A Chiral Adamantanophane: Preparation, Enantiomer Separation, Theoretical and Experimental Circular Dichroism and Absolute Configuration

Stefan Grimme*[a], Ralf Lemmerz[b], and Fritz Vögtle*[b]

Institut für Physikalische Chemie und Theoretische Chemie der Universität Bonn[a], Wegelerstraße 12, 53115 Bonn, Germany

Institut für Organische Chemie und Biochemie der Universität Bonn[b], Gerhard-Domagk-Straße 1, D-53121 Bonn, Germany

Received May 2, 1994

Key Words: Adamantanophanes / Calculations, CI / Circular dichroism / Cyclophanes / Strain energy

Exchange of *aro*matic units (e.g. benzene) for *ali*phatic/*ali*cyclic building blocks (e.g. adamantane) in cyclophanes leads to molecules of the "*arali*phane" type. The synthesis of the highly strained [2.2](1,3)adamantanometacyclophanes **5a–c** is described. The cyclophane skeletons of these molecules are conformationally rigid and therefore **5a–c** are planar-chiral. The circular dichroism of **5c** has been calculated theoretically with NDDO/MRD-CI methods and was measured. Agreement of theory and experiment is good, a comparison of both allows the assignment of the absolute configuration of the two enantiomers of **5c** with high probability. Furthermore, analysis of the $n\pi^*$ band in the CD spectrum yields a simple general rule to determine the conformation of the carboxyl group in phenyl ester substructures. Theoretical calculations of the strain energy (E_s) of **5c** reveal the distribution of strain within the molecule.

The bridgehead bond angles of adamantane, clamped in the 1- und 3-positions, are similar to those of the *meta*-phenylene unit. We have been able to perform the formal exchange of these two building blocks in various examples[1–3]. Bridging of an arene with the alicyclus adamantane leads to cyclophane analogues of the *arali*phane type (for nomenclature see ref.[4]). The properties of the members of this newly defined family of compounds differ significantly from those of e. g. the [2.2]metacyclophane system. They are more strained, the distortion of the bridged arenes is stronger, and their conformational behaviour is different.

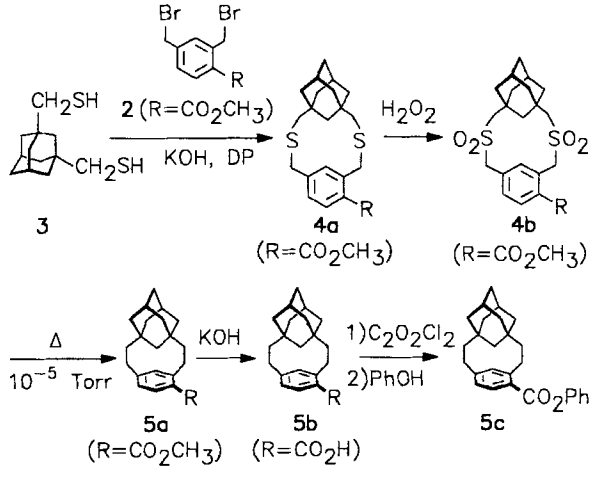
In this paper we describe the syntheses of the planar-chiral [2.2]adamantane-*arali*phanes **5a–c**, the enantiomer separation of **5c** and its circular dichroism (CD). The CD spectrum of **5c** has also been calculated theoretically with a combination of MRD-CI (multireference single/double configurational interaction) and semiempirical NDDO methods[5,10]. Comparison of the experimental CD spectrum with the results of the calculation allows the assignment of the absolute configuration of the two enantiomers of **5c** with high probability. Furthermore, the theoretical analysis of the $n\pi^*$ band in the CD spectrum yields a simple rule of general applicability to the determination of the conformation of the carboxyl group in the phenyl ester substructure.

1. Syntheses

The preparation of the adamantane-*arali*phanes follows the dithiacyclophane route[6] with subsequent oxidation and sulfone pyrolysis[7].

NBS bromination of methyl 2,4-dimethylbenzoate leads to methyl 2,4-bis(bromomethyl)benzoate (**2**) in 38% yield.

Scheme 1. Synthesis of the planar-chiral [2.2]adamantanophanes **5a–c**



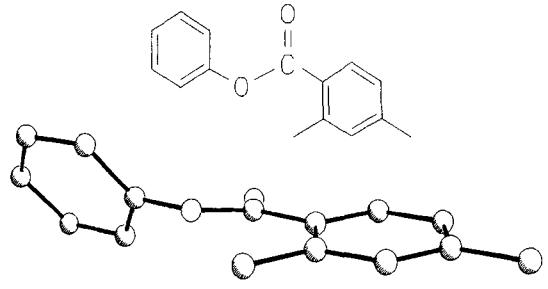
Cyclization of **2** with 1,3-bis(mercaptomethyl)adamantane (**3**) under dilution principle conditions[8] yields methyl 2,15-dithia[3.3](1,3)adamantanometacyclophane-18-carboxylate (**4a**, 28%). Oxidation of **4a** to the corresponding disulfone **4b** and subsequent sulfone pyrolysis of **4b** to methyl [2.2](1,3)adamantanometacyclophane-16-carboxylate (**5a**) proceed in satisfying yields (62 and 63%)[9]. Hydrolysis of the methyl ester **5a** furnishes the carboxylic acid **5b** (85%), esterification with phenol via the corresponding acyl chloride leads to **5c** in 52% yield.

NMR Spectroscopy and Conformational Analysis

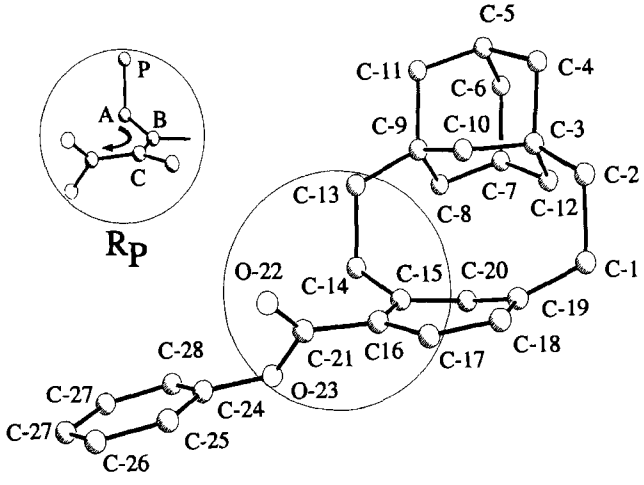
The 250-MHz NMR spectra of **5a–c** show AX systems of strongly upfield-shifted signals for the intraanular ada-

  0009–2940/94/1010–2081 $ 10.00+.25/0

mantane hydrogen atoms at C-10 [δ = −0.47/0.91 (**5a**), −0.35/1.06 (**5b**), and −0.42/1.05 (**5c**)] due to their close proximity to the benzene ring[1,2]. The spectrum of the unsubstituted [2.2](1,3)adamantanometacyclophane exhibits similar chemical shifts for these hydrogen atoms (δ = −0.10/0.06). This allows to conclude that the change of conformation due to insertion of the substituents in **5a–c** relative to the unsubstituted parent compound is small (our examinations have shown that the influence of ring substituents on the shielding effect of the benzene ring is only small[3]). Furthermore, the calculated minimum-energy conformation[10] of **5c** is very similar to the crystal structure arrangement of this parent compound[1].



