The First Internally Functionalized Chiral [2.2]Metacyclophanes

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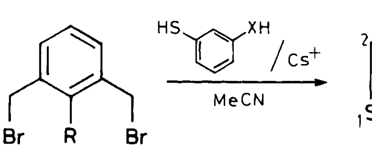
The new medium membered heterocycles (2c—i), additionally strained due to internal substituents, could be obtained after optimization of a simple one-step cyclisation reaction; the barrier of the restricted rotations of the phenyl ring in (2h) and of the t-butyl group in (2i) were measured; the *X*-ray, NMR, and CD data of the stable enantiomers of (2c—i) are compared with those of the less strained parent skeleton (2a).

Helical dihetero[2.2]cyclophanes substituted in 1,10-positions with sulphur and oxygen (**2a**) or nitrogen (**2b**) are known since 1984[1] and are compounds exhibiting interesting chiroptical properties due to their propeller-shaped molecular skeleton. Applying a one-step cyclisation technique,[2] we were able to obtain intra-annularly functionalized helical [2.2]phanes (**2c—i**). Such rigid and highly strained compounds with large substituents inside the 10-membered ring[3] like t-butyl (**2i**),[4] phenyl (**2h**),[5] or CO_2Me (**2f**) are interesting due to the influence of strong through-space interactions and the distortion of the aromatic chromophores affecting the chiroptical properties[6] (Scheme 1).

After many attempts, we were able to obtain (**2c—i**) in remarkably good yields, despite the high strain of the ring-system. The synthesis was achieved *via* a simple one-step reaction by cyclisation of the bromomethyl compounds (**1c—i**)[4,7] with 1-(toluene-*p*-sulphonyl)amino-3-benzenethiol under application of the 'caesium-effect' and under conditions of high dilution (2C-DP-apparatus),[8] using acetonitrile as the preferred solvent[2] (Table 1). The yields of the phanes (**2c—e**) obtained by using the improved method exceed those we reported previously for (**2b**)[1] and decrease, as expected, with growing size of the inner substitutuent R.

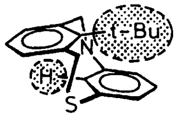
For compounds (**2d**) and (**2f**) the *anti*-conformations of the aromatic rings could be proven by *X*-ray analysis (Figures 1 and 2).† Due to the *anti*-conformation, strong high-field shifts of the intra-annular hydrogen atom H_i (Table 1) are found in the ^{1}H NMR spectra. The increase of the high-field shifts of H_i is dependent on the growing size of the internal substituent forcing the H_i into the π-cloud of the opposite benzene ring [Scheme 2, (**2i**)]. Compound (**2i**) so far exhibits the highest field ^{1}H NMR absorption of an aromatic proton in this sequence of compounds. Surprisingly,[4] restricted rotation of the t-butyl substituent is found: ^{1}H NMR measurements at −70 °C (400 MHz) revealed a characteristic broadening of the singlet of the t-butyl group, whereas other signals remain sharp.



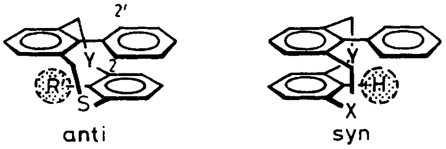
(1) (2)

a; X = O, R = H
b; X = NTos, R = H
c; X = NTos, R = Me
d; X = NTos, R = OMe
e; X = NTos, R = SMe
f; X = NTos, R = CO_2Me
g; X = NTos, R = SO_2Me
h; X = NTos, R = Ph
i; X = NTos, R = Bu^t

Scheme 1



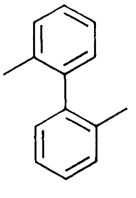
(2i)



anti
A

syn
B

(2h) X = S, Y = NTos, R′ = H
(3a) X, Y = CH_2, R′ = H
(3b) X, Y = CH_2, R′ = Me



(4)

