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Conformation in the Solid State and in Solution of (9R, 10R, 21R,-22R)-9, 10, 21, 22-Tetramethyl-9, 10, 21, 22-tetrahydro-7*H*, 12*H*,-19*H*, 24*H*-dinaphtho-[1, 8-f, g: 1', 8'o, p][1.4.10.13]-tetraoxacyclooctadecin†

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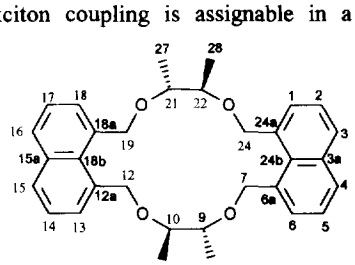
Abstract: The helical conformation of a new, optically active heterocyclic system **1** in solution has been determined from CD spectra by application of the exciton coupling theory. The molecule in the crystal adopts a conformation possessing an approximate 2-fold axis, with naphthyl groups nearly coplanar. Absolute configuration at four chiral centres as determined unequivocally by X-ray anomalous scattering method agrees with the known configuration of the starting (R,R)-2,3-butanediol. The conformations in the solid state and in solution are compared with those resulting from AM1 calculations.

The chiral exciton coupling theory has been widely used for determining the absolute configuration and conformation of various types of natural and synthetic organic compounds.[1,2] As the stereochemistry of the compounds exhibiting split CD Cotton effects due to chiral exciton coupling is assignable in a nonempirical manner, we have chosen this method to establish the conformation of the new, optically active, heterocyclic system possessing an 18-membered ring (**1**). This compound was obtained by alkylation of (-) (R,R)-2,3-butanediol with 1,8-dibromomethyl naphthalene. The conformation in solution has been compared with the solid state geometry determined by X-ray analysis as well as with those calculated by the semi-empirical AM1 method.



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† Dedicated to the memory of Prof. Dr. Dr. h. c. Günther Snatzke - 26 October 1928 - 14 January 1992

Results and Discussion

CD Spectra

The UV spectra of the title compound taken for the isooctane and acetonitrile solutions exhibit an intense band of the ^1B_b transition at λ = 226.7 nm (ε = 124500) and 226.3 nm (ε = 122400), respectively. The ^1L_a transition showing complex vibrational structure is located over 250 - 320 nm with maxima at λ = 285.9 nm (ε = 28400) in isooctane and 285.9 nm (ε = 22800) in acetonitrile solutions. This band is flanked by a low intensity band at about 315 nm related to the ^1L_b electronic transition. Thus, the whole pattern of the spectra is quite similar to that of naphthalene, which means that homoconjugation between the two naphthalene chromophores is negligible.

