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Tetrahedron: *Asymmetry*

A DFT study of the geometric, magnetic NMR chemical shifts and optical rotation properties of Tröger's bases

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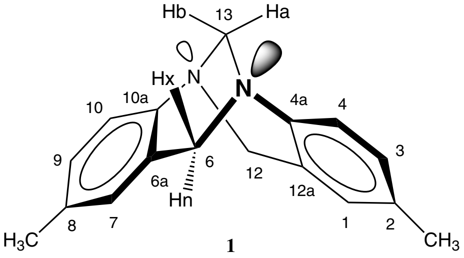
Abstract—A DFT computational study of Tröger's bases and related compounds (TBs) has been used to satisfactorily explain their geometry (including the flexibility aspect), the ^{1}H NMR chemical shifts of the *endo*/*exo* protons and their optical properties. The Cambridge Structural Database has been searched to collect 34 structures of TBs that have been analyzed with respect to the folding angle ϕ. The GIAO approach has been used to calculate the absolute shieldings of TB and a quinoline analogue providing an explanation for the dependence of the relative position of the *endo*/*exo* protons on the structure of the TBs. Finally, the specific rotations of several molecules related to TBs have been calculated at the B3LYP/6-311++G(2s,2p) level. The $[\alpha]_D$ values are strongly dependent on relatively small structural variations.

1. Introduction

Although the base of Tröger **1** and its derivatives have been recognized as 'fascinating molecules' for a long time,[1,2] there is still increasing interest to this day.[3] However, some aspects are still under debate, for instance, in recent reviews,[4–6] three such aspects have been discussed. The first one concerns the ϕ angle formed by the planes of the two aromatic (or heteroaromatic) rings in the V-shaped structure characteristic of the Tröger's bases. The second one is related to the assignment of the *exo* and *endo* protons of the methylenes at the 6- and 12-positions, whose relative chemical shifts appears to be dependent on the nature of the aromatic (heteroaromatic) rings. The last one concerns the absolute configuration of **1**.



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We decided to study these three aspects by examining the experimental results on the basis of DFT computational calculations.

2. Results and discussion

2.1. Molecular geometry of Tröger's bases

We have summarized in Scheme 1 the relevant crystallographic information concerning Tröger's bases as reported in the CSD version 5.26 (updated August 2005, CSD refcodes given in bold).[7] The search was carried out for any six- or five-membered ring with any atom and any type of bond. The angle ϕ is the angle formed by the planes (defined as mean-square planes) containing the two aromatic rings. For most compounds, only one value of ϕ is given in Scheme 1, but there are several molecules for which two values are reported (two different determinations, were reported for **SIRWIZ** and **DEFQAG**, but the angles are identical or very similar). The two cases could be distinguished as

(i) Double molecules, such as **WOKNUF** (two identical TBs linked by an Hg atom), **XICROQ**, **XICRIK** and **EWACEK** (these three being bis-TBs). For these molecules, two angles are expected, but most of these molecules have an element of symmetry,

