12] Crystal data are: $Ba(C_9H_{11}O_4)_2 \cdot C_9H_{12}O_4 \cdot H_2O$, a = 20.031 (6), b = 10.955 (4), and c = 6.788 (4) Å, β = 94.83 (5)°, V = 1484.3 Å^3, d_{obsd} = 1.49 g cm^{-3} (flotation method, room temperature), Z = 2, d_{calcd} = 1.58 g cm^{-3} (−160°), $F(000)$ = 716, μ(Mo Kα) = 14.5 cm^{-1}. The unit cell dimensions were calculated from the observed θ and ϕ values for axial reflections; the standard deviations given were estimated from the spread of the individual values.

Intensities were measured by the θ–2θ scan technique with θ scans taken at the rate of 1.25°/min over a range of $(0.9 + 0.5 \tan \theta)°$. Every 50 measurements the intensity of one out of three standard reflections was recorded. Of the 4548 independent reflections ($k,l \geq 0$) measured out to $2\theta = 60°$ ($\sin \theta/\lambda$ = 0.704 Å^{-1}), exactly 4500 reflections had a net intensity greater than zero. These intensities were corrected for the variations in the standard reflections, for Lorentz and polarization effects, and for absorption[13] (transmission factors ranging from 0.57 to 0.72).

Solution and Refinement of the Structure. The x and z coordinates of the one independent barium atom were obtained from a two-dimensional Patterson synthesis. The y coordinate of the barium atom was fixed at ¼ in order to define the origin of the unit cell. To determine the positions of the carbon and oxygen atoms an observed Fourier synthesis was calculated with phases obtained from the barium atom. Because there are two barium atoms in the unit cell, located at x, ¼, z and $-x$, −¼, $-z$, this Fourier map had an inversion center at the origin and contained mirror planes at y = ¼ and ¾. In the Fourier map therefore peaks were found corresponding with two images of each of the three independent Fecht acid molecules, in positions related to each other by the mirror planes. Nevertheless, by making use of the known geometry of Fecht acid,[7] reasonable models for all three molecules could be obtained from this map. In consequence of the two possible positions for each molecule, the three molecules could be combined in eight different ways, giving rise to four different crystal structures along with a mirror image of each. In only one of these four structures there were no improbably short intermolecular distances, and in this structure all three molecules had the same handedness. With this model for the structure the Fourier map still contained a large unexplained peak. This peak was assumed to indicate the presence of a molecule of water, which accordingly was included in the model.

The structure was refined by a block-diagonal least-squares method, the quantity minimized being $\Sigma w \Delta^2$ ($\Delta = |F_o| - S|F_c|$, where $1/S$ is the scale factor for $|F_c|$). Atomic scattering factors for neutral atoms were used.[14] Four cycles of isotropic refinement, with w = 1, reduced the discrepancy factor $R = [\Sigma\Delta^2/\Sigma|F_o|^2]^{1/2}$ to 6.45% for all 4500 reflections. At this point a difference Fourier map was calculated from the data with $\sin \theta/\lambda$ less than 0.5 Å^{-1}, which revealed residual electron density at the expected positions of the hydrogen atoms. These atoms were included into the structure in geometrically reasonable positions, with fixed bond lengths (C–H = 1.08 Å, O–H = 1.00 Å in the carbonyl groups and 0.96 Å in the water molecule) and with isotropic thermal parameters B 1.0 Å^2 larger than those of the nonhydrogen atoms to which they are bonded. During further refinement new hydrogen atom parameters were calculated after each refinement cycle. In three more cycles, with anisotropic thermal parameters for the nonhydrogen atoms, R decreased to 3.38%. At this stage it was noticed that for a number of relatively weak reflections $|F_o|$ was considerably smaller than $|F_c|$. The recorded intensity profiles of these reflections indicated that their measured background was too large (presumably due to interference by neighboring reflections), and these reflections were omitted from further calculations. No evidence was found that the intensities had been affected by extinction. The 4470 remaining reflections were assigned individual weights according to

Table I. Final Positional and Anisotropic Thermal Parameters for the Nonhydrogen Atoms ($\times 10^4$)[a,b]