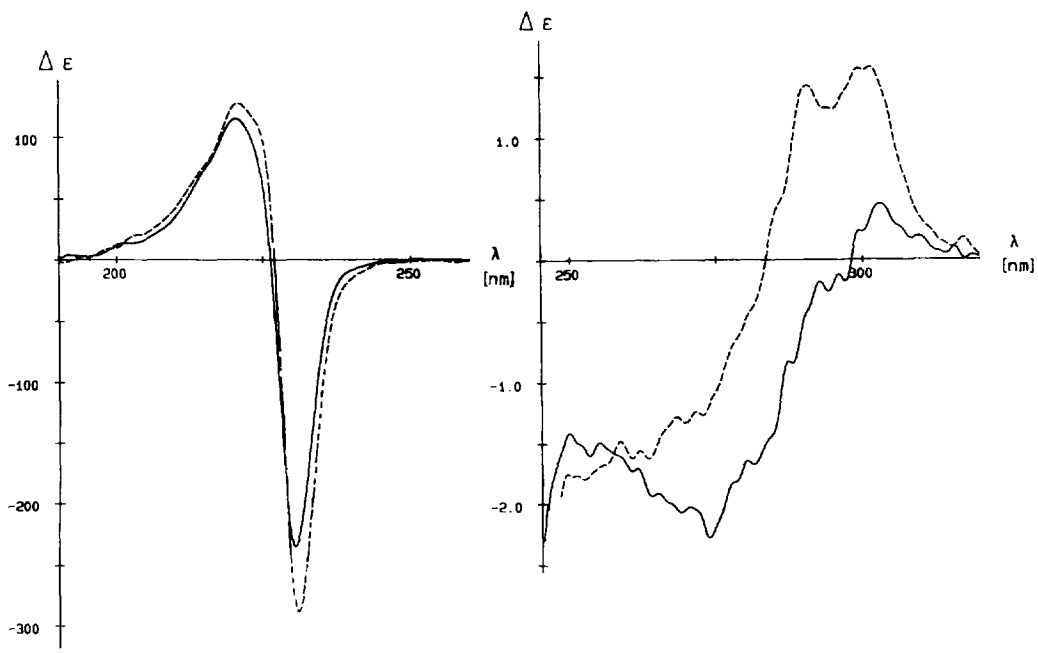

Figure 1. CD spectra taken for isooctane - - - - - and acetonotrile ——— solutions of **1**.

In the CD curves taken for both solutions four Cotton effects were found. In isooctane the first weak Cotton effect is observed at λ = 301 nm ($\Delta\varepsilon$ = 1.57), the second negative one at λ = 263 nm ($\Delta\varepsilon$ = -1.63). The allowed ^1B_b transition generates two very intense Cotton effects of opposite sign: a negative one at λ = 231 nm ($\Delta\varepsilon$ = -288.7) and a positive one at λ = 220.8 nm ($\Delta\varepsilon$ = 128.1). The intersection points of bisignate couplets are located at 283.7 and 227.2 nm, respectively (Figure 1). The peak areas of the Cotton effects in the ^1B_b transition region are almost identical, proving that they are due to the chiral exciton coupling mechanism. The short wavelength CD couplet in the spectrum taken for acetonitrile solution is very similar to that in isooctane with CEs at 230.6 nm($\Delta\varepsilon$ = -235.8) and 220.6 nm ($\Delta\varepsilon$ = 115.4) and $\Delta\varepsilon$ = 0 (intersection point) at

226.6 nm. On the other hand, both Cotton effects at longer wavelengths are red shifted to 303.1 nm ($\Delta\varepsilon$ = 0.46) and 273.7 nm ($\Delta\varepsilon$ = -2.28), respectively. The difference between the intersection point of these two extrema and the position of the UV absorption maximum is equal to 12.4 nm.

The electronic transitions of naphthalene chromophore are well characterised.[3,4] For the ^1B_b band the electric transition moment lies along the longitudinal axis of the naphthalene chromophore. On the other hand, the polarization of the transition moment of the ^1L_a band is perpendicular to that axis (see Chart 1).

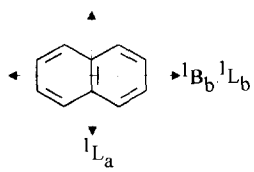

Chart 1

Similar polarisation of the transition moments was found for acenaphthene, the molecule possessing methylene groups as substituents at 1,8 positions.[5]

The shape of the CD spectrum in the range of the ^1B_b transition can be considered as a typical CD couplet. This type of CD spectrum can only occur if the molecule adopts a conformation in which exciton interaction (the electric transition dipol coupling) between both chromophores takes place. Thus, the naphthalene rings have to diverge from coplanarity. Since a negative CD couplet was found in the spectrum, the exciton chirality between two transition dipol moments has to be negative. Namely, the chirality of the two long axes of the chromophores is of left-handed screwness, so the molecule has to be twisted along the longitudinal axis and adopts a left-handed helical conformation. Moreover, in isooctane for the ^1L_a transition exciton coupling is observed as well, which indicates that the corresponding electric transition moments are also not parallel. The changes in the ^1L_a transition pattern in the spectrum taken for the polar acetonitrile solution can be interpreted as stabilizing of the conformation with almost collinear arrangement of the ^1L_a transition dipole moments.[6]

X-ray analysis

A perspective view of the molecule is shown in Fig. 2. Selected structural parameters are listed in Table 2. The molecule possesses an approximate 2-fold axis parallel to the [001] direction. The axis passes through the centres of bonds between chiral carbons C9-C10 and C21-C22, respectively (see Fig. 2). The deviations from exact symmetry are within 0.03 Å, except for 2 pairs of methyl substituents, C25, C26, and C27, C28, for which the deviation is larger (0.2 Å). There are two groups of intramolecular hydrogen bonds between carbon and oxygen atoms. The shortest ones involve C1 and O23 and symmetry-related C18 and O20 (2.68 Å). Four longer hydrogen bonds (2.91 Å), also symmetry-related, are between the methyls and oxygen atoms (see Fig. 2).