1



5c

Figure 1. Energy-minimized structure (AM1) of **5c**, P = pilot atom, A, B, C = descending priority of atoms in the chirality plane (bottom); energy-minimized structure of **1** (top)

The unsubstituted skeleton is conformationally rigid [no coalescence of the 10-H NMR signals at 126°C ($C_2D_2Cl_4$)[4]], the ring inversion barrier is ≥ 82 kJ/mol. Therefore, the racemization barrier of **5a–c** seems to be large enough to allow an enantiomer separation.

3. Enantiomer Separation and Experimental CD Spectrum of 5c

The enantiomers of **5c** are separated by application of a HPLC column filled with the chiral stationary phase cellulosetris(3,5-dimethylphenyl)carbamate (CDMPC)[11] [enantiomeric excess (ee) = 88%; eluent: *n*-hexane/2-propanol, 99.6:0.4]. The column is cooled to 0°C as no satisfying separation is obtained at room temperature. The retention times are 37.8 min for the dextrorotatory and 40.4 min for the laevorotatory enantiomer of **5c**. Figure 2 (bottom) shows the experimental circular dichroism of the two enantiomers of **5c** and the CD spectrum calculated for the Rp enantiomer (for a detailed discussion see Section 4.2).

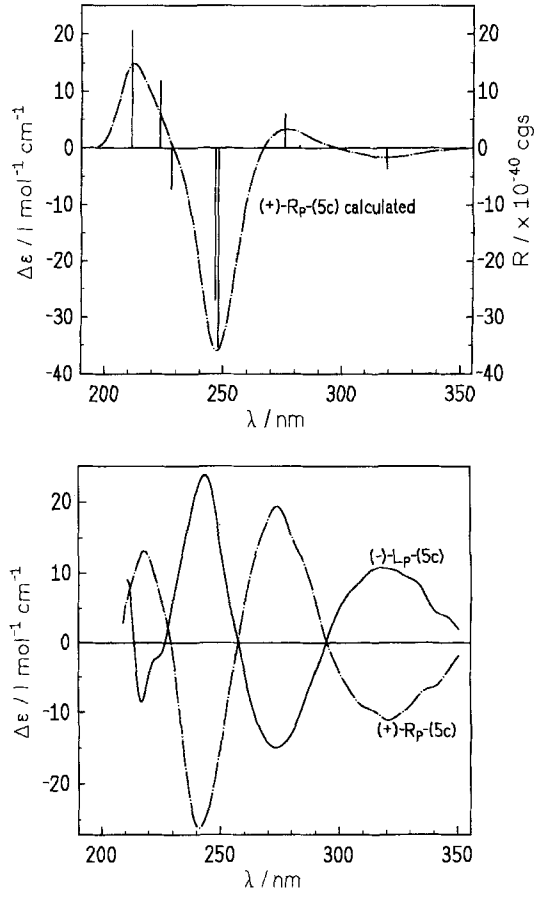


Figure 2. Experimental CD spectra of the two enantiomers of **5c** in hexafluoroisopropanol (spectropolarimeter JASCO J-720) (bottom); theoretically calculated CD spectrum of the (+)-Rp enantiomer of **5c** [obtained by summing rotatory strength-weighted (designated by sticks) Gaussian curves with Δ_{fwhm} = 0.3 eV for each calculated CD transition] (top)

4. Theoretical Results and Discussion of the UV and CD Spectra of 5c[10]

4.1 Geometry and Strain Energy

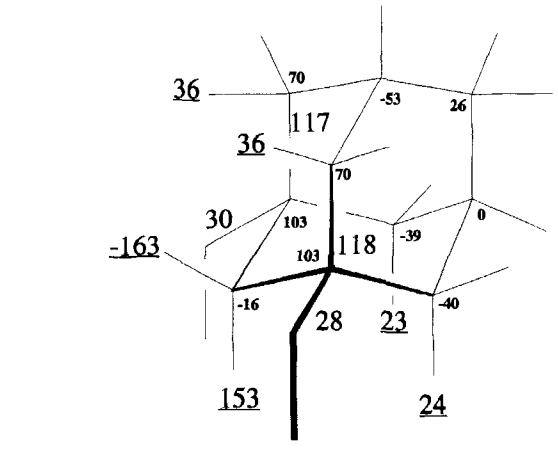
The most surprising features of the theoretically calculated geometry of **5c** are the strongly compressed (C-4/C-3/C-10, 100.6° and C-11/C-9/C-10, 100.6°) and opened (C-11/C-9/C-13, 117.5° and C-4/C-3/C-2, 117.5°) bond angles in the adamantane moiety which deviate by ≈ 10° from the tetrahedral angle of 109.5° (AM1 results[10a]). These distortions are induced by the close proximity of the intraannular adamantane methylene group (C-10) to the aromatic ring. X-ray data of the unsubstituted parent compound reveal

bond angles of 100.4 and 117.7° for the corresponding C–C–C bonds (average values from ref.[1]) that fit the theoretical AM1 data for **5c** nicely. The benzene ring has a boat-type-shaped geometry as in other para- or metacyclophane molecules. The characteristic deformation angles[6] at C-20 and C-17 are calculated to be 17.9 and 5.2°, respectively, in good agreement with the X ray data of the unsubstituted parent compound (14.3 and 6.5°). The tendency of the semiempirical NDDO methods to overestimate these deformation angles is known from calculations on [n]paracyclophanes[12] and [2.2]metacyclophanes[5].

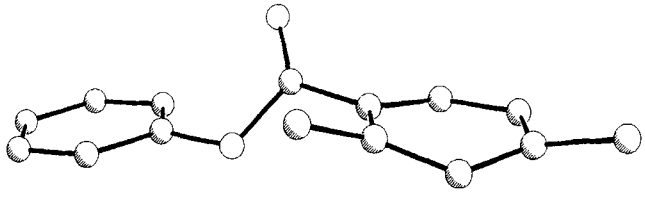
The plane of the carbonyl group of the phenyl ester moiety is twisted by −49° (dihedral angle Θ: O-22/C-21/C-16/C-15, see numbering scheme in Figure 1) out of the plane of the benzene ring. The AM1 calculations for phenyl 2,4-dimethylbenzoate (**1**) as an unstrained reference compound yield Θ = 7.9°. An explanation of this difference can be found in the fixed conformation of the CH_2CH_2 bridge in **5c** which interferes with the optimally planar (maximum conjugation of the π system) arrangement of the O=COPh group. In **1** a lower repulsive interaction between the O=CO moiety and the adjacent CH_3 group (the 14-H/O-23 distance in **5c** is only 243 pm) can be achieved since the methyl groups can rotate freely to obtain an optimal position. As will be shown in the next section the dihedral angle Θ exerts some significant effects on the sign and intensity of the nπ* CD band.