Atom[c]	x	y	z	U_{11}	U_{22}	U_{33}	$2U_{12}$	$2U_{13}$	$2U_{23}$
Ba	2 471.9 (1)	2 500[d]	1 673.7 (2)	132.4 (6)	166.7 (6)	174.0 (6)	−1.9 (22)	75.3 (9)	78.5 (20)
C1-1	5 661 (2)	1 285 (3)	6 197 (5)	231 (16)	164 (15)	192 (14)	50 (25)	188 (24)	−14 (24)
C2-1	5 970 (2)	−17 (3)	6 447 (5)	190 (15)	173 (15)	174 (13)	36 (24)	141 (22)	−47 (23)
C3-1	5 244 (2)	−490 (3)	6 688 (5)	175 (14)	166 (15)	236 (15)	39 (24)	136 (23)	20 (25)
C4-1	5 054 (2)	812 (3)	7 249 (5)	170 (14)	210 (16)	160 (13)	70 (24)	84 (22)	40 (24)
C5-1	5 058 (2)	1 179 (4)	9 463 (5)	194 (15)	288 (18)	162 (14)	137 (27)	60 (23)	13 (26)
C6-1	4 534 (2)	2 173 (3)	8 819 (5)	163 (14)	204 (15)	159 (13)	30 (21)	123 (22)	0 (21)
C7-1	4 369 (2)	1 439 (4)	6 866 (5)	184 (15)	228 (16)	173 (14)	127 (25)	49 (23)	−24 (25)
C8-1	6 318 (2)	−594 (3)	4 814 (5)	175 (14)	148 (14)	192 (14)	3 (23)	94 (22)	−16 (23)
C9-1	3 941 (1)	2 399 (4)	10 012 (4)	170 (12)	220 (15)	145 (11)	21 (28)	124 (18)	−12 (27)
O1-1	6 072 (1)	−278 (2)	3 307 (4)	265 (13)	206 (12)	178 (11)	157 (20)	103 (18)	−31 (19)
O2-1	6 777 (1)	−1 338 (3)	5 131 (4)	236 (12)	232 (13)	194 (11)	154 (21)	113 (18)	13 (20)
O3-1	3 768 (1)	1 611 (3)	11 218 (4)	266 (13)	260 (14)	343 (14)	143 (22)	335 (22)	263 (23)
O4-1	3 613 (1)	3 378 (2)	9 718 (3)	197 (11)	198 (11)	139 (9)	−29 (19)	110 (16)	8 (18)
C1-2	−776 (2)	4 333 (4)	7 465 (5)	207 (16)	275 (18)	178 (14)	43 (27)	87 (23)	−18 (26)
C2-2	−699 (2)	4 383 (4)	9 751 (5)	212 (16)	241 (17)	186 (14)	73 (27)	103 (24)	−34 (26)
C3-2	53 (2)	4 732 (5)	9 625 (5)	216 (17)	443 (25)	227 (18)	−1 (34)	55 (27)	−180 (31)
C4-2	−2 (2)	4 216 (4)	7 525 (5)	204 (15)	236 (17)	163 (13)	53 (26)	101 (23)	0 (24)
C5-2	266 (2)	2 912 (4)	7 191 (5)	289 (18)	255 (16)	255 (16)	139 (27)	302 (27)	139 (27)
C6-2	471 (2)	3 323 (4)	5 170 (5)	227 (16)	263 (17)	209 (15)	4 (28)	131 (24)	29 (27)
C7-2	400 (2)	4 671 (4)	5 833 (6)	270 (18)	227 (18)	287 (17)	33 (29)	236 (28)	47 (29)
C8-2	−1 096 (2)	5 296 (3)	10 807 (5)	208 (15)	211 (16)	165 (14)	−41 (25)	131 (22)	−11 (24)
C9-2	1 142 (2)	2 934 (3)	4 499 (5)	186 (14)	237 (14)	191 (14)	−52 (24)	159 (23)	−17 (24)
O1-2	−964 (1)	5 213 (3)	12 761 (4)	294 (14)	297 (14)	138 (10)	108 (23)	82 (18)	−12 (20)
O2-2	−1 462 (1)	6 072 (3)	10 019 (4)	260 (13)	312 (15)	207 (11)	175 (23)	35 (19)	−58 (22)
O3-2	1 417 (2)	3 637 (3)	3 320 (4)	324 (15)	274 (14)	378 (15)	47 (24)	482 (24)	146 (25)
O4-2	1 403 (1)	1 941 (3)	5 059 (4)	209 (12)	269 (13)	167 (10)	81 (20)	59 (18)	8 (19)
C1-3	2 645 (2)	9 086 (4)	7 166 (6)	422 (22)	229 (19)	304 (18)	87 (34)	237 (33)	62 (31)
C2-3	3 189 (2)	8 786 (4)	5 736 (6)	278 (18)	227 (18)	288 (18)	25 (29)	100 (28)	202 (29)
C3-3	2 848 (2)	7 515 (7)	5 362 (5)	363 (16)	191 (13)	335 (15)	16 (61)	305 (25)	−59 (56)
C4-3	2 543 (2)	7 693 (3)	7 356 (5)	264 (15)	155 (21)	252 (14)	50 (25)	184 (22)	111 (25)
C5-3	2 853 (2)	7 104 (4)	9 278 (6)	324 (21)	320 (19)	328 (20)	21 (32)	86 (32)	259 (32)
C6-3	2 140 (2)	7 002 (4)	9 992 (6)	340 (21)	257 (18)	289 (18)	171 (33)	213 (31)	272 (31)
C7-3	1 853 (2)	7 150 (4)	7 786 (6)	240 (17)	356 (21)	286 (17)	62 (28)	130 (28)	211 (29)
C8-3	3 216 (2)	9 612 (3)	3 961 (5)	258 (17)	177 (16)	281 (17)	15 (27)	103 (27)	149 (27)
C9-3	1 971 (2)	5 814 (4)	10 939 (6)	294 (19)	251 (18)	298 (18)	121 (31)	220 (29)	209 (30)
O1-3	3 796 (1)	9 566 (3)	3 155 (4)	296 (14)	249 (14)	272 (13)	153 (22)	230 (21)	197 (22)
O2-3	2 759 (2)	10 273 (3)	3 361 (5)	193 (12)	380 (17)	489 (18)	92 (25)	172 (23)	501 (29)
O3-3	1 508 (2)	5 887 (3)	12 182 (4)	315 (15)	251 (14)	377 (15)	13 (24)	367 (24)	74 (24)
O4-3	2 236 (3)	4 864 (4)	10 577 (8)	999 (34)	343 (20)	1234 (39)	686 (44)	1909 (65)	886 (49)
O(W)	2 527 (2)	2 237 (3)	7 668 (4)	389 (16)	537 (27)	241 (12)	−411 (28)	−9 (21)	110 (25)

[a] The anisotropic temperature factors are of the form $\exp[-2\pi^2(U_{11}h^2a^{*2} + \ldots + 2U_{23}klb^*c^*)]$. [b] Numbers in parentheses are estimated standard deviations in units of the last decimal place. [c] C2-1 is atom C2 of molecule 1, etc. (the numbering scheme is shown in Figure 2). [d] Parameter held constant to define the origin.

the formula $w = [\sigma^2(F) + (0.01|F_o|)^2]^{-1}$, wherein $\sigma^2(F)$ is the variance of $|F_o|$ based on counting statistics. Three more cycles of refinement reduced R to 3.00% and $R_w = [\Sigma w\Delta^2/\Sigma w|F_o|^2]^{1/2}$ to 3.23%.