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† *Crystal data* for (**2d**): $C_{22}H_{21}NO_3S_2$, M = 411.5, triclinic, a = 7.261(1), b = 9.791(3), c = 14.857(4) Å, α = 94.55(2), β = 99.19(3), γ = 101.37(2)°, U = 1.015 nm^3, D_c = 1.345 g cm^{-3}, space group $P\bar{1}$, colourless crystals, dimensions 0.4 × 0.3 × 0.6 mm^3, $\mu(\text{Mo-}K_\alpha)$ = 2.7 cm^{-1}, 4871 reflections with $|F| > 4\sigma(F)$ were used for the structure solution (direct methods, Enraf-Nonius SDP[13]) and refinement (253 parameters, Enraf-Nonius SDP[11]), non-hydrogen atoms were refined anisotropically, H-atoms using a 'riding'-model, R = 0.045. (**2f**): $C_{23}H_{21}NO_4S_2$, M = 439.5, triclinic, a = 8.783(1), b = 10.820(1), c = 12.746(1) Å, α = 113.92(1), β = 100.08(1), γ = 97.93(1)°, U = 1.060 nm^3, Z = 2, D_c = 1.377 g cm^{-3}, $\mu(\text{Mo-K}_\alpha)$ = 2.34 cm^{-1}, space group $P\bar{1}$, colourless crystals, dimensions 0.45 × 0.53 × 0.61 mm^3, 4563 symmetry independent reflections were measured ($2\theta_{max}$ = 56.0°), from which 3731 reflections with $|F| > 4\sigma(F)$ were used for structure solution (direct methods, SHELXS 86[14]) and refinement (full-matrix least-squares, 272 parameters, SHELX 76[15]). Non-hydrogen atoms were refined anisotropically, hydrogen atoms using a 'riding'-model and a common isotropical temperature factor, R = 0.052. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

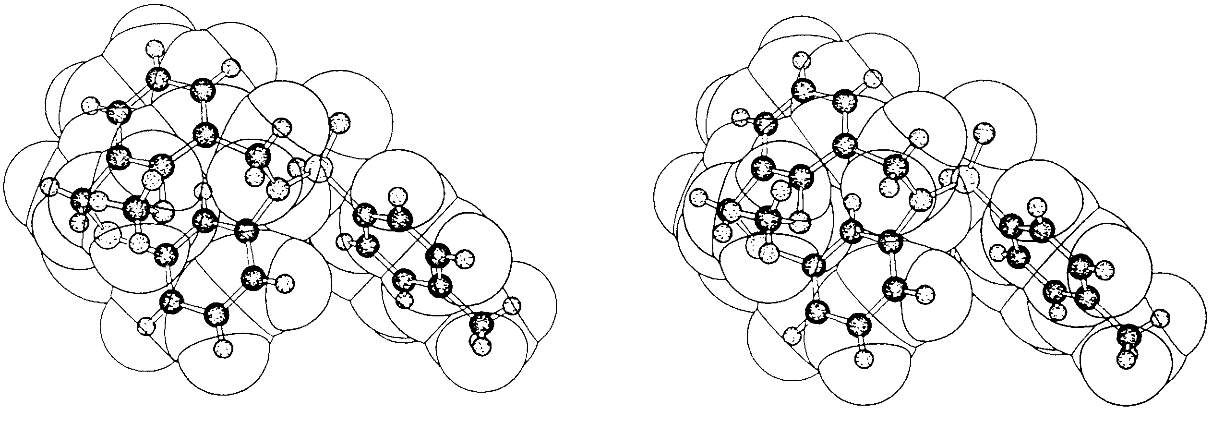

Figure 1. Crystal structure of (**2d**) (stereo view); angles α to δ, *cf.* Table 2.