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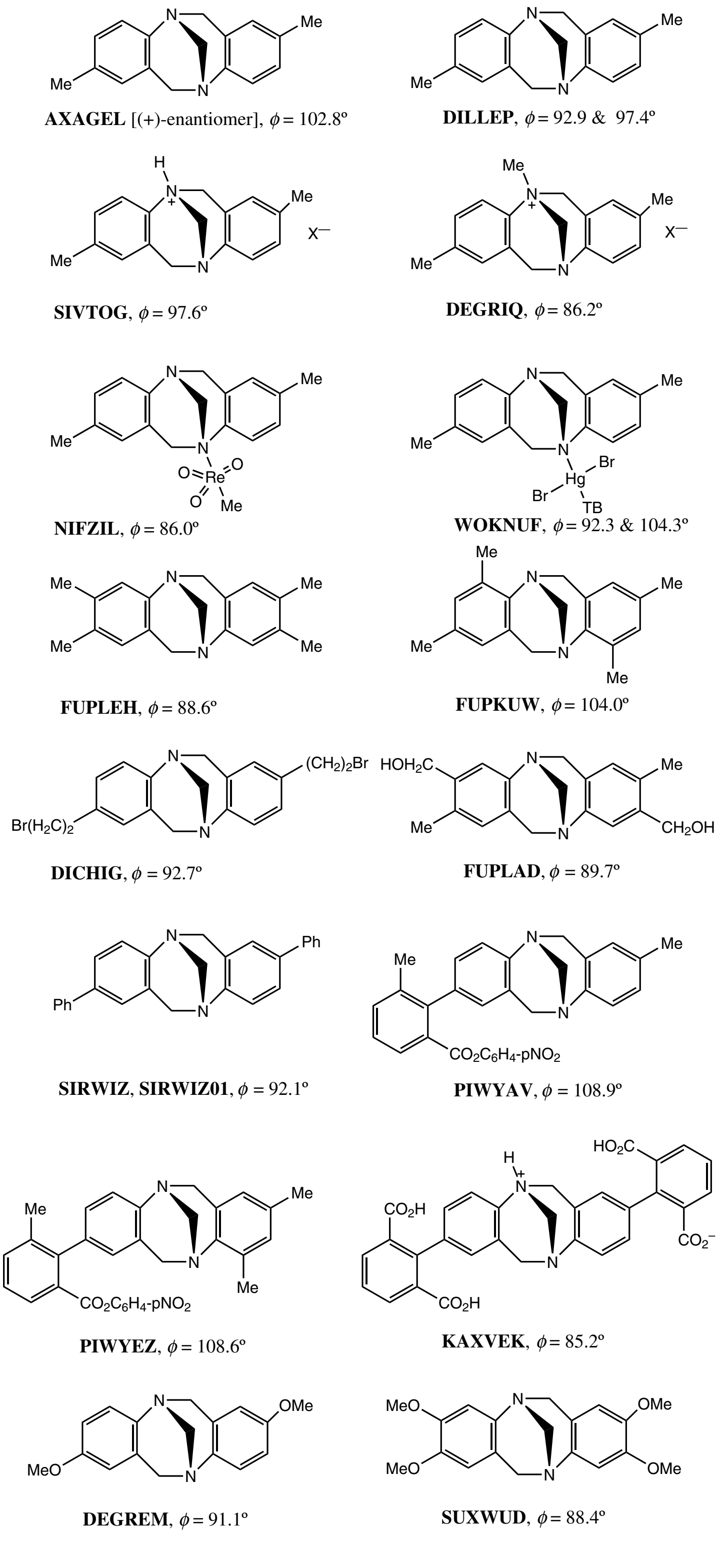
the angles should be similar, which is not the case: 92.3°/104.3° (12.0°), 96.6°/100.7° (4.1°) and 89.4°/103.8° (14.4°). In the case of the 'asymmetric' **XICRIK**, the difference is 15.7° (88.6°/104.3°).

(ii) Tröger's bases with two independent molecules in the unit cell: **DILLEP** 92.9°/97.4° (4.5°) [note that the (+)-enantiomer has $\phi = 102.8°$], **QIHZIQ** 93.2°/94.1° (0.9°), and **YUKFEP** 80.2°/89.6° (9.4°) (these are the angles we measured on **YUKFEP**, in the original article the angles are reported as 81.0° and 89.7°).

The straightforward conclusion is that crystal-packing effects are important and can cause deformations of


