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The Absolute Chirality of (+)-12-Bromo-[2.2]metacyclophane-4-carbonitrile[1]

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The absolute configuration of (+)-12-bromo-[2.2]metacyclophane-4-carbonitril [(+)-**4e**] was determined by the *Bijvoet* X-ray diffraction method as $(R)_p$ (Fig. 1). This result allows the unambiguous assignment of the absolute chiralities of all optically active 4-monosubstituted, 4,14-homodisubstituted, 4,12- and 4,14-heterodisubstituted [2.2]metacyclophanes chemically correlated with (+)-**4e**. The result is compared with those obtained by other methods for establishing the absolute configuration.

(Keywords: Bijvoet X-ray diffraction method; Circular dichroism; Exciton model; Kinetic resolution)

Die absolute Chiralität von (+)-12-Brom-[2.2]metacyclophan-4-carbonitril[1]

Die absolute Konfiguration von (+)-12-Brom-[2.2]metacyclophan-4-carbonitril [(+)-**4e**] wurde mit Hilfe der anomalen Röntgenbeugung (*Bijvoet*-Methode) als $(R)_p$ (Fig. 1) ermittelt. Damit sind auch die Konfigurationen aller optisch aktiven 4-monosubstituierten, 4,14-homodisubstituierten sowie der 4,12- und 4,14-heterodisubstituierten [2.2]Metacyclophane bekannt, die mit (+)-**4e** eindeutig chemisch korreliert sind. Dieses Ergebnis wird mit jenen verglichen, die mit Hilfe anderer Methoden zur Konfigurationsermittlung erhalten wurden.

Introduction

[2.2]Metacyclophanes are of increasing importance as vehicles in stereochemical and conformational studies (cf.[2–5] and references cited therein). In this context we have described the syntheses, optical

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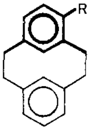
resolution and enantiomeric purities of a variety of chiral [2.2]metacyclophanes with various substitution patterns belonging to the point groups C_1 and C_2, resp.[1, 2, 6, 7]. A tentative proposal as to the absolute configuration was based on the result of the kinetic resolution of the anhydride of (±)-[2.2]metacyclophane-4-carboxylic acid (**1f**) with (—)(S)-phenethylamine[6] and subsequently from the circular dichroism (CD) spectra[4]. These results led to the configuration $(S)_p$ for (—)-**1f**.

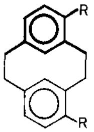
Kinetic resolutions had been successfully employed to carboxylic acids of systems with related topology, such as ferrocene, benchrotrene, cymantrene, [2.2]paracyclophane, [10]paracyclophane, methano[10]annulene and dihydroethanoanthracene[8]. For the metallocenes and [2.2]paracyclophane the absolute configuration derived from these results had subsequently been confirmed by the X-ray diffraction method[9].

We report now the absolute chirality of the title compound (+)-**4e** established by the *Bijvoet* method. The knowledge of the configuration of this key compound **4e** renders possible the unambiguous configurational assignment of all optically active [2.2]metacyclophanes which had been previously correlated with (+)-**4e** (see Table 1).

Table 1. *Absolute configurations of mono- and disubstituted [2.2]metacyclophanes*



1



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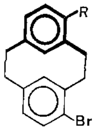

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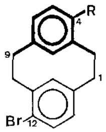

4

1	2	*R*	3	4
(—)-**a**	(—)-**a**	CH_3	—	—
(—)-**b**	(—)-**b**	CH_2OH	—	—
(+)-**c**	(+)-**c**	CH_2Br	—	—
(—)-**d**	(—)-**d**	CHO	—	—
(—)-**e**	(+)-**e**	$COCH_3$	—	—
(+)-**f**	(—)-**f**	COOH	(+)-**a**	(—)-**a**
(—)-**g**	(—)-**g**	COO^-	(+)-**b**	(—)-**b**
(+)-**h**	(+)-**h**	$COOCH_3$	(+)-**c**	(—)-**c**
(—)-**i**	(—)-**i**	$CONH_2$	(+)-**d**	(—)-**d**
(+)-**j**	(+)-**j**	CN	(+)-**e**	(+)-**e**

Materials and Methods

Optically pure (+)-**4e** was prepared as described in ref.[2]. The sample was characterized by its mp. (175–177 °C), rotation ($[\alpha]_D^{20}$ + 9° in ethanol) and mass spectrum (*m*/e 313, 311). The CD-spectrum was recorded at 20 ± 0.1 °C with the dichrograph Mark III (*Jobin-Yvon*) in ethanol using cyclindrical quartz cuvettes of variable path lengths (0.1-1.0 cm). $\Delta\varepsilon$ (λ, nm): +23 (202), —21 (216), +6.3 (255), —0.56 (297), cf. Fig. 2.