The total strain energy (E_s) of **5c** at the AM1 level of theory is found to be 115 kJ/mol. The contribution of the adamantane moiety to E_s is 71 kJ/mol. This is greater than the remaining contribution of the substituted benzene ring (44 kJ/mol). The 2:1 ratio is in qualitative agreement with the moderate deformation angles of the benzene ring and the strong distortion in the adamantane skeleton. To gain more insight into this fact we have investigated the energetic balances in the adamantane moiety of **5c** in more detail. For this purpose, E_s is further partitioned into contributions for individual bonds by the use of localized molecular orbitals and the total energy partitioning scheme, first introduced by England and Gordon[13]. Here the total energy of a molecular system in the Hartree-Fock approximation is attributed to chemically relevant units (bonds) so that each bond is assigned an energy (LBE, localized bond energy). The LBE values are compared to a reference compound (in this case 1,3-dimethyladamantane) to give a detailed insight into the origin of the total strain energy. The differences in the LBE values of the adamantane fragment in **5c** and unsubstituted 1,3-dimethyladamantane are given in Figure 3 (ΔLBE values; top). Positive values indicate that the bond is more stable in the relaxed 1,3-dimethyladamantane structure while the opposite is true for negative values.

The largest values (153 and −163 kJ/mol) are obtained for the CH_2 unit directed towards the benzene ring (C-10) where the equatorial C-H bond compensates the instability of the axial one. A strong decrease in the bond energies (ΔLBE = 117 and 118 kJ/mol) of **5c** is seen for the C-3/C-4 and C-9/C-11 bonds where the bond angles are strongly



5c



6

Figure 3. Localized bond energies in kJ/mol (ΔLBE, see text) for C–C and C–H bonds and ΣΔLBE values for C atoms in the adamantane skeleton of **5c**. (ΔLBE values for C–C bonds are written beside the bond axes, for C–H bonds at the end of the axes and underlined. ΣΔLBE values for C atoms are written smaller and located at the corresponding atom. Missing values are <10 kJ/mol) (top); **6** (**1** in the conformation calculated for **5c**) (bottom)

compressed. By adding all four ΔLBE values for a given carbon atom one sees that the strain energy is mainly concentrated at C-3, C-9, C-4, C-11 (ΣΔLBE = 103 and 70 kJ/mol respectively) while the contributions at the other carbon centers tend to oscillate along the cyclohexane units. Surprisingly, atom C-10 which is in closest proximity to the benzene ring shows a slight increase in bond energy (ΣΔLBE = −16 kJ/mol). This compares well with the quite "normal" bond angle C-3/C-10/C-9 of 111.3°. It is important to mention that the ΔLBE values do poorly correlate with differences in bond lengths, thus giving more detailed and direct information on the distribution of strain in a molecule.

4.2 UV and CD spectra

The basic chromophore of **5c** is composed of two (substituted) benzene π systems connected by the carboxyl group. Thus, at least two perturbed benzene-type-excited ππ* states for each ring (L_b, L_a in the nomenclature of Platt[14]) and one excited nπ* state of the carbonyl group are to be expected in the measured energy range (> 200 nm). Due to the (weak) conjugation and the donor-acceptor character (OPh vs. O=CPh) of the π systems an additional low-lying

charge-transfer band (CT) may exist. All these transitions are indeed found in our theoretical investigation and can be assigned to experimental CD bands.

Comparative calculations on **5c** and **1** have shown that the adamantane moiety in **5c** acts sterically but not electronically (see the preceding section). Therefore, it can be replaced by two methyl groups which cause a small red shift for the locally O=CPh excited states. This is demonstrated by the fact that calculations of **1** in the geometry of **5c** give nearly identical results for the theoretically calculated UV and CD data as compared to **5c** itself. Thus, the computational effort is reduced considerably. All the theoretical data presented for **5c** are therefore obtained with the model compound **6** (**1** in the geometry of **5c**, see Figure 3, below). However, it should be mentioned that the relaxed structure **1** shows significantly different excitation energies and transition moments both experimentally and theoretically (especially in the CD spectrum where several bands are inverted).

UV Spectrum of 5c

The agreement of the theoretical and experimental UV spectra is reasonable (see Table 1 and Figure 4) considering that solvent effects and our rigid-structure approximation (the barriers for rotation of the OPh group may be small) may introduce some systematic errors. The two lowest states of **1** are the localized L_b-type $\pi\pi^*$ states, followed by a weak UV absorption for the $n\pi^*$ state. Next come the two L_a-type $\pi\pi^*$ states, the CT band, which is weak in intensity due to small orbital overlaps, and two higher excited $\pi\pi^*$ states of the O=CPh fragment. This assignment based only on the UV absorption data (see Figure 4) is not unambiguous (the bands overlap strongly so that a detailed comparison of the calculated and experimental data seems difficult) but can be validated by the good agreement of the calculated and experimental CD data (see Figure 2).

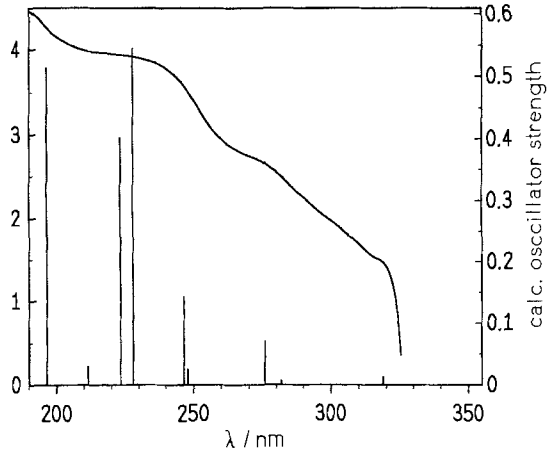


Figure 4. Experimental (solid line) and calculated (oscillator strengths for each transition designated by sticks) UV spectra of **5c**

Comparison of the calculated UV data (Table 1) of **1** and **5c** shows the effect of the deformation of the benzene ring connected with the adamantane moiety and of the twisting of the O=C−OPh group with respect to the other benzene ring. The deformation effects are demonstrated by a significant red shift (in **5c** with respect to **1**) of all localized $\pi\pi^*$ transitions in the O=CPh fragment while the corresponding OPh states are nearly unaffected. The twisting effects, on the other hand, are seen by the blue shift of the $n\pi^*$ and $\pi\pi^*$ (CT) transitions due to the decreased conjugation of the O=C group with the benzene ring in **5c**.

Table 1. Comparison of calculated and experimental vertical excitation energies ΔE[a] (in nm) and oscillator strengths (f) of **1** and **5c**. Experimental values (estimated band maxima in hexafluoro-2-propanol) are given in parentheses

1		5c		
ΔE	f	ΔE	f	Excited state
302 (290)	0.032	320 (320)	0.013	L_b (O=CPh)
282	0.006	282 (270)	0.007	L_b (OPh)
264	0.006	248 (248)	0.026	$n\pi^*$
263 (240-250)	0.180	276 (270)	0.072	L_a (O=CPh)
248	0.100	247 (240)	0.148	L_a (OPh)
223	0.061	211	0.030	$\pi\pi^*$ (O=CPh)
211 (210)	0.976	228 (210-230)	0.555	$\pi\pi^*$ (O=CPh)
208 (195)	0.606	223 (210-230)	0.409	$\pi\pi^*$ (O=CPh)

[a] The calculated ΔE values have been shifted by −0.7 eV to obtain agreement between the calculated and experimental data for the first band of **5c**.