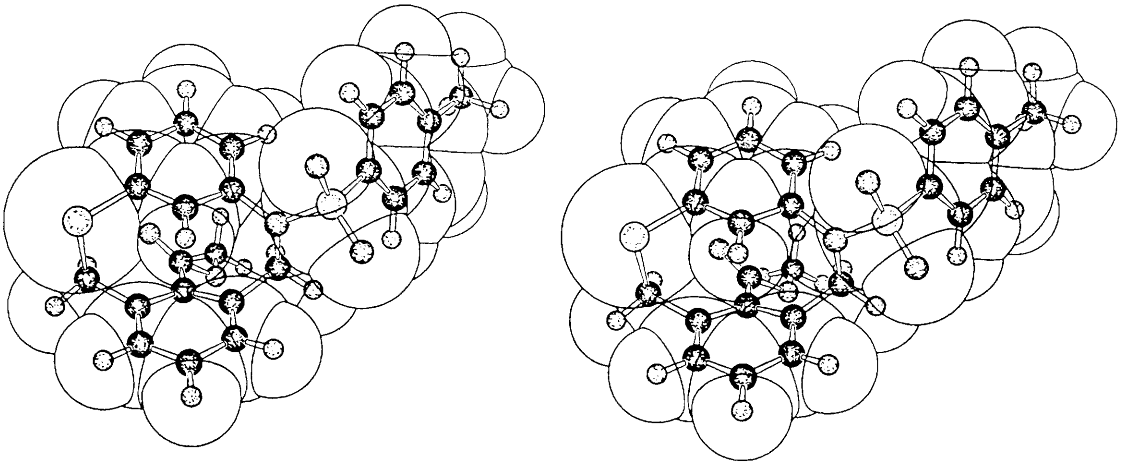

Figure 2. Crystal structure of (**2f**) (stereo view); angles α to δ, *cf.* Table 2.

Table 1. Comparison of the yields and ^1H NMR data of the inner hydrogens H_i and inner methyl groups of the [2.2]phanes (**2c**) to (**2i**) [X = NTos (Tos = *p*-$OSO_2C_6H_4Me$)] and (**2b**).

	R	Yield /%	δ H_i	δ Me
(**2b**)	H	77[2]	4.57, 4.76[1]	—
(**2c**)	Me	27	4.13	0.63
(**2d**)	OMe	21	4.54	3.05
(**2e**)	SMe	22	4.23	1.73
(**2f**)	CO_2Me	5.5	4.18	3.38
(**2g**)	SO_2Me	0.7	4.41	3.39
(**2h**)	Ph	2.5	3.93	—
(**2i**)	Bu^t	2.7	3.75	0.74

Table 2. Comparison of characteristic structural data of (**2b**), (**2d**) and (**2f**), for a definition of angles α—δ *cf.*[1]

	d/pm	α/°	β/°	γ/°	δ/°
(**2b**)[1]	257	2.4	4.9	6.9	5.4
(**2d**)	268	5.45	4.01	6.77	5.78
(**2f**)	272	15.65	4.92	3.63	15.1

For R = phenyl (**2h**) a differentiation between *anti*- and *syn*-conformation [Scheme 2, (**2h**), **A** and **B**] based on the H_i-shifts is not possible, because in both cases the inner hydrogens would be pointing into the cavity of the opposite π-cloud. An assignment of the *anti*-conformation (**2h**) **A** could be proven by the ^1H NMR high-field shifts of the 2,2′-protons of the biphenyl system which appear as broad singlets at δ 5.33 and 6.49, the broadening of the signals pointing to a hindered rotation of the inner phenyl ring. We were able to determine the barrier of hindered rotation by variable temperature NMR[9] as 63.9 kJ mol^{-1}, a value between those found for (**3a**) ($\Delta G^{\ddagger}$ = 43.5 kJ mol^{-1}),[5a] (**3b**) ($\Delta G^{\ddagger}$ = 54 kJ mol^{-1}),[5b] and (**4**) ($\Delta G^{\ddagger}$ = 78.5 kJ mol^{-1}),[10] showing the sensitivity of the barrier to the geometry of the skeleton (Scheme 1). The *X*-ray analyses of both compounds (**2d**) and (**2f**) ascertain the