The absolute configuration was determined by two methods using anomalous dispersion of oxygen. The cumulative enantiomer correctness indicator, the Flack coefficient[7] converged to -0.2 with esd 0.3, indicating R absolute configuration at four chiral centres (C9, C10, C21, C22). A comparative test carried out using azimuthal scan curves[8] recorded for 13 most sensitive Bijvoet pairs confirmed that configuration.

In spite of the flexible 18-membered hetero-ring, the best LSQ planes fitted to the peripheral naphthyl groups are almost parallel, forming an angle of 5° with each other. However, it should be noted that both naphthyl groups deviate significantly from planarity: distances from LSQ planes are in the range -0.10 Å to 0.11 Å for individual atoms. Such deformation could be attributed to repulsion between two methylene groups at 1,8 positions[9] as well as the influence of the intramolecular hydrogen bonds. It is worth noticing that in the crystalline state the molecule possesses left screwness, similarly to the conformation in solution.

Figure 3 illustrates the packing scheme. Analysis of intermolecular close contacts indicates that crystal cohesion is due to van der Waals interactions, since analysis of intermolecular distances did not reveal intermolecular hydrogen bonds

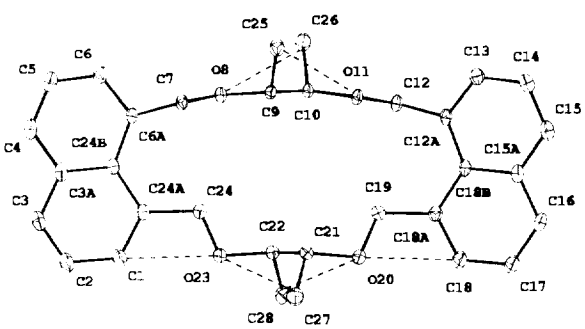

Figure 2. Perspective drawing of the molecule with the atom numbering scheme. Intramolecular hydrogen bonds are marked by dashed lines

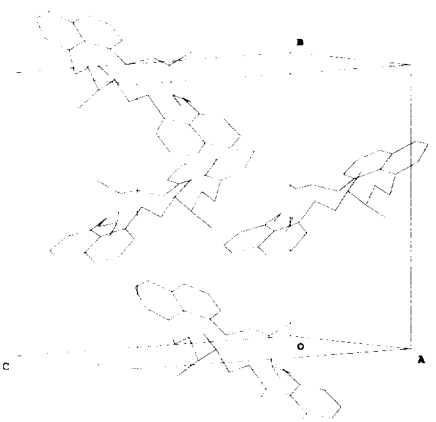

Figure 3. Packing scheme of the crystal structure.[10]

AM1 calculation

It follows from the calculation that the conformation adopted by the molecule in the crystal is the ground-state geometry (Chart 2 **A**) and that the main features of the X-ray structure are well reproduced (see Table 2). Starting from the ground-state conformation a conformational search has been performed by varying both O-CH-CH-O dihedral angles, which allowed to find the second energy minimum (Chart 2 **B** and Tab. 2) only 0.3 kcal/mol above the ground state conformation. In this conformation both naphthalene rings are placed on different planes and the dihedral angle between them is equal to 55 deg. This value of the dihedral angle is in very good agreement with that calculated from CD spectra.[6] Moreover, this geometry involves inclined arrangement of the short axes of the chromophores, as it was found in the spectra for the ^1L_a transition. It can therefore be concluded that geometry **B** represents the main features of conformation adopted in solution.

The distance between the centres of the chromophores, in both the crystal-state conformation and the calculated geometry **B**, is in the range of 10.5 Å. It should be noted that even with such a big separation of the chromophores a relatively strong split Cotton effect is observed.