CD Spectrum of 5c

The experimental CD spectrum of the (+)-conformer of **5c** in the range 210−350 nm (see Figure 2, bottom) shows four bands with alternating CD signs and similar intensities $|\Delta\varepsilon| = 10-20\ l\ mol^{-1}\ cm^{-1}$. The longest wavelength band is negative and is attributed to the first L_b state of the O=CPh fragment while the electric dipole moment for the L_b transition of the O−Ph group is too low to be observable in the CD spectrum. The calculated rotatory strengths (R values, in the following given in 10^{-40} cgs units) are a little bit too low compared to the other bands. This is due to the fact that these transitions, which are magnetically and electrically dipole-forbidden in benzene itself, borrow intensity from vibrational coupling which is absent in our theoretical investigation.

The second band is positive and originates from the L_a transition of the O=CPh group; it has opposite sign to the L_b band. The angle between the electric (μ) and the magnetic transition dipole moment vectors (m) is 84 (L_b) and 94 (L_a) degrees, respectively, which shows that the chiral perturbations due to the deformations, substituents, and twisting effects are small (for perpendicular μ and m the rotatory strength R vanishes) for these states. The strongest CD band (negative sign, maximum at approx. 240 nm) originates from the $n\pi^*$ and the L_a states of the *O*-substituted arene. In contrast to saturated carbonyl compounds with low rotatory strengths for the $n\pi^*$ transitions, the corresponding R value of **5c** (−35.4) is very large.

This can be explained by a more detailed symmetry analysis of the $n\pi^*$ state in an O=CPh environment. For a planar arrangement of the plane of the carbonyl group with respect to the benzene ring, the system has C_s symmetry with the $n\pi^*$ state being of A" character (Figure 5a). The

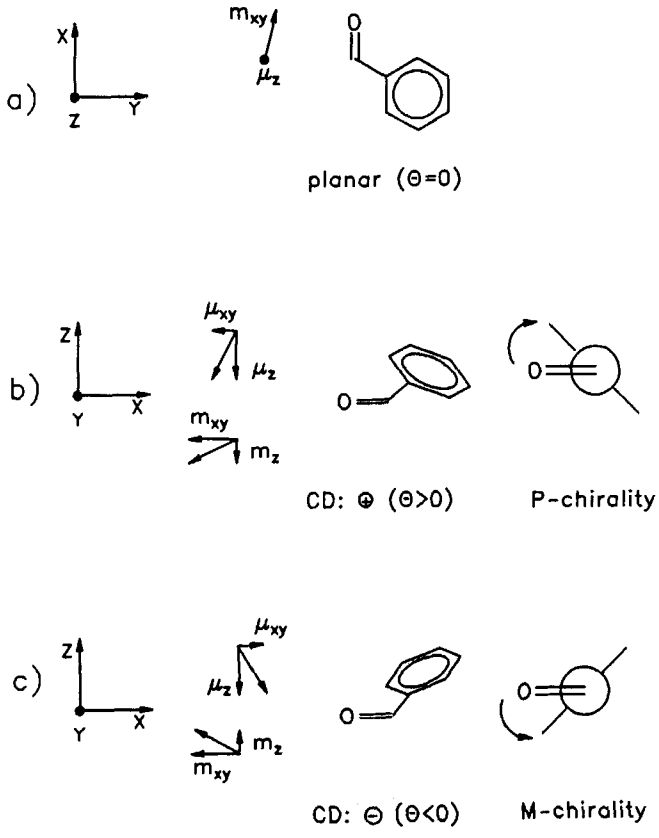


Figure 5. Schematic representation of the origin of the circular dichroism of a nπ* transition in an O=CPh fragment. μ and *m* are the electric and magnetic dipole transition moment vectors. For a detailed discussion see text. – a) planar arrangement with Θ = 0; m_z and μ_{xy} are zero. b) P-chiral twisting, c) M-chiral twisting

electric transition is then allowed in the *z* direction while the magnetic component is mainly aligned along the O=C axes (in the *xy* plane, the *z* component is zero) as in saturated carbonyl systems. Twisting of the benzene ring plane (Figure 5b and c) with respect to the carbonyl group results in a m_z contribution from A′ states (which have $m_z \neq 0$ in C_s), so that the total transition vectors become more parallel or antiparallel, depending on the sign of the twisting angle (the CD is positive for positive dihedral angles Θ). The second mechanism comes from the μ_{xy} components which gain intensity for greater twisting angles (the direction of μ_{xy} is inverted for the enantiomer), so that the combination with the allowed m_{xy} also gives a significant contribution to the rotatory strength.

With this simple rule the relative orientation of a carbonyl group with respect to a directly connected benzene ring can be determined from the sign of the corresponding nπ* CD band. This is also confirmed by the relaxed structure **1** for which Θ = 8.5° (−49° in **5c**) and $R(n\pi^*)$ = +4.5 (−35.4 for **5c**).

The fact that the third negative band in the CD spectrum is calculated to be too strong may be attributed to the large contribution of the L_a transition of the *O*-substituted arene, which may be averaged out to zero when nearly free rotation is reached at 298 K (the rotational barrier of the OH bond in phenol is only 14 kJ/mol[15]).

The last negative CD band in the high-energy region around 210 nm is assigned to the CT band and further ππ* transitions.

A comparison of the simulated and experimental CD spectrum of **5c** (see Figure 2) shows the predictive quality of the semiempirical NDDO/MRD-CI calculations. Based on these calculations with the structure of **5c** given above we can assign the absolute Rp configuration to the dextrorotatory enantiomer of **5c**.

In summary, our theoretical analysis of the CD spectrum of **5c** shows that its chirality originates mainly from:
a) the fixed conformation of the bridging methylene groups which induces the preferred orientation of the carbonyl group
b) the 2,4-substitution pattern (this aligns the μ vectors of the ππ* (O=CPh) transitions) and
c) the boat-type deformation of the benzene ring geometry which induces out-of-plane components of transition dipole moment vectors.

Table 2. Calculated vertical excitation energies ΔE[a] (in nm) and rotatory strengths *R* (in 10^{-40} cgs units[b]) of (+)-Rp-**5c**. Experimental ΔE values (in hexafluoro-2-propanol) are given in parentheses along with the experimental sign of the CD band

ΔE	R	Exp. CD-sign	Excited state
319 (320)	-3.6	-	L_b (O=CPh)
282 (270)	+0.4		L_b (OPh)
248 (240)	+6.0	+	L_a (O=CPh)
276 (270)	-35.4	-	*nπ**
247 (240)	-27.0	-	L_a (OPh)
211	-7.2		*ππ** (O=CPh)
228 (210-230)	+11.9	+	*ππ** (O=CPh)
223 (210-230)	+20.6	+	*ππ** (CT)

[a] The calculated ΔE values have been shifted by −0.7 eV to obtain agreement between the calculated and experimental data for the first band of **5c**. – [b] In cgs, *R* has units of esu cm erg/G. This corresponds to $3.336 \cdot 10^{-15}\ C^2\ s^{-1}\ m^3$.