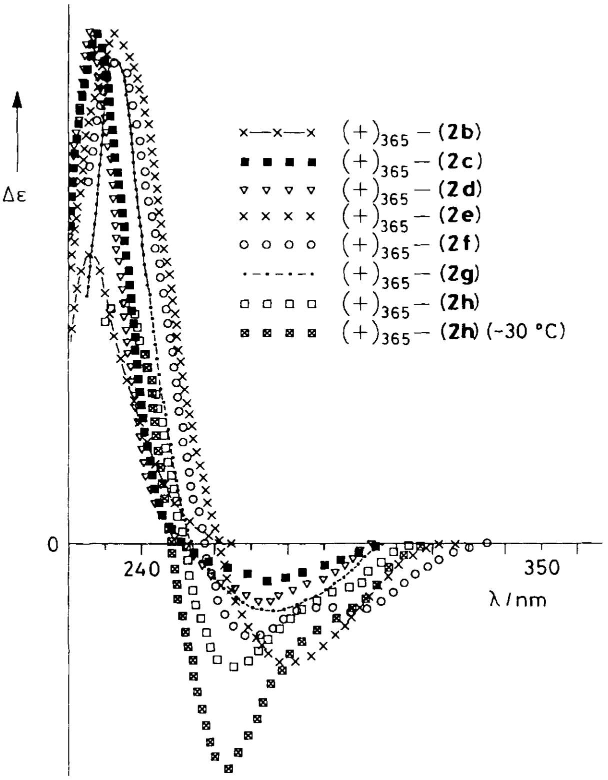

Figure 3. CD spectra of (**2c—d**), compared to (**2b**). (**2c**): $\Delta\varepsilon_{227} = +60.8$, $\Delta\varepsilon_{276} = -4.7$; (**2d**): $\Delta\varepsilon_{227} = +80.4$, $\Delta\varepsilon_{276} = -6.5$, $\Delta\varepsilon_{291} = -4.0$; (**2e**): $\Delta\varepsilon_{232} = +31.2$, $\Delta\varepsilon_{278} = -7.7$; (**2d**): $\Delta\varepsilon_{232} = +23.5$, $\Delta\varepsilon_{270} = -4.4$, $\Delta\varepsilon_{295} = -3.2$; (**2e**): $\Delta\varepsilon_{232} = +23.4$, $\Delta\varepsilon_{276} = -3.2$; (**2f**): $\Delta\varepsilon_{235} = +11.5$, $\Delta\varepsilon_{265} = -5.9$, $\Delta\varepsilon_{295} = -1.8$.

anti-conformation; with increasing size of the inner substituent, the distance, *d*, of C(8)–C(16) rises and the values for the angles α to δ, describing the helical torsion of the phane-ring system,[1] increase (Table 2).

The torsional angle of the carbonyl-group in (**2f**) towards the plane of the aromatic ring C(3,4,6,7) is 41°, a value similar to the out-of-plane torsion found earlier for the nitro-group (45°) in the less strained skeleton of 8-nitro-1,10-dithia[2.2]metacyclophane [(**2**) X = S, R = NO_2].[11]

The separation of enrichment of the enantiomers of the new chiral compounds (**2c—i**) was successfully accomplished using HPLC and (+)-PTrMA ('Okamoto-resin')[12] as stationary phase. All enantiomers are stable at room-temperature,[1,6] no racemisation could be observed by heating to 175 °C (n-butanol, sealed capillary tube), at higher temperatures decomposition of the phanes takes place.

The CD spectra of (**2c—h**) compared with (**2b**)[1] (Figure 3) show similar structures. If R ≠ H one or more (**2d, f** and **h**) additional negative Cotton effects in the region of 270 to 300 nm are observed, followed by strong positive Cotton effects at shorter wavelengths (230 nm). For R = Phe (**2h**) an interesting temperature-dependency of the negative Cotton effect at 265 nm is observed: by lowering the temperature we found a strong increase in intensity from $\Delta\varepsilon_{265} = -5.86$ (room temp.) to $\Delta\varepsilon_{265} = -10.75$ (−30 °C). We explain this by effects on the conjugation of the biphenyl system caused by freezing in the phenyl rotation. Interestingly no influence of temperature on the other Cotton effects is observed.

Nevertheless these new compounds challenge theoreticians as well as preparative chemists because of their simple and rigid skeletons which can be easily varied in a controlled manner by introduction of different substituents. Further challenges are the maximum degree of steric strain achievable by introduction of large substituents and possible applications of related compounds as chiral auxiliaries.