At this stage the anomalous dispersion effect of the barium atom was taken into account.[15] Both the enantiomorph chosen at the beginning of the refinement (structure I) and its mirror image (structure II) were now independently refined. As expected,[17] with the y coordinate of the barium atom fixed at ¼, inclusion of the anomalous scattering of barium caused all other atoms to shift along the polar y axis. For all atoms the shift accumulated in the last four refinement cycles was nearly the same, the average values being 0.024 Å for structure I and 0.023 Å for structure II, thus causing the two structures to differ by 0.047 Å. For both structures the average change in coordinates and thermal parameters in the final refinement cycle was 0.1σ. The final discrepancy factors are R = 2.88, R_w = 3.10%, and R = 3.30, R_w = 3.62% for structure I and II, respectively. Application of Hamilton's R-factor ratio test[18] shows that the probability that the difference between the R_w factors could arise by chance is much less than 0.5%, thus firmly establishing that structure I corresponds with the correct enantiomorphic structure. The final positional and thermal parameters for the nonhydrogen atoms of structure I in a right-handed coordinate system are given in Table I.[19]

In a difference map based on the final parameters of structure I, the positions of most maxima and minima were two by two related to each other by pseudomirror planes at y = ¼ and ¾. This pseudosymmetry may indicate that these peaks and holes are due to the barium atom. Most maxima and minima in the Fourier map were within the range ±0.5 e/Å^3 (σ = 0.1 e/Å^3), except for a number of peaks and troughs ranging from −0.7 to +1.2 e/Å^3 in the vicinity of the barium atom, a large negative region down to −0.7 e/Å^3 between barium atoms one unit cell apart in the z direction, and two peaks of +0.8 e/Å^3 just half-way between the pseudomirror planes (i.e., at y = 0 and y = ½) and with approximately the same x and z coordinates as the barium atom.

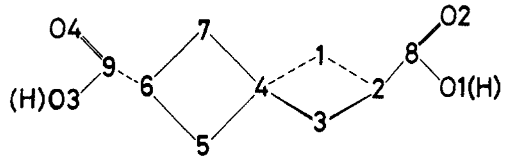


Figure 2. Atomic numbering scheme for the Fecht acid molecules.

Description of the Structure. The atomic numbering scheme used for the Fecht acid molecules is shown in Figure 2. For two of the three molecules in the asymmetric unit (molecules 1 and 2) one carboxyl group (C9, O3, O4) is ionized. The bond lengths and angles in the three Fecht acid molecules and the values of some dihedral angles are

Table II. Distances (Å) and Angles (deg) for the Barium Salt of *d*-Fecht Acid (**13**)[a]

	Molecule 1		Molecule 2		Molecule 3		*d*-Fecht acid (**1**)[b]
			(a) Intramolecular Bond Lengths				
C4-C1, C4-C5	1.549 (5)	1.555 (5)	1.552 (5)	1.549 (5)	1.547 (6)	1.538 (5)	1.546
C1-C2, C5-C6	1.559 (5)	1.549 (5)	1.548 (5)	1.533 (5)	1.553 (6)	1.550 (6)	1.546
C2-C3, C6-C7	1.566 (5)	1.562 (5)	1.563 (5)	1.554 (6)	1.563 (8)	1.567 (6)	1.564
C3-C4, C7-C4	1.532 (5)	1.538 (5)	1.529 (5)	1.540 (5)	1.544 (4)	1.555 (5)	1.539
C2-C8, C6-C9	1.499 (4)	1.513 (4)	1.497 (5)	1.515 (5)	1.512 (5)	1.503 (6)	1.496
C8-O1, C9-O3	1.311 (4)	1.258 (4)[c]	1.334 (4)	1.269 (4)[c]	1.327 (5)	1.308 (5)	1.322
C8-O2, C9-O4	1.234 (4)	1.265 (5)[c]	1.217 (5)	1.252 (5)[c]	1.210 (5)	1.203 (6)	1.225
			(b) Intramolecular Bond Angles				
C4-C1-C2, C4-C5-C6	87.9 (3)	87.8 (2)	87.8 (3)	89.0 (3)	87.0 (3)	88.8 (3)	88.4
C1-C2-C3, C5-C6-C7	87.1 (2)	88.1 (2)	88.2 (3)	89.0 (3)	88.3 (3)	88.1 (3)	88.0
C2-C3-C4, C6-C7-C4	88.3 (3)	87.9 (3)	88.1 (3)	88.5 (3)	86.8 (3)	87.6 (3)	88.0
C3-C4-C1, C7-C4-C5	88.7 (2)	88.8 (2)	89.3 (3)	88.9 (3)	89.2 (3)	89.0 (3)	88.9
C1-C4-C7, C3-C4-C5	119.8 (3)	120.0 (3)	122.5 (3)	118.6 (3)	121.3 (3)	121.9 (3)	120.4
C1-C4-C5	114.8 (3)		115.5 (3)		115.9 (3)		114.8
C3-C4-C7	127.6 (3)		125.0 (3)		122.7 (3)		126.2
C1-C2-C8, C5-C6-C9	120.7 (3)	120.5 (3)	119.4 (3)	119.8 (3)	116.5 (3)	116.3 (3)	117.8
C3-C2-C8, C7-C6-C9	115.6 (3)	114.7 (3)	114.5 (3)	117.4 (3)	116.7 (3)	114.8 (4)	116.7
C2-C8-O1, C6-C9-O3	114.0 (3)	120.5 (3)[c]	111.2 (3)	117.5 (3)[c]	113.4 (3)	114.9 (3)	113.8
C2-C8-O2, C6-C9-O4	122.4 (3)	118.4 (3)[c]	125.5 (3)	120.8 (3)[c]	123.3 (3)	122.9 (4)	123.5
O1-C8-O2, O3-C9-O4	123.5 (3)	121.1 (3)[c]	123.1 (3)	121.7 (3)[c]	123.3 (3)	122.2 (4)	122.7
			(c) Dihedral Angles				
d	149.9	151.1	152.4	157.0	148.5	152.8	152.6
e	76.3	65.5	55.5	37.0	64.2	72.4	64.4