5. Conclusion

These results show that a trustworthy calculation of chiroptical properties is no longer restricted to very small molecules[16] but can also be applied to macrocyclic compounds. Progress in computational chemistry now allows the assignment of absolute configurations to chiral cyclophanes[17,18] and other macrocyclic molecules. Application of this method can be a useful supplement to other methods for the determination of absolute configurations like the exciton chirality method[19] or methods based on the anomalous dipersion of X-radiation. In cases where these methods are not applicable the simulation of the CD spectra is an interesting alternative.

We thank the *Deutsche Forschungsgemeinschaft* for support (Sonderforschungsbereich 334, „Wechselwirkungen in Molekülen") and *G. Harder, F. Ott*, and *W. Schmidt* for recording the NMR spectra. We are also grateful to Dr. *G. Eckhardt* and Dr. *S. Schuth* for recording the mass spectra and to *D. Müller* for measuring the UV and CD spectra. S. G. thanks Prof. Dr. *S. D. Peyerimhoff* for helpful discussions.

Experimental

^1H and ^{13}C NMR: WM 250 (250 resp. 62.90 MHz) and AW 80 (80 MHz), Bruker Physik AG. – MS (EI, 70 eV): MS 50, A. E. I. – Melting points: Kofler Mikroskop-Heiztisch, Reichert. – Microanalyses: Mikroanalytische Abteilung des Instituts für Organische Chemie, Universität Bonn. – Column chromatography: Silica gel 60 (0.063–0.100 mm, Macherey, Nagel & Co., Düren). – Thin layer chromatography: Silica gel $60F_{254}$ (Merck). – Adamantane and 2,4-dimethylbenzoic acid: Janssen. – Denomination of the different groups of hydrogen atoms in the adamantane skeleton: H_a = methylene hydrogen atoms between the cyclophane bridges, H_b = methylene hydrogen atoms adjacent to the cyclophane bridges, H_c = methine hydrogen atoms, H_d = methylene hydrogen atoms between the methine groups.

Adamantane-1,3-dicarboxylic Acid[20]: 56 ml of HNO_3 (65%), 280 ml of oleum (65%), and 560 ml of conc. H_2SO_4 (in this order) were combined with intensive ice cooling and stirring. The mixture became very hot. After cooling to room temp., 30.00 g of adamantane (0.22 mol) was added, and the dropwise addition of 53 ml of conc. formic acid within 3 h was started **immediately** (otherwise, yields were poor). The brown reaction mixture was stirred for another hour and then carefully poured on 3 l of ice/water to give a white precipitate. After filtering off, the residue was washed with water until neutral and dissolved in a 10% sodium hydroxide solution. The solution was again filtered, and the filtrate was treated with 2 N HCl to precipitate the diacid. Intensive washing and drying furnished 35.1 g (156.7 mmol) of adamantane-1,3-dicarboxylic acid (yield 71%), m.p. 275°C. – ^1H NMR (80 MHz, [D$_6$]DMSO/$TMS_{int.}$): δ = 1.55–1.80 (m, 12H, H_a, H_b, H_d), 1.80–2.10 (m, 2H, H_c), altern. (s, 2H, CO_2H). – ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 27.39, 35.00, 37.6, 39.79, 39.92, 178.00. – MS, *m/z* (%): 224 (2) [M^+], 179 (100), 133 (49).

1,3-Bis(hydroxymethyl)adamantane[21]: 8.90 g (234.5 mmol) of $LiAlH_4$ was suspended in 120 ml of anhydrous tetrahydrofuran under argon, and the mixture was stirred and heated to reflux. A solution of 32.00 g (142.7 mmol) of adamantane-1,3-dicarboxylic acid in 550 ml of anhydrous THF was added dropwise within 2 h. After 2 h of additional stirring the mixture was cooled to room temp., and 20 ml of water and 250 ml of 2 N H_2SO_4 were added carefully. Addition of ether induced phase separation, the organic layer was separated, and the aqueous layer was extracted with ether. The combined organic phases were dried ($MgSO_4$), evaporation of the solvent afforded 27.5 g (140.1 mmol) of 1,3-bis(hydroxymethyl)adamantane (yield 98%), m.p. 182°C. – ^1H NMR (80 MHz, $CDCl_3/TMS_{int.}$): δ = 1.10 (m, 2H, H_a), 1.33 (m, 8H, H_b), 1.48 (s, 2H, H_d), 1.90 (m, 2H, H_c), 2.92 (d, 4H, $^3J_{HH}$ = 6 Hz, CH_2O), 4.25 (t, 2H, $^3J_{HH}$ = 6 Hz, OH). – ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 27.85, 34.68, 36.59, 38.79, 40.89, 71.74. – MS, *m/z* (%): 196 (4) [M^+], 179 (5), 165 (100), 147 (33), 105 (37). – $C_{12}H_{20}O_2$: calcd. 196.1458; found 196.1430 (MS).

1,3-Bis[(p-tolylsulfonyloxy)methyl]adamantane[22]: A solution of 5.00 g (25.5 mmol) of 1,3-bis(hydroxymethyl)adamantane in 60 ml of oxygen-free pyridine was cooled to 0°C and stirred under argon. After addition of 11.60 g (60.8 mmol) of *p*-toluenesulfonyl chloride the mixture was allowed to warm to room temp. and stirred for another 18 h. The reaction mixture was poured on 500 ml of ice/water and stirred for 2 h. The mixture was extracted with trichloromethane. Drying of the organic layer ($MgSO_4$) and evaporation of the solvent furnished 10.02 g (20.0 mmol) of 1,3-bis[(*p*-tolylsulfonyloxy)methyl]adamantane (yield 78%), m.p. 130–131°C (ethanol). R_f = 0.32 [trichloromethane/petroleum ether, b.p. 40–60°C, 3:1]. – ^1H NMR (80 MHz, $CDCl_3/TMS_{int.}$): δ = 1.2–2.3 (m, 14H, ada), 2.5 (s, 6H, CH_3), 3.6 (s, 4H, CH_2O), 7.3 (d, 4H, $^3J_{HH}$ = 8.5 Hz, H_{ar}), 7.8 (d, 4H, $^3J_{HH}$ = 8.5 Hz, H_{ar}). – ^{13}C NMR (22.64 MHz, $CDCl_3$): δ = 21.6, 27.5, 33.8, 35.8, 37.9, 39.7, 78.9, 127.9, 129.9, 132.9, 144.8. – MS, *m/z* (%): 504 (0.1) [M^+], 333 (30), 162 (33), 147 (100), 91 (86). – $C_{26}H_{32}S_2O_6$: calcd. 504.1640; found 504.1636 (MS). – (504.7): calcd. C 61.88, H 6.3; found C 61.74, H 6.49.