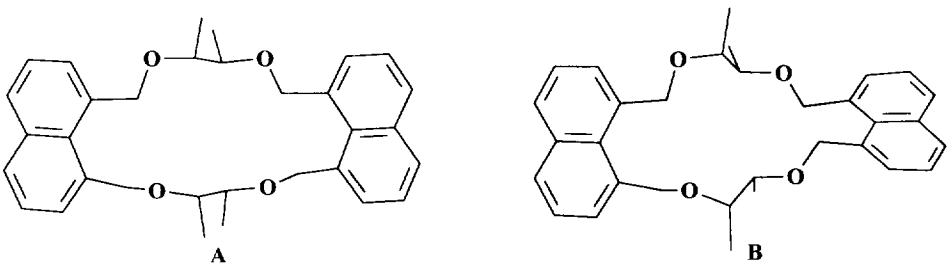

Chart 2

Table 1. Comparison of torsional angles within the 18-membered ring as found by X-ray analysis and calculated by AM1 method.

Dihedral angle	X-ray	AM1	
		A	**B**
C6a - C7 - O8 - C9	-168.53	-175.4	178.2
C7 - O8 - C9 - C10	173.82	168.7	159.7
O8 - C9 - C10 - O11	-169.75	-167.8	-140.6
C9 - C10 - O11 - C12	171.95	169.4	-66.1
C10 - O11 - C12 - C12a	-172.43	-175.0	-167.7
O11 - C12 - C12a - C18b	95.53	94.8	-93.9
C12 - C12a - C18b - C18a	-16.86	-12.8	12.9
C12a - C18b - C18a - C19	-9.36	-10.0	9.4
C18b - C18a - C19 - O20	-147.95	-157.0	154.6
C18a - C19 - O20 - C21	160.86	159.7	-178.2
C19 - O20 - C21 - C22	69.51	71.9	82.2
O20 - C21 - C22 - O23	171.18	174.9	-168.0
C21 - C22 - O23 - C24	69.66	71.9	149.9
C22 - O23 - C24 - C24a	162.07	159.8	171.1
O23 - C24 - C24a - C24b	-148.07	-157.0	98.3
C24 - C24a - C24b - C6a	-10.09	-10.0	-14.2
C24a - C24b - C6a - C7	-16.55	-12.7	-14.3
C24b - C6a - C7 - O8	96.30	94.7	100.1

Conclusions

The absolute conformations of the molecule as deduced from CD measurements and determined by X-ray diffraction method are similar and characterized by a left-handed helical arrangement of the naphthyl moieties. However, dihedral angles between the naphthyl moieties' planes are different with the values of -55 ^{o} for solution and -5° for the solid state conformation. The AM1 calculations show that the geometry adopted in solution and that in the solid state are fairly close in the energy. Absolute configuration at four chiral centres is R.

Experimental

The CD spectra were taken with a JASCO J-600 spectropolarimeter for 0.74 mmol/l solution in isooctane and 0.61 mmol/l in acetonitrile. The UV spectra were taken for the same solution on PU 8740UV/VIS scanning spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded at 400.1 and 100.6 MHz respectively, with a Bruker AM 400 spectrometer for deuteriochloroform solution of the samples; chemical shifts are referenced to tetramethylsilane. IR spectrum was obtained from Bruker IFS 48 spectrophotometer in potassium bromide pellet and MS spectra with VG Autospec.

Molecular modelling was carried out using HyperChem™ software.[11] The starting geometry was taken from the crystallographic coordinates and minimized with AM1 method. Searching for energy minima on the potential energy surface of the molecule was done by varying the dihedral angles of both O-CH-CH-O bridges and force-field (MM+) minimization. The energy minima found were subjected to geometry optimization with the AM1 method. This was performed with the Polak-Riebiere optimizer and the covergence RMS gradient was 0.01 kcal/Åmol.