(d) Ba-O Distances[f]

Ba-O3-1 $(x, y, z-1)$	2.815 (3)
Ba-O4-1 $(x, y, z-1)$	2.901 (2)
Ba-O3-2 (x, y, z)	2.769 (3)
Ba-O4-2 (x, y, z)	3.327 (3)
Ba-O2-1 $(1-x, y+\frac{1}{2}, 1-z)$	2.835 (3)
Ba-O2-2 $(-x, y-\frac{1}{2}, 1-z)$	2.733 (3)
Ba-O2-3 $(x, y-1, z)$	2.736 (3)
Ba-O4-3 $(x, y, z-1)$	2.725 (4)
Ba-O(W) $(x, y, z-1)$	2.746 (3)

(e) Hydrogen Bonds[f]

O4-1...(H)O1-1 $(1-x, y+\frac{1}{2}, 1-z)$	2.503 (3)
O4-2...(H)O1-2 $(-x, y-\frac{1}{2}, 2-z)$	2.602 (4)
O3-1...(H)O1-3$(x, y-1, z+1)$	2.596 (4)
O3-2...(H)O3-3 $(x, y, z-1)$	2.594 (4)

(f) O(W)...O Distances[f]

O(W)...O4-1 (x, y, z)	2.779 (4)
O(W)...O4-2 (x, y, z)	2.763 (4)
O(W)...O2-1 $(1-x, y+\frac{1}{2}, 1-z)$	2.905 (4)
O(W)...O2-2 $(-x, y-\frac{1}{2}, 2-z)$	3.034 (4)

[a] See footnote *b*, Table I. [b] Reference 7. [c] Bond lengths and bond angles involving the oxygen atoms of the ionized carboxyl groups. [d] Angles between three-atom planes in the four-membered rings. For each molecule the two values given are the angles between the planes through C1-C4-C3 and C1-C2-C3 and through C5-C4-C7 and C5-C6-C7, respectively. [e] Angles between the best planes through the carboxyl groups and the best planes through the adjacent four-membered rings. For each molecule the two values given are the angles between the planes through C2-C8-O1-O2 and C1-C2-C3-C4 and through C6-C9-O3-O4 and C5-C6-C7-C4, respectively. [f] See footnote *c*, Table I.

listed in Table II. The carbon skeleton of each Fecht acid molecule has approximate twofold symmetry, with C1 related to C5, C3 to C7, etc. The distances and angles given in Table II are grouped according to this symmetry for easy comparison with the values found in the structure determination of *d*-Fecht acid (**1**) itself,[7] where the molecule had crystallographic twofold symmetry. These values also are given in Table II, which further contains Ba-O distances and some short O$\cdots$O distances. All distances are uncorrected for thermal motion.

The differences between corresponding bond lengths and angles within the four-membered rings of the three Fecht acid molecules in the present study are generally not significant, and these bond lengths and angles are also in good agreement with the values found in the previous x-ray analysis of *d*-Fecht acid (**1**) itself.[7] For the bond lengths and angles outside the four-membered rings larger differences occur. In each Fecht acid molecule, both in the present study and in the x-ray analysis of *d*-**1** itself,[7] the angles C1-C4-C5 and C3-C4-C7 differ considerably. It is also noteworthy that in all four-membered rings the C2-C3 (C6-C7) bond length is consistently the largest of the four C-C distances within the ring. The four-membered rings are not planar, as may be inferred from the values of the dihedral angles between the three-atom planes in the rings given in Table II. The dihedral angles between the best planes through the carboxyl groups and the best planes through the adjacent four-membered rings show a large spread. This presumably is due to the fact that the orientations of the carboxyl groups are controlled primarily by the requirements for strong Ba-O interactions and strong hydrogen bonds (vide infra).

A stereoscopic view of the molecular packing is shown in Figure 3. The barium atom is surrounded by nine oxygen atoms, which all are coordinated to only one barium atom. The only oxygen atoms not bonded to a barium atom are the hydroxyl oxygens of the four unionized carboxyl groups, for which the Ba-O distances are larger than 4.2 Å. The Ba-O distances for the other oxygen atoms are given in Table II. From these data it may be seen that the distance from barium to the carboxylate oxygen O4-2 is considerably larger than the other Ba-O distances. This long distance presumably results from crystal packing requirements. The nine-coordination group around the barium atom is probably best described as an octahedron, in which two opposite equatorial positions are both occupied by the two oxygen atoms of a carboxylate group, and in which one apical position is occupied by the carbonyl oxygen O2-2 and the water molecule. It is noteworthy that the four carboxylate oxygens surrounding a barium atom are practically coplanar (within ±0.002 Å). The other two oxygen atoms in the equatorial plane (O2-3 and O4-3) deviate from this plane by 0.492 and 0.033 Å, respectively, while the barium atom

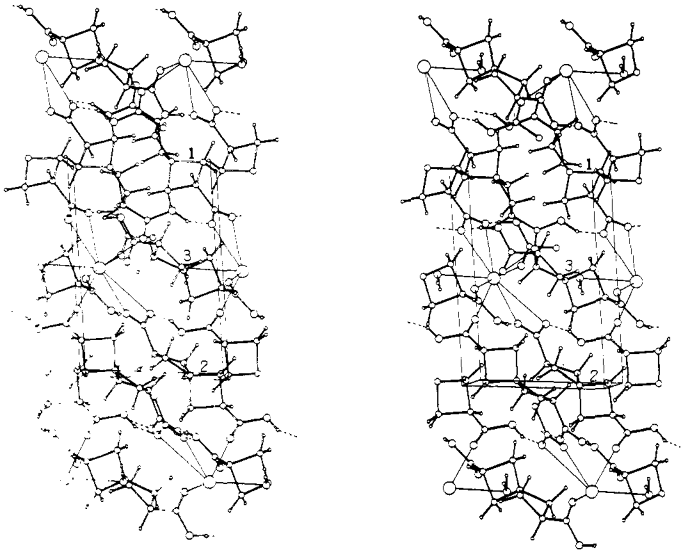


Figure 3. Stereoscopic view of the packing looking nearly down the *b* axis. The axial system is right handed, with the *a* axis nearly vertical and the *c* axis pointing to the right. In the *a* direction only half the cell outline has been drawn. The Ba–O contacts are indicated by full lines and the hydrogen bonds by broken lines. The molecules labeled 1, 2, and 3 are the molecules for which the atomic parameters are listed in Table I. (This drawing was made with the ORTEP program written by C. K. Johnson.)