Crystals for the X-ray analysis were obtained by slow evaporation of an ether solution at room temperature.

The following crystal data were obtained:
monoclinic, space group $P2_1$
$a = 13.635\,(2)$ $b = 7.899\,(1)$ $c = 6.345\,(1)$ Å
$\beta = 94.18\,(1)^\circ$ $D = 1.52\,\mathrm{g \cdot cm^{-3}}$ $(Z = 2)$

4,706 reflections were measured with a STOE Four-circle diffractometer.

Averaging equivalent reflections yielded 2 411 symmetry independent reflections, of which 2 272 were employed for the refinement. The final weighted R-factor amounted to 2.45%. All crystallographic calculations were performed with the program SHELX*, modified for use at a small computer.

Results and Discussion

The geometry of the skeleton of (+)-**4e** closely resembles that of achiral [2.2]metacyclophanes. Thus the distortions of the single and double bonds (cf. Fig. 1) are very similar to [2.2]metacyclophane[10, 11] itself, its 8,16-dimethyl[12]-, 8,16-dibromomethyl[13]- and 8,16-difluoroderivative[14] as well as to related tribenzaspirophanes[11]. As in those compounds the distortions observed in (+)-**4e** are due to a steric compression of the intraanular positions 8 and 16 forcing the benzene rings into a boat like conformation. The rather insignificant differences in the geometric parameters of **4e** as compared with [2.2]metacyclophane are in agreement with earlier findings, showing that the deviations from the C_{2h}-symmetry of the parent hydrocarbon by substitution in the extraanular aromatic positions ought to be very small[2].

A comparison of the R-factors obtained for the possible configurations**(6.1 and 3.6%, resp.) of **4e** ascribed the configuration as shown in Fig. 1C** to the dextrorotatory enantiomer (+)-**4e**.

Thus, according to previous correlations with other 4,12-heterodisubstituted (**4a**-**4d**)[2], with 4,14-heterodisubstituted (**3a**-**3e**)[1], with 4,14-homodisubstituted (**2a**-**2j**)[1] and especially with 4-monosubstituted[2.2]metacyclophanes (**1a**-**1j**)[6] the absolute configurations as listed in Table **1** result.

This assignment of the absolute configurations of mono- and disubstituted [2.2]metacyclophanes by correlation with the key compound (+)-**4e** is much more straightforward than the recent laborious

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* *G. M. Sheldrick*, Cambridge 1976, private communication.

** According to Ref.[15] C-9 (see Table **1**) is the "pilot atom" responsible for the orientation of the molecule in applying the (R)(S) nomenclature for planar chiral compounds. Accordingly, (+)-**4e** has the configuration $(R)_p$.

deduction of the absolute configuration of 4-methyl-[2.2]metacyclophane (**1a**)[16] from the 1-oxo-derivative[17] and avoids any assumption. The result reported in[16]—$(R)_p$ for (+)-**1a**—is based on the—albeit very plausible—assumption that methyl has no influence on the sign of the carbonyl *Cotton* effect.