We are obliged to the 'Deutsche Forschungsgemeinschaft' for financial support (Sonderforschungsbereich 334). We thank Prof. Y. Okamoto (Osaka) and Prof. K.-H. Büchel (Bayer AG) for generous gifts of PTrMA and Dr. J. Peter-Katalinić for recording the FAB mass spectra.

Received, 28th June 1989; Com. 9/02750E

References

1 K. Meurer, F. Vögtle, A. Mannschreck, G. Stühler, H. Puff, and A. Roloff, *J. Org. Chem.*, 1984, **49**, 3484.
2 A. Ostrowicki and F. Vögtle, *Synthesis*, 1988, 1003.
3 F. Vögtle, W. Wieder, and H. Förster, *Tetrahedron Lett.*, 1974, 4361; F. Vögtle and R. Nätscher, *Chem. Ber.*, 1976, **109**, 994; W. Wieder, R. Nätscher, and F. Vögtle, *Liebigs Ann. Chem.*, 1976, 924; F. Vögtle and K. Böckmann, *Chem. Ber.*, 1979, **112**, 1400; M. Tashiro and T. Yamato, *J. Org. Chem.*, 1981, **46**, 1543; M. Tashiro, K. Koya, and T. Yamato, *J. Am. Chem. Soc.*, 1982, **104**, 3707; M. Tashiro and T. Yamato, *J. Org. Chem.*, 1985, **50**, 2939; Y.-L. Mao and V. Boekelheide, *ibid.*, 1980, **45**, 2746.
4 R. H. Mitchell, K. S. Weerawarna, and G. Bushnell, *Tetrahedron Lett.*, 1984, 907.
5 (a) K. Böckmann and F. Vogtle, *Chem. Ber.*, 1981, **114**, 1048; 1981, **114**, 1065; F. Vögtle and B. Klieser, *Synthesis*, 1982, 294; (b) R. H. Mitchell, in 'Cyclophanes,' eds. P. M. Keehn and B. Klieser, Academic Press, New York, 1983; R. Mitchell and W. Anker, *Tetrahedron Lett.*, 1981, 5135; W. Anker, K. A. Beveridge, G. W. Bushnell, and R. H. Mitchell, *Can. J. Chem.*, 1984, **62**, 661.
6 K. J. Przybilla, F. Vögtle, M. Nieger, and S. Franken, *Angew. Chem.*, 1988, **100**, 987; *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 976; F. Vögtle, K. J. Przybilla, A. Mannschreck, N. Pustet, P. Büllesbach, H. Reuter, and H. Puff, *Chem. Ber.*, 1988, **121**, 823; S. Billen and F. Vögtle, *Chem. Ber.*, in the press; F. Vögtle, K. Mittelbach, J. Struck, and M. Nieger, *J. Chem. Soc., Chem. Commun.*, 1989, 65; V. Buss and M. Klein, *Chem. Ber.*, 1988, **121**, 89.
7 F. Vögtle, J. Grütze, R. Nätscher, W. Wieder, E. Weber, and R. Grün, *Chem. Ber.*, 1975, **108**, 1694.
8 F. Vögtle, *Chem. Ind.* (*London*), 1972, 346.
9 H. S. Gutowsky and C. H. Holm, *J. Chem. Phys.*, 1956, **25**, 1228.
10 W. Theilacker and H. Böhm, *Angew. Chem.*, 1967, **79**, 232; *Angew. Chem., Int. Ed. Engl.*, 1967, **6**, 251.
11 S. Kiryu and W. Nowacki, *Z. Kristallogr. Kristallgeom., Kristallphys., Kristallchem.*, 1975, **142**, 108.
12 Y. Okamoto, S. Honda, I. Okamoto, H. Yuki, S. Murata, R. Noyori, and H. Takaya, *J. Am. Chem. Soc.*, 1981, **103**, 6971.
13 Enraf-Nonius, *Structure Determination Package*, Delft 1985.
14 G. M. Sheldrick, 'Program for crystal structure determination,' Göttingen, 1986.
15 G. M. Sheldrick, 'Program for crystal structure determination,' Cambridge, 1976.