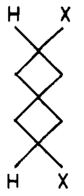
is displaced by 0.466 Å. The displacements are all toward the apex occupied by two oxygen atoms.

There are four independent hydrogen bonds between the Fecht acid molecules, which are all between the hydroxyl oxygens of the un-ionized carboxyl groups and the oxygen atoms of the carboxylate groups (see Table II). The carbonyl oxygens of the un-ionized carboxyl groups thus do not participate in hydrogen bonds between the Fecht acid molecules. The hydroxyl oxygen O1 of molecule 1 is involved in a hydrogen bond to the carboxylate oxygen O4 of another molecule 1, related to the first by a screw operation. As a result an infinite zig-zag chain along the *b* axis is formed around the screw axis ½, *y*, ½. In exactly the same way molecules 2 form an infinite chain around the screw axis 0, *y*, 0. Chains of molecules 1 and molecules 2 are cross-linked by molecules 3, of which the hydroxyl oxygens O1 and O3 are hydrogen bonded to the carboxylate oxygens O3 of molecules 1 and molecules 2, respectively. The stability of the three-dimensional network formed in this way is increased by the fact that the barium atom is coordinated to oxygen atoms of six different Fecht acid molecules (see Figure 3). Apart from the hydrogen bonds the closest intermolecular approaches involving the nonhydrogen atoms of the Fecht acid molecules are at normal van der Waals values.

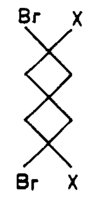
The water molecule is in close contact with four oxygen atoms (see Table II), which are approximately coplanar, the largest deviation from their best plane being 0.064 Å. The water molecule is 0.316 Å away from this plane. The positions of the hydrogen atoms of the water molecule are somewhat uncertain. Although difference Fourier maps showed two peaks of about 0.5 e/Å^3 in the vicinity of the water molecule, these peaks were related to each other by a pseudomirror plane at y = ¼, and gave rise to a rather long O(W)–H distance of 1.3 Å. Also the hydrogen bonding scheme resulting from these hydrogen atom positions was not very reasonable. One hydrogen atom could be assumed to be involved in a bifurcated hydrogen bond to the oxygen atoms O2-2 and O4-2 (H···O distances of 2.3 Å), but the other hydrogen atom was more than 2.7 Å away from all oxygen atoms surrounding the water molecule. The water molecule is certainly not an acceptor for a hydrogen bond, since all O(W)···H distances are larger than 3.0 Å.

II. Application of Lowe's Rule

In an effort to clarify the chirality of a series of 16 representatives of 2,6-disubstituted spiro[3.3]heptanes Wynberg and Houbiers[2] illustrated that the low optical activity of these compounds at the sodium D line gives rise to many exceptions to Lowe's rule.[5] Other factors like solvent effects, dominating Cotton effects, and conformational dissymmetry of the substituents affected the sign of the low optical activity.[2] We extended the series mentioned above with compounds **2–7**[20] and found that the chiroptical behavior of these additional compounds was analogous to that studied previously. Again due to solvent effects or substituent effects a really reliable configurational assignment could not be made.



2: X = NH_2
3: X = $N(O)(CH_3)_2$
4: X = $CONH_2$
5: X = COCl
6: X = $N(CH_3)_2$
7: X = CN
8: X = $N(CH_3)_3I$



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Compounds **2–5** are levorotatory and are configurationally related to *d*-**1**.[2] Compounds **6** and **7**, however, are dextrorotatory (see Experimental Section). Taking into consideration the possible factors mentioned above which might change the sign of the optical rotation,[2] we mainly used *l*-**5** in making a configurational assignment. This compound shows clearly that its Cotton effect and the rotation at the sodium D line have opposite signs. Sign reversal in optical rotation occurred when tertiary amine **6** was converted either to **3** through oxidation, to **8** through quaternization, or to protonated **6** through acidification. These observations[3] indicate that the n–σ^* transition of the lone pairs on nitrogen in **6** has been extinguished, thus diminishing the contribution of the dominating Cotton effect to the net optical activity. The substituents in **2** may occur in asymmetric conformations, but this conjecture is not of importance in view of possible hydrogen bridge formation. Moreover, its optical rotation has the same sign as the hydrogen chloride salt of **2**.[8] Nitrile **7** seems to constitute an exception.

The levorotation observed for most of the spiranes mentioned above is in accordance with Lowe's rule. Provided that the rule is applicable here, the levorotation requires that these compounds have the *R* configuration. Extrapolation of this conclusion to Fecht acid (**1**) itself suggests the *R* configuration for dextrorotatory **1**.

III. Application of Klyne's Sector Rule

The stereochemical information that resulted from the x-ray study of **1**[7] can be used in principle for determination of the absolute configuration of **1**. Because the conformational situation of the carboxyl groups in **1** has now been clarified, interpretation of the positive Cotton effect at 203 nm for *d*-**1**[2] is possible according to Klyne's sector rule for carboxylic acids.[23] On the basis of sectors in space composed by superposition of octants and on the basis of a set of signs determined by this rule,[23] the sector rule was applied successfully in elucidating the chirality of a large number of carboxylic acids, esters, and lactones.[23]

Figure 4 shows a view along an axis perpendicular to the ground plane of the carboxyl group and gives the orientation of the *S* configuration. The greater part of the molecule is located in the negative sectors. This is confirmed by a picture (Figure 5) where a side view projection along the long axis of the molecule is given. The rule states that groups of atoms situated in sectors with a negative sign give negative contributions to the Cotton effect of the n–π^* transitions. Consequently, we may conclude that the *S* configuration has a negative Cotton effect and by consequence that *d*-**1** has the *R* configuration.