1,3-Bis(mercaptomethyl)adamantane (**3**): 15.00 g (29.8 mmol) of 1,3-bis[(*p*-tolylsulfonyloxy)methyl]adamantane[3] and 33.60 g (0.6 mol) of NaSH were suspended in 150 ml of oxygen-free ethyleneglycol monomethyl ether in a glas autoclave. The autoclave was closed carefully, the contents was heated to 170°C with vigorous stirring for 4 h. After cooling to room temp. the autoclave was opened and the contents acidified carefully with 2 N HCl. The reaction mixture was extracted several times with trichloromethane, the combined organic phases were washed with water and dried ($MgSO_4$). After evaporation of the solvent the residual crude oil was distilled under reduced pressure, b.p. of the obtained dithiol 190°C/0.6 Torr, yield 4.9 g (21.5 mmol, 72%), of a turbid oil. The dithiol was stable for several months at –40°C. R_f = 0.75 [trichloromethane/petroleum ether (40/60), 3:1], m.p. 26°C. – ^1H NMR (80 MHz, $CDCl_3/TMS_{int.}$): δ = 1.10 (t, 2H, $^3J_{HH}$ = 5.5 Hz, SH), 1.14–2.03 (m, 14H, ada), 2.35 (d, 4H, $^3J_{HH}$ = 5.5 Hz, CH_2SH). – ^{13}C-NMR (62.90 MHz, $CDCl_3$): δ = 28.8, 34.1, 36.1, 38.2, 40.4, 44.3. – MS, *m/z* (%): 228 (25) [M^+], 181 (100), 147 (54), 105 (36), 91 (35). – $C_{12}H_{20}S_2$: calcd. 228.1006; found 228.1013 (MS). – (248.4): calcd. C 63.10, H 8.83; found C 62.92, H 8.60.

Methyl 2,4-Bis(bromomethyl)benzoate (**2**): 11.12 g of *N*-bromosuccinimide (62.5 mmol) and a slight amount of AIBN were added to a solution of 5.00 g of methyl 2,4-dimethylbenzoate[23] (30.5 mmol) in 125 ml of tetrachloromethane. The reaction mixture was heated to reflux with irradiation with two 200-W bulbs for 2 h. After cooling the succinimide was filtered off and the solvent evaporated from the filtrate under reduced pressure. The resulting crude oil was treated with 150 ml of petroleum ether. The suspension was stirred, and trichloromethane was added dropwise until the oil had dissolved. The white solid that crystallized out at –40°C was recrystallized from petroleum ether (40/60) to afford 3.75 g (11.6 mmol) of **2** (38%). R_f = 0.4 [trichloromethane/petroleum ether (40/60), 1:1], m.p. 72°C. – ^1H NMR (80 MHz, $CDCl_3/TMS_{int.}$): δ = 3.85 (s, 3H, CO_2CH_3), 4.6 (s, 2H, CH_2), 4.8 (s, 2H, CH_2), 7.4–7.9 (m, 3H, H_{ar}). – MS, *m/z* (%): 322 (25) [M^+], 291 (12), 241/243 (100/96), 162 (76), 147 (32). – $C_{10}H_{10}Br_2O_2$: calcd. 321.9020; found 321.9016 (MS).

Methyl 2,15-Dithia[3.3](1,3)adamantanometacyclophane-18-carboxylate (**4a**): A solution of a pinch of a caesium carbonate[8a] in 1 l of ethanol was filled into a two-component dilution apparatus[8b] under argon, stirred and heated to reflux. Then a solution of 1.63 g of methyl 2,4-bis(bromomethyl)benzoate (**2**) (5.06 mmol) in 250 ml of benzene as well as a solution of 1.37 g (6 mmol) of 1,3-bis(mercaptomethyl)adamantane (**3**) and 706 mg (12.36 mmol) of potassium hydroxide in 240 ml of ethanol and 10 ml of water were synchronously added dropwise within 8 h (all solvents had to be oxygen-free). After 3 h of additional reflux the solvents were evaporated under reduced pressure. The residue was heated to reflux with 200 ml of trichloromethane and filtered. The filtrate was concentrated and the residue subjected to column chromatography to afford 0.54 g (1.4 mmol) of **4a** (28%), R_f = 0.54 [trichloromethane/petroleum ether (40/60), 3:1], m.p. 149°C. – ^1H NMR (250 MHz, $CDCl_3$): δ = 0.9–1.3 (br, 10H, H_a + H_b), 1.4 (m, 2H, H_d), 1.9 (m, 2H, H_c), 2.0–2.7 (br, 4H, SCH_2-ada), 3.72 (s, 4H, SCH_2-arene), 3.90 (s, 3H, CH_3), 6.97/7.73 (AX-system, 2H, $^3J_{HH}$ = 8 Hz,

H_{ar}), 7.63 (s, 1H, H_{ar}). – ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 28.85, 28.89, 33.4, 33.6, 34.9, 36.4, 37.6, 40.6, 40.9, 41.1, 43.7, 52.0, 52.1, 54.8, 128.1, 129.8, 131.5, 132.0, 136.1, 142.0, 167.7. – MS, *m/z* (%): 388 (100) [M^+], 356 (39), 191 (25), 162 (98). – $C_{22}H_{28}S_2O_2$: calcd. 388.1531; found 388.1536 (MS).

Methyl 2,15-Dithia[3.3](1,3)adamantanometacyclophane-18-carboxylate 2,2,15,15-Tetraoxide (**4b**): 350 mg (0.9 mmol) of **4a** was dissolved in 4 ml of glacial acetic acid and 1.5 ml of benzene at 80°C. Then 3.2 ml of hydrogen peroxide (35%) was added to the resulting solution, and the reaction mixture was heated to reflux for 5 h. The solution was cooled to 5°C and allowed to stand for 12 h. Filtration of the precipitated sulfone, intensive washing with water, and drying yielded 254 mg (0.56 mmol, 62%) of **4b**, m.p. >300°C. – ^1H NMR (250 MHz, [D$_6$]DMSO): δ = 0.7–1.1 (br, 1H, H_a), 1.1–1.5 (m, 9H, H_b + H_a), 1.7–2.1 (br, 4H, H_c + H_d), 2.7–3.1 (br, 3H, SO_2CH_2-ada), 3.3 (s, 2H, SO_2CH_2-arene), 3.85 (s, 3H, CH_3), 4.62 (s, 2H, SO_2CH_2-arene), 5.23 (m, 1H, SO_2CH_2-ada), 7.64 (d, 1H, $^3J_{HH}$ = 8.1 Hz, H_{ar}), 7.77 (s, 1H, H_{ar}), 7.96 (d, 1H, ^3J_H = 8.1 Hz, H_{ar}). – ^{13}C NMR (62.9 MHz, [D$_6$]DMSO): δ = 28.0, 32.7, 32.8, 35.2, 52.5, 61.7, 63.3, 65.2, 129.7, 131.0, 132.1, 133.2, 135.4, 161.7. – MS, *m/z* (%): 452 (17) [M^+], 388 (100), 358 (10), 324 (27), 162 (51). – $C_{22}H_{28}S_2O_6$: calcd. 452.1327; found 452.1335 (MS).