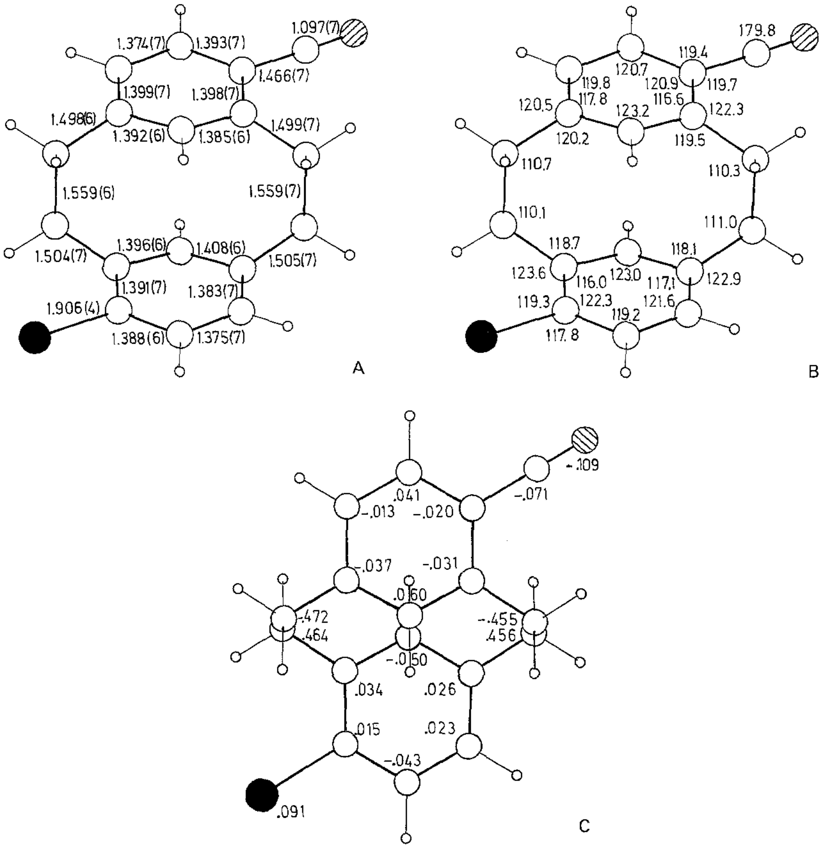

Fig. 1. Structure of (+)-12-bromo-[2.2]metacyclophane-4-carbonitrile (**4e**), ● = Br; ▨ = N. *A* Bond lengths (Å), *B* Bond angles, *C* Deviations of atom (Å) from the best planes of the benzene rings

It seemed of interest to compare the configuration derived from the unambiguous X-ray diffraction with the results gained by means of other methods. The method of kinetic resolution[6] obviously failed in the case of the [2.2]metacyclophane system. As mentioned above this method had given good results in several other cases, especially for [2.2]paracyclophane-carboxylic acid[9].

At the present it is not clear whether the failure of this method is due only to the special topology of the [2.2]metacyclophane system where the difference between "above" and "beneath" for a substrate approaching the 4-position on which this method is based, is not so pronounced as for instance in [2.2]paracyclophane. It should be emphasized in this context, however, that only the *relative* configurations of the metacyclophanes were relevant for the studies as described in refs.[1,2,4,6]. The conclusions drawn are *independent* from the *absolute* configuration.

A further method for the assignment of the absolute configuration of bichromophoric systems is based on the application of the coupled oscillator model[18]. However, in analogy to the 4-monosubstituted [2.2]metacyclophanes[4] studied so far (**1a**–**1j**) no bisignate *Cotton* effect is observed either in the ^1L_b- nor in the ^1L_a-transition region of the CD spectrum of (+)-**4e** (Fig. 2), indicating that the electronic interactions between the two aromatic moieties in **4e** are weak. Accordingly, a band splitting of the ^1L_a-*Cotton* effect will occur only in the CD spectra of derivatives where both aromatic rings carry substituents with large spectroscopic moments[4]. Thus—and since the molecule exhibits C_1-symmetry—the point dipole approximation cannot be applied to (+)-**4e**. For this purpose, a derivative like (+)-**2h** with two methoxycarbonyl ligands was chosen.

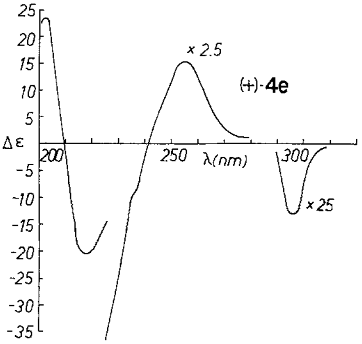

Fig. 2. CD-spectrum of (+)-**4e** in ethanol

The coordinate system was chosen so that the x-axis transfixes the centres of both aromatic rings and the z-axis is parallel to the C_2-axis of the molecule. The ^1L_a-transition moment of $(R)_p$-**2h** comprises the angles $r = 106°$, $t = 101°$ and $v = 160°$ with the coordinate axes, so that according to equations (4) and (5) in ref.[4] $\nu_A - \nu_B > 0$ results for the band splitting and $R_A > 0$, $R_B < 0$ for the rotational strengths of the bands with A and B symmetry*.

A comparison with the actual CD spectrum yields the configuration $(R)_p$ for (—)-**2h**. On the basis of the chemical correlation this is in agreement with the X-ray configuration determination for (+)-**4e** (cf. Table **1**).

Acknowledgements

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* The sign of $\nu_A - \nu_B$ has erronously been interchanged in ref.[4] resulting in the antipodal configuration for (+)-**2h**.