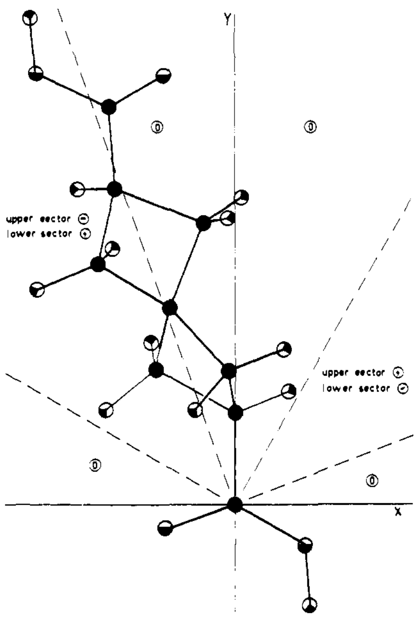


Figure 4. Projection of S-1 along an axis (z) perpendicular to the ground plane of the carboxyl group.

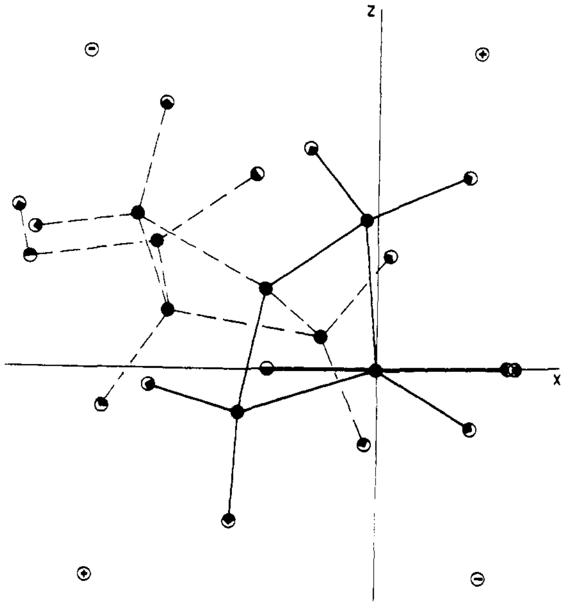


Figure 5. Projection of S-1 along the long axis (y) of the molecule.

IV. Optical Activity Calculations

Brewster's uniform conductor model[24] and Kirkwood's polarizability model[25] to which Lowe's rule is related, were applied to some characteristic examples of spiro[3.3]heptanes. For both models the structural parameters based upon the x-ray study of **1**[7] were used. It is clear from a recent nmr investigation on some of these compounds[26] that the preferred conformation in the solid phase does not differ greatly from that in solution wherein the optical activity is measured. Brewster[24] pointed out that both theoretical models of optical activity, including the one-electron models, lead to the same results in almost all cases studied with respect to the relation between the chirality of a dissymmetric system and the sign of the optical rotation in the visible wavelength region of the ORD spectrum. If this rotation is not controlled by other effects as mentioned in section II, the absolute configuration can be derived. Therefore, we chose 2,6-dimethylspiro[3.3]heptane (**10** in Figure 6) as the best representative of this type of compound for use with either model. In addition, the optical activity of some other spiranes has been computed.

(a) **Brewster's Model.** Using Brewster's deduction of the molecular rotation at the sodium D line for a screw shaped conductor[24]

$$[\Phi]_{\mathrm{D}} = \Sigma[\Delta\Phi]_{\mathrm{D}} = \Sigma 652.4\,\frac{d_1 d_2 d_3}{2(d_1 + d_2 + d_3)^2} \times \sin\alpha \sin\beta \sin\gamma\, \Sigma\Delta R_{\mathrm{D}} f(n) \qquad (1)$$

and making use of the known geometry of the spiranes,[7] the calculations were performed for compounds **1** and **10.** The assumption was made necessarily that the helicity of the system originates solely from the orientations of the substituents, excluding thus the dissymmetric character of the spiro skeleton.[7] The results of the calculations are depicted in Figure 6. Correspondence between the experimentally found sign reversal in optical rotation at the sodium D line observed during conversion of **1** into **10**[2] and the previously derived chirality[2,6,7] was only obtained when the parameter for the group refraction of the spiroheptane skeleton (x) had a value of 16.6.[27] Although the correspondence between experiment and theory seems to be reasonable,[27,30] the crucial point in using this model remains the fact that not all of the conformational skews can be taken into account.

The fact, however, that the molecular rotation of these compounds generally is small can be explained by qualitative arguments. X-ray analysis of **1** revealed puckering of the four-membered rings, resulting in higher values for the angles α and β (approaching to 180°) and thus lower values for the molecular rotation (eq 1) that anticipated for a planar form of both spiro rings.