Methyl [2.2](1,3)Adamantanometacyclophane-16-carboxylate (**5a**): 230 mg (0.51 mmol) of the disulfone **4b** was divided into 3 portions. Each portion was pyrolyzed in an apparatus[7] consisting of a horizontal tube (10 mm in diameter) passing through two ring furnaces. The first provided a temperature that induced sublimation of the sulfone (280°C), the second was used at 500°C to assure pyrolysis. A vacuum pump was connected with the exit of the glass tube to reduce the pressure to 10^{-4}–10^{-5} Torr. Upon heating of the sulfone a turbid oil condensed behind the pyrolysis zone. The oil was dissolved in trichloromethane, and the solvent was evaporated from the solution under reduced pressure. The residue was subjected to column chromatography furnishing 105 mg (0.32 mmol, 63%) of **5a**, R_f = 0.71 [trichloromethane/petroleum ether (40/60), 3:1], m.p. 78–79°C. – ^1H NMR (250 MHz, $CDCl_3$): δ = −0.47/0.91 (AX system, 2H, $^2J_{HH}$ = 16 Hz, H_a), 0.8–1.1 (m, 2H, H_b), 1.30 (m, 6H, H_b), 1.35–1.50 (m, 2H, CH_2-ada), 1.55–1.62 (m, 2H, CH_2-ada), 1.9 (m, 1H, H_c), 2.2 (m, 1H, H_c), 2.25–2.42 (m, 2H, H_d), 2.63–2.75 (m, 1H, CH_2-arene), 2.88–3.16 (m, 2H, CH_2-arene), 3.65–3.79 (m, 1H, CH_2-arene), 3.88 (s, 3H, CO_2CH_3), 6.96 (d, $^3J_{HH}$ = 8 Hz, 1H, H_{ar}), 7.73 (d $^3J_{HH}$ = 8 Hz, 1H, H_{ar}), 7.79 (s, 1H, H_{ar}). – ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 29.3, 29.9, 32.12, 32.15, 32.2, 32.5, 37.8, 38.2, 38.8, 42.0, 42.7, 43.6, 49.0, 49.1, 51.8, 127.1, 127.9, 131.8, 131.9, 144.6, 147.9, 150.4, 168.1. – MS, *m/z* (%): 324 (53) [M^+], 292 (41), 265 (100), 149 (51), 105 (38). – $C_{22}H_{28}O_2$: calcd. 324.2089; found 324.2085 (MS).

[2.2](1,3)Adamantanometacyclophane-16-carboxylic Acid (**5b**): 94 mg (0.31 mmol) of **5a** and 61 mg (1.2 mmol) of potassium hydroxide were heated to reflux in 5 ml of water/ethanol (3:1) for 5 h. The bulk of the ethanol was evaporated under reduced pressure, and 10 ml of water was added to the residual solution. The mixture was cooled to 0°C and acidified to pH 1 with conc. hydrochloric acid. The resulting precipitate was filtered off, washed with water, and dried to give 82 mg (0.26 mmol, 85%) of **5b**, R_f = 0.83 (trichloromethane/methanol, 10:1), m.p. 94°C. – ^1H NMR (250 MHz, $CDCl_3$): δ = −0.42/1.05 (AX system, 2H, $^2J_{HH}$ = 16 Hz, H_a), 0.8–1.05 (m, 2H, H_b), 1.3 (m, 6H, H_b), 1.4–1.52 (m, 2H, CH_2-ada), 1.6 (m, 2H, CH_2-ada), 1.9 (m, 1H, H_c), 2.2 (m, 1H, H_c), 2.25–2.4 (m, 2H, H_d), 2.65–2.75 (m, 1H, CH_2-arene), 2.91–3.16 (m, 2H, CH_2-arene), 3.83–3.95 (m, 1H, CH_2-arene), 7.02 (d, $^3J_{HH}$ = 8 Hz, 1H, H_{ar}), 7.82 (s, 1H, H_{ar}), 7.90 (d, $^3J_{HH}$ = 8 Hz, 1H, H_{ar}). – ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 29.4, 30.2, 32.2, 32.3, 32.4, 32.6, 38.0, 38.3, 39.7, 42.3, 42.9, 44.3, 48.7, 48.8, 126.6, 127.2, 132.9, 145.3, 149.3, 151.9, 173.6. – MS, *m/z* (%): 310 (79) [M^+], 292 (40), 265 (93), 161 (79), 149 (100), 105 (70). – $C_{21}H_{26}O_2$: calcd. 310.1933, found 310.1930 (MS). – (310.4): calcd. C 81.25, H 8.44; found C 80.55, H 8.41.

Phenyl [2.2](1,3)Adamantanometacyclophane-16-carboxylate (**5c**): 30 mg of **5b** was dissolved in 2 ml of benzene at 45°C, and 100 ml of oxalyl chloride (145.5 mg, 1.14 mmol) and a drop of pyridine were added to the resulting solution. Additional 100 ml of oxalyl chloride was added after 24 h. After 48 h at 45°C the solvent was evaporated under reduced pressure, and the residue was dried at 0.1 Torr for 1 d. A solution of 40 mg of phenol (0.43 mmol) in 3 ml of benzene was added, and the reaction mixture was allowed to stirr at room temp. for 1 d. The solvent was again evaporated at reduced pressure, the residue was subjected to column chromatography yielding 21 mg (0.05 mmol, 52%) of **5c**, m.p. 119°C, R_f = 0.61 [dichloromethane/petroleum ether (40/60), 1:1]. – ^1H NMR (250 MHz, $CDCl_3$): δ = −0.35/1.06 (AX system, 2H, $^2J_{HH}$ = 14.8 Hz, H_a), 0.8–1.15 (m, 2H, H_b), 1.3 (m, 6H, H_b), 1.4–1.54 (m, 2H, CH_2-ada), 1.6 (m, 2H, CH_2-ada), 1.9 (m, 1H, H_c), 2.2 (m, 1H, H_c), 2.25–2.42 (m, 2H, H_d), 2.67–2.78 (m, 1H, CH_2-arene), 2.93–3.18 (m, 2H, CH_2-arene), 3.83–3.95 (m, 1H, CH_2-arene), 7.02 (d, $^3J_{HH}$ = 8 Hz, 1H, H_{ar}), 7.15–7.46 (m, 5H, CO_2Ph), 7.82 (s, 1H, H_{ar}), 7.90 (d, $^3J_{HH}$ = 8 Hz, 1H, H_{ar}). – MS, *m/z* (%): 386 (5) [M^+], 293 (100), 265 (11), 131 (10). – $C_{27}H_{30}O_6$: calcd. 386.2246; found 386.2260 (MS).