X-ray crystal structure determination[12] was carried out on a colourless sample of irregular shape - (001) platelet of 0.07 x 0.2 x 0.25 mm in size. Details of data collection parameters and refinement results are given in Table 2. The unit cell parameters were determined by least-squares fit to 25 reference reflections. Two standard reflections were measured every hour to control intensity and orientation variations. No significant variation was observed within exposure time of six days. However, during remeasurements of the most sensitive Bijvoet pairs carried out two month after the principal data collection, an increase in the crystal mosaicity was observed together with a significant decrease in the scattering power of the sample. For that reason several samples were taken for remeasurement. It seems that it could be attributed to a slow decomposition of the crystal or the molecule induces by X-ray radiation. The intensity data were reduced using a local program DAREX and corrected for Lorentz and polarization effects. No absorption correction was applied. The structure was solved by direct methods with SHELXS86 program.[13] The structure refinement was carried out using full-matrix least squares method with SHELXL93.[14] All non-hydrogen atoms were refined anisotropically, while hydrogen atoms, located from difference Fourier map, were refined isotropically.

Table 2. Crystal Data, Data Collection and Refinement Parameters[15]

Formula	$C_{32}H_{36}O_4$	index ranges	$-10 \le h \le 10$, $0 \le k \le 16$, $-20 \le l \le 20$
Fw	484.61	scan mode	$\omega/2\theta$
cryst syst	orthorhombic	θ range, deg	3.85 to 59.95
space group	$P2_12_12_1$	total data collected	8110
cryst. dimens, mm	0.07x0.2x0.25	unique data	3891
a, Å	9.7295(5)	R(int)	0.0337
b, Å	14.6503(5)	data/restraints/parameters	3891 / 69 / 326
c, Å	18.4256(5)	final shift/error, max and avg	0.001, 0.000
Z	4	Absolute structure parameter	-0.2(3)
V, $Å^3$	2626.4(2)	Extinction coefficient	0.0013(4)
r(calcd), g cm^{-3}	1.226	max resid density, e/$Å^3$	0.662 and -0.287
radiation	CuKα	Final R indices [I>2σ(I)]	R1=0.0642,
abs coeff (m) mm^{-1}	0.627		wR2=0.1475
F(000), e	1040	Final R indices (all data)	R1=0.0828,
temp, K	293		wR2=0.1639
diffractometer	Enraf-Nonius CAD4	GOF	1.069

Synthetic procedure: To a suspension of NaH (1g, 50% in mineral oil) in 100 ml of dry, peroxide-free THF 0.01 mol of (-)(R,R)-2,3-butandiol was added. The reaction mixture was stirred and refluxed for 1 h then 0.01 mol (3.14 g) of 1.8-bis(bromomethyl)naphthalene was added in one portion and refluxed for 10 h. THF was distilled off under reduced pressure and $CHCl_3$ was added. Insoluble solid was removed by filtration and then, after evaporation of the solvent the residue was purified by column chromatography (silica gel/$CHCl_3$). Analytically pure sample was obtained after crystallization from benzene / n-hexane 1 : 1. Colourless crystals mp. 177-179. $[\alpha]^{23}_{578}$ = -56.6 $CHCl_3$ c = 3.12 g/100 ml; yield: 0.36 g (15%). **^{1}H NMR**: 1.30(d, J=6.1Hz, 12H, C<u>H</u>$_3$); 4.04(dq, J=4.75Hz, 4H, C<u>H</u>), 5.21(AB_q, J_{AB}=12Hz, 8H, C<u>H</u>$_2$), 7.46(dd, J=8.0Hz, J=7.1Hz, 4H); 7.71(dd, J=7.1Hz, J=1.2Hz, 4H); 7.84(dd, J=8.0Hz, J=1.2Hz, 4H). **^{13}C NMR**: 14.6 (CH_3), 71.9(CH_2), 77.9 (CH), 125.1, 129.3 130.0, 131.2, 134.9, 135.6. **IR**: 440, 571, 773, 817, 829, 916, 1000, 1021, 1033, 1043, 1071, 1098, 1112, 1161, 1174, 1244, 1300, 1318, 1331, 1371, 1389, 1446, 1460, 1472, 1494, 1595, 2859, 2891, 2923, 2935, 2978, 2991, 3017, 3034, 3050. **MS** (FAB) m/z (intensity,%): 485 $(M+1)^+$(9); EI(15 eV) 484 (M^+,0.3), 241(43), 159(75), 154(98), 153(100). Anal. Calc. for $C_{32}H_{36}O_4$: C, 79.31; H, 7.49%. Found: C, 79.03; H, 7.82%.

Acknowledgement

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[15] The atomic coordinates for the X-ray structure have been deposited with the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, United Kingdom.

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