(b) **Kirkwood's Model.** Another theory of optical rotatory power, which has been used in our calculations on compounds containing the spiro[3.3]heptane skeleton, was Kirkwood's polarizability model. It may be readily applied to assign absolute configurations and to estimate the magnitude of optical rotation. Basically, this model is concerned with the magnetic moment produced by electrical displacements along axes of polarizability that are neither colinear nor coplanar. In this model of optical activity, it is considered that the rotatory effects in consequence of polarizability or refraction properties are combined with the coupling by dipole-dipole interactions of the groups into which the molecule has been divided.[24,25] The equations of the Kirkwood model in the adapted formulation of Looyenga,[25] viz., a numerical calculation in a Cartesian coordinate system, are depicted in eq 2.

$$[\alpha]_{\mathrm{D}} = -821.9\,\frac{n^2 + 3}{2}\,\frac{100}{M} \sum_{i \neq j} \alpha_i \alpha_j \beta_i \beta_j S_{ij} D_{ij} \qquad (2)$$

$$S_{ij} = \frac{1}{R_{ij}^{\,5}}\{3(b_{ix}r_{ijx} + b_{iy}r_{ijy} + b_{iz}r_{ijz})(b_{jx}r_{ijx} + b_{jy}r_{ijy} + b_{jz}r_{ijz}) - R_{ij}^{\,2}(b_{ix}b_{jx} + b_{iy}b_{jy} + b_{iz}b_{jz})\}$$

$$D_{ij} = \begin{vmatrix} r_{ijx} & r_{ijy} & r_{ijz} \\ b_{ix} & b_{iy} & b_{iz} \\ b_{jx} & b_{jy} & b_{jz} \end{vmatrix}$$

821.9 is a constant derived from the wavelength used and Avogadro's number; n is the refractive index of the solvent; M is molecular weight of the substrate; R_{ij} is the vectorial distance between groups i and j with components r_{ijx}, r_{ijy}, and r_{ijz} along the x, y, and z axes, respectively; b_{ix} is the direction cosine of the latter bond which one encounters going from the spiro atom via the bonds to group i; α_i is the mean polarizability of group i; and β_i is the anisotropy ratio of group i.

In the calculations all mutual interactions between all bonds and groups in compounds **1, 4, 5, 10,** and **11** (in Table III) have

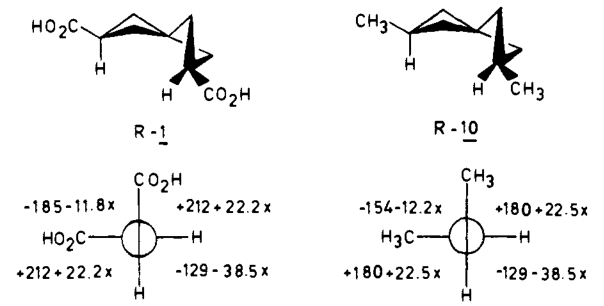
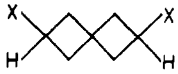


Figure 6. The results of optical activity calculations according to Brewster's model. *R*-**1**: $[\Phi]_D = +109 - 5.9x$, $[\Phi]_{D\text{calcd}} = +10°$, $[\Phi]_{D\text{exptl}} = +8.6°$.[2] *R*-**10**: $[\Phi]_D = +77 - 5.6x$, $[\Phi]_{D\text{calcd}} = -16°$, $[\Phi]_{D\text{exptl}} = -5.8°$.[2]

Table III. Results of Kirkwood's Model



Compd	Chirality	Solvent	$[\Phi]_{D\text{calcd}}$, deg	$[\Phi]_{578,\text{exptl}}$, deg
X = CO_2H	*R*-**1**	Acetone	+1.5	+8.7[a]
X = CH_3	*R*-**10**	Cyclohexane	−2.9	−5.7[a]
X = CO_2CH_3	*R*-**11**	Acetone	−9.4	+3.2[a]
X = COCl	*R*-**5**	Pentane	−2.4	−18.0[b]
X = $CONH_2$	*R*-**4**	Methanol	~0	−11.7[b]

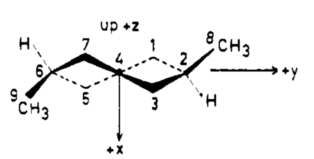
[a] Reference 2. [b] This work.

been taken into account. This computational approach in Fecht acid (**1**) involved 91 interactions. The molecular geometry of the various compounds was based on the x-ray study of **1**[7] and has been adapted, where necessary, by taking into account the mean values of the interatomic distances and bond angles of several compounds.[31] The values for α_i and β_i were taken from Fitts[25] or, where necessary, were calculated.[24,25,32] A computer program was developed. The results are compiled in Table III.

Despite the known disadvantages[24,25] of using this model of optical activity, the observed sign reversal in the optical rotation of **1** and **10** is calculated correctly. Moreover, the *R* configuration has been calculated for *d*-Fecht acid (**1**). On the other hand, the examples **4**, **5**, and **11** in Table III indicate that Kirkwood's model should be applied with care.[33] Nevertheless, in view of the results obtained in the previous experiments in determining the chirality of *d*-**1**, we may conclude that both theoretical models mentioned in this section tend to give additional support to the other internally consistent methods.

V. Application of the Eyring-Jones Model[34]

Eyring and Jones have presented an interesting model[24,35] that is easy to apply in molecules with C_2 symmetry where it acts like an octant rule. To avoid the possible influence of any interfering effect (section II) on the optical rotation at the sodium D line, spirane **10** was chosen for testing the model. The spiro atom in **10** was placed at the origin in a right-handed coordinate system. Subsequently, the *R* configuration of **10** was rotated until the twofold axis of the molecule coincided with the *z* axis of the coordinate system. The various groups in the molecule were now found in octants characterized by the sign of the coordinates (Figure 7). According to the theory the sign of the long-wavelength rotation is opposite to that of the product of signs of the coordinates. In this case the resulting rotation effect was negative.[36] By consequence,[2] *d*-acid **1** should have the *R* configuration.



1 : -x,+y,-z : ⊖
2 : +x,+y,-z : ⊕
3 : +x,+y,+z : ⊖
4 : 0, 0, 0 : 0
5 : +x,-y,-z : ⊖
6 : -x,-y,-z : ⊕
7 : -x,-y,+z : ⊖
8 : -x,+y,-z : ⊖
9 : +x,-y,-z : ⊖

Figure 7. *R*-**10** shown in the puckered conformation based on the x-ray model of **1** (left) and the rotation effects of the various groups (right).