Enantiomer Separation of **5c** *by HPLC:* Column: Cellulosetris(3,5-dimethylphenyl)carbamate (CDMPC)[11], 500 × 4.6 mm, eluent *n*-Hexane/2-propanol (99.6:0.4). Eluate: A solution of **5c** in *n*-hexane/2-propanol (10:1), 1 mg/ml, flow rate 0.3 ml/min, 273 K, detection: UV, λ = 254 nm. t_R [(+)-**5c**] = 37.8 min, t_r [(−)-**5c**] = 40.4 min, $[\alpha]_D^{25}$ = [(+)-**5c**] = 85 (*c* = 0.02 in $CHCl_3$). – CD (hexafluoro-2-propanol, 25°C): Δε [(+)-**5c**]/1 mol^{-1} cm^{-1} (λ/nm) + 13 (220), 0 (229), −26 (240), 0 (257), +19 (270), 0 (294), −12 (320).

[1] F. Vögtle, J. Dohm, K. Rissanen, *Angew. Chem.* **1990**, *102*, 943–945; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 902–904; the crystal structure of [2.2](1,3)adamantanometacyclophane is described therein.

[2] R. Lemmerz, M. Nieger, F. Vögtle, *Chem. Commun.* **1993**, 1168–1170.

[3] R. Lemmerz, M. Nieger, F. Vögtle, *Chem. Ber.* **1994**, *127*, 1147–1155.

[4] J. Dohm, M. Nieger, K. Rissanen, F. Vögtle, *Chem. Ber.* **1991**, *124*, 915–921.

[5] S. Grimme, S. D. Peyerimhoff, S. Bartram, F. Vögtle, A. Brest, J. Hormes, *Chem. Phys. Lett.* **1993**, *213*, 32–40.

[6] F. Vögtle, *Cyclophane Chemistry*, Wiley, Chichester, **1993**; *Cyclophan-Chemie*, Teubner, Stuttgart, **1990**.

[7] J. Dohm, F. Vögtle, *Top. Curr. Chem.* **1992**, *161*, 69–107.

[8] [8a] A. Ostrowicki, E. Koepp, F. Vögtle, *Top. Curr. Chem.* **1991**, *161*, 37–67. – [8b] P. Knops, N. Sendhoff, H.-B. Mekelburger, F. Vögtle, *Top. Curr. Chem.* **1991**, *161*, 3–36.

[9] During the cyclization of **2** with **3** in benzene/ethanol the methyl ester function of the resulting **4** has in part (<10%) been transesterified to the corresponding ethyl ester. We have not separated these two esters because ester hydrolysis of **5a** to carboxylic acid **5b** has solved this problem without further efforts. Therefore, no microanalyses for the compounds **4a,b** and **5a** are available.

[10] Theoretical methods: All geometry optimizations with the AM1-Hamiltonian [10a] have been performed with a modified version of the MOPAC 6.0 program system[10b]. The calculations of UV and CD spectra have been carried out with a modified PM3[10c] parameter set which has been optimized for

the description of excited states of organic molecules (H,C,N,O parameters)[10d]. Our standard multireference singles/doubles configurational interaction (MRD-CI) calculation scheme [10e,f] has been used for the correlated wave functions by distributing 20 electrons of the highest occupied ground-state SCF molecular orbitals (MOs) in all available virtual MOs. This choice includes all of those orbitals (the five π and one lone-pair MOs in the occupied space) which are most important for the description of the first few valence excited states. A threshold of $T = 1\mu\ E_h$ has been used in the selection of spin-adapted configurations which yields CI-secular equation sizes of about 20000–25000 for the ten lowest roots. Oscillator and rotatory strengths have been calculated exactly on the orthogonalized AO basis with the length formalism as described in ref. [5]. Localized molecular orbitals (LMO) for the calculation of the localized bond energies (LBE)[13] have been obtained with the method of Pipek and Mezey [10g]. – [10a] M. J. S. Dewar, E. G. Zoebisch, E. F. Healy, J. J. P. Stewart, *J. Am. Chem. Soc.* **1985**, *107*, 3902. – [10b] J. J. P. Stewart, *QPCE Bull.* **1990**, *10*, 86. – [10c] J. J. P. Stewart, *J. Comp. Chem.* **1989**, *10*, 209. – [10d] R. Kluck, S. Grimme, unpublished. The parameters are available on request from one of the authors. – [10e] R. J. Buenker, S. D. Peyerimhoff, *Theor. Chim. Acta* **1974**, *35*, 33. – [10f] R. J. Buenker, S. D. Peyerimhoff, *Theor. Chim. Acta* **1974**, *35*, 17. – [10g] J. Pipek, P. G. Mezey, *J. Chem. Phys.* **1989**, *90*, 4916; **1975**, *39*, 217.

[11] J. Okamoto, R. Aburatani, K. Hatamo, K. Hatada, *J. Liq. Chromatogr.* **1988**, *11*, 2147; J. Okamoto, R. Aburatani, K. Hatamo, K. Hatada, *Chem. Lett.* **1989**, 715–718; cf.: H. Hopf, W. Grahn, D. G. Barrett, A. Gerdes, J. Hilmer, J. Hucker, Y. Okamoto, Y. Kaida, *Chem. Ber.* **1990**, *123*, 841–845.

[12] [12a] S. Grimme, *J. Am. Chem. Soc.* **1992**, *114*, 10542–10547. – [12b] J. Frank, S. Grimme, S. D. Peyerimhoff, *J. Am. Chem. Soc.*, accepted for publication.

[13] W. England, M. S. Gordon, *J. Am. Chem. Soc.* **1971**, *93*, 4649.

[14] J. R. Platt, *J. Chem. Phys.* **1949**, *17*, 484.

[15] E. Mathier, D. Welti, A. Bauder, Hs. H. Günthard, *J. Mol. Spectrosc.* **1971**, *31*, 63–67.

[16] M. Carnell, S. D. Peyerimhoff, A. Breest, K. H. Gödderz, P. Ochmann, J. Hormes, *Chem. Phys. Lett.* **1991**, *180*, 477–481; M. Carnell, S. Grimme, S. D. Peyerimhoff, *Chem. Phys.* **1994**, *179*, 385–394.

[17] V. Buss, M. Klein, *Chem. Ber.* **1988**, *121*, 89–93.

[18] G. Bringmann, K.-P. Gulden, H. Busse, J. Fleischhauer, B. Kramer, E. Zobel, *Tetrahedron* **1993**, *49*, 3305–3312.

[19] N. Harada, K. Nakanishi, *Circular Dichroism Spectroscopy – Exciton Coupling in Organic Stereochemistry*, University Science Books, Mill Valley, CA, **1993**, and Oxford University Press, Oxford, **1993**.

[20] L. N. Butenko, P. A. Protopopov, V. A. Derbisher, A. P. Khardin, *Synth. Commun.* **1984**, *14*, 113–116.

[21] S. Landa, Z. Kamycek, *Collect. Czech. Chem. Commun.* **1959**, *24*, 1320–1323.

[22] J. Dohm, PhD Thesis, University of Bonn, **1990**.

[23] F. Vögtle, J. Grütze, R. Nätscher, W. Wieder, E. Weber, R. Grün, *Chem. Ber.* **1975**, *108*, 1694–1711.

[160/94]