VI. Determination of the Absolute Configuration of *d*-Fecht Acid (1) by X-Ray Methods

(a) Results with Barium Salt 13. In the x-ray analysis of the *d*-barium salt of *d*-Fecht acid (**13**) the refinement of both enantiomorphs resulted in a significant difference between the R_w factors of the two structures (see Experimental Section). Inspection of these two enantiomorphic structures showed that in the structure with the lower R_w factor all three independent Fecht acid molecules had the *S* configuration. This result contradicts the conclusions arrived at the previous sections, and we therefore decided to check this configurational assignment by comparing the intensities of a number of Bijvoet pairs. Structure factor calculations based on the final parameters of the structure with the lower R_w factor and with inclusion of the anomalous scattering of barium, oxygen, and carbon[37] showed that with Cu radiation for a great number of reflections the differences between pairs $I(hkl)$ and $I(h\bar{k}l)$ should be easily observable on Weissenberg photographs (for some reflections with $|F_c| > 40$ the calculated intensity difference was greater than 50%). Weissenberg photographs of the *hk*0, *hk*1, and *hk*2 layers were taken at −160°, using a fragment of a very large crystal that was shaped into a cylindrical form (0.2 mm in diameter) in order to minimize errors due to absorption. About 25 pairs of reflections were examined and for all these pairs the observed intensity order corresponded with that calculated for the *S* configuration.

The link between chirality and optical rotation of the barium salt was made by measuring the optical rotation of the solution obtained by dissolving in water the large crystal of which a fragment had been used for the Weissenberg photographs. The specific rotation (see Experimental Section) was exactly the same as that for a solution of barium hydroxide and dextrorotatory Fecht acid (**1**) in the correct stoichiometric proportions.

(b) Results with *d*-Fecht Acid (1) Itself. In the earlier reported x-ray analysis of *d*-**1**,[7] the acid was assigned the *R* configuration on the basis of intensity differences observed on Weissenberg photographs. Reflections with low intensity were thereby selected, because on the average the relative intensity differences increase with decreasing intensity. The observability of the differences, however, is then severely hampered by relatively large background effects. Moreover, the chance of having detectable intensity differences in a compound containing only oxygen, carbon, and hydrogen is, of course, much less than in the rather favorable case of a barium salt of such a compound. In the x-ray study of *d*-**1**[7] the intensity differences were very small and for only 75% of the examined Bijvoet pairs the observed intensity order corresponded with that calculated for the *R* configuration. It is now evident that this correspondence, as compared to the normal 50% no-choice case, is insufficient to allow an unambiguous configurational assignment. In addition, with all reflections gathered by Mo radiation and using the anomalous scattering factors of carbon and oxygen, three refinement cycles for both enantiomorphic structures did not result in a significant difference between the R_w factors of these two structures.

In order to determine the absolute configuration of *d*-**1** using the acid itself, we measured the intensities of a number of Bijvoet pairs very accurately on a diffractometer. Ten pairs of reflections with moderate intensity were selected, for which the calculated intensity differences using the anomalous scattering of oxygen and carbon[37] ranged from 1.3 to 3.4%. The intensities were recorded using Ni-filtered Cu radiation, spending about 10 min counting time for each reflection. The intensity data were carefully corrected for absorption.[13] For eight pairs the observed intensity difference was significantly larger than the standard deviation. For seven of these pairs the observed difference was in agreement with the *S* configuration and for one pair with the *R* configuration.

Discussion

The crystallographic approaches described above to the determination of the absolute configuration of *d*-Fecht acid (**1**) all lead to the same result: dextrorotatory Fecht acid (**1**) has the *S* configuration. It is evident then that application of Lowe's rule to the 2,6-disubstituted spiro[3.3]heptane system and of the sector rule of Klyne to **1** has failed. Apparently, these empirical rules are not valid for these particular spiro systems. Wynberg and Houbiers[2] used Lowe's rule for a whole series of derivatives of Fecht acid (**1**), but not for the acid itself. Although application of Lowe's rule to *d*-**1** would have given the correct answer (viz., the *S* configuration), this would have been fortuitous because of the interfering Cotton effect[38] of the carboxyl chromophore. Moreover, several exceptions to Lowe's rule in the spirane area have been recorded recently.[39-45] Originally, the rule dealt with allenes and alkylidenecycloalkanes. These parent systems represent a better conductor (π systems) that a spirane system does, giving rise to high values of optical activity as compared to spiranes (σ systems). The low optical activity inherent in the dissymmetric 2,6-disubstituted spiro[3.3]heptane system leads to a situation in which the influence of Cotton effects of substituents in the visible wavelength region becomes very important in most cases, more important than in the case of the allenes.[24,46] Klyne's rule does not hold in our case either. It should be stressed in this regard that the conformational situation of **1** in the solid phase does not differ from that in solution according to NMR investigations.[26]

The reasons for the failing of the major models of optical activity is to be found in the limitations imposed by the overriding need for simplicity and by the fact that these models rest upon a number of arguments by analogy.[24] They do not take into account in their crude approximation all possible contributions to the net optical activity in the longer wavelength region. The low optical activity of our spiranes fortuitously revealed the discrepancy of these models. The rather abnormal geometry of this particular series of spiranes, viz., (a) the puckering of the four-membered rings, (b) the asymmetric character of the spiro system by inequivalence of the methylene groups in the ring, and (c) the distortion of the whole skeleton by the deviations from the tetrahedral values of the angles at the spiro atom, might give rise to an unexpected orientation of the resulting electric and magnetic dipole transition moments in these compounds. This situation led to a wrong prediction of chirality by use of the present major theoretical models of optical activity, resulting in an anti-Klyne's and anti-Lowe's behavior of Fecht acid and derivatives.

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Supplementary Material Available: a listing of the final hydrogen atom coordinates (× 10^4) and thermal parameters and of the observed and calculated structure factors (10 $|F_o|$, 10 $|F_c|$, 10A_c, 10B_c) (4 pages). Ordering information is given on any current masthead page.

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