AXAGEL [(+)-enantiomer], $\phi = 102.8°$

DILLEP, $\phi = 92.9$ & 97.4°

SIVTOG, $\phi = 97.6°$

DEGRIQ, $\phi = 86.2°$

NIFZIL, $\phi = 86.0°$

WOKNUF, $\phi = 92.3$ & 104.3°

FUPLEH, $\phi = 88.6°$

FUPKUW, $\phi = 104.0°$

DICHIG, $\phi = 92.7°$

FUPLAD, $\phi = 89.7°$

SIRWIZ, **SIRWIZ01**, $\phi = 92.1°$

PIWYAV, $\phi = 108.9°$

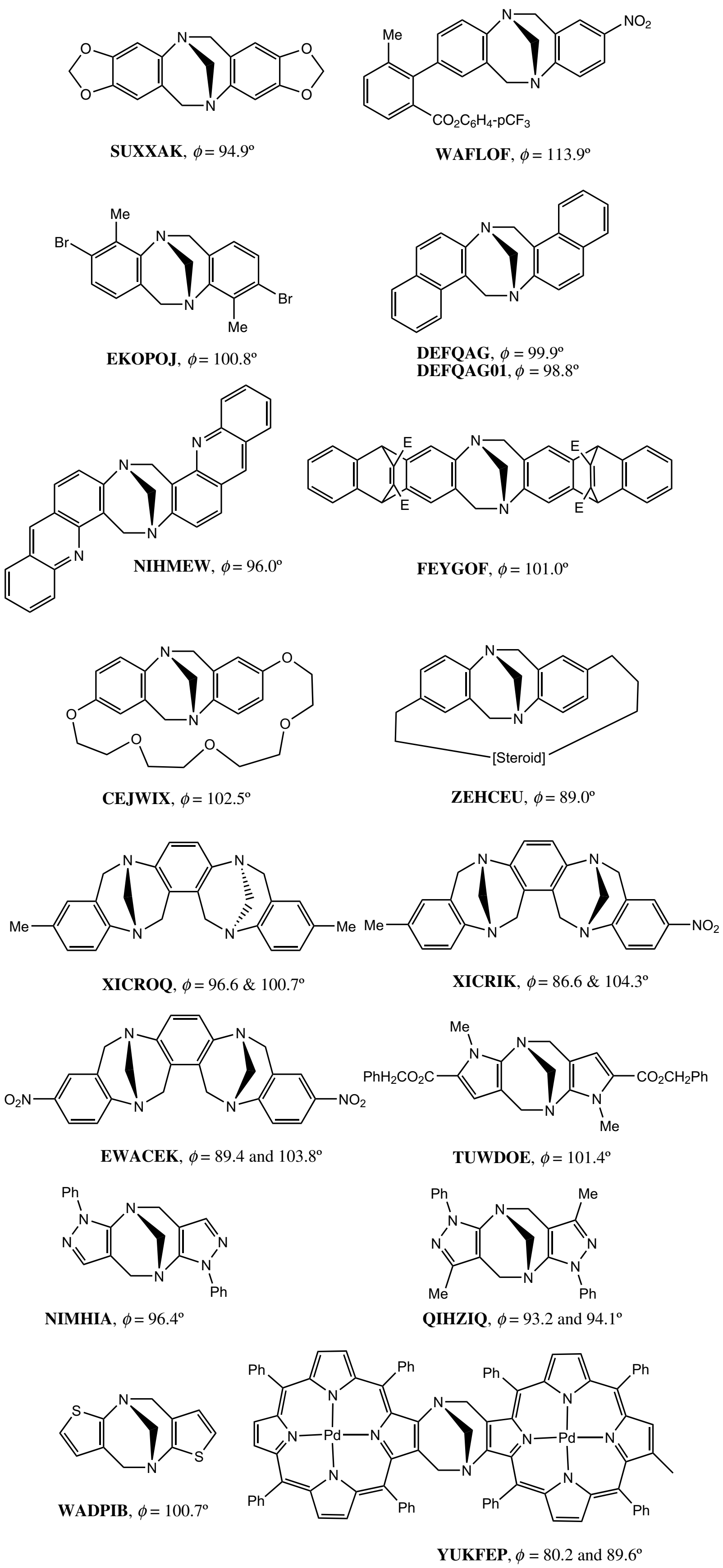
PIWYEZ, $\phi = 108.6°$

KAXVEK, $\phi = 85.2°$

DEGREM, $\phi = 91.1°$

SUXWUD, $\phi = 88.4°$

Scheme 1. The 34 X-ray structures.



SUXXAK, ϕ = 94.9°

WAFLOF, ϕ = 113.9°

EKOPOJ, ϕ = 100.8°

DEFQAG, ϕ = 99.9°
DEFQAG01, ϕ = 98.8°

NIHMEW, ϕ = 96.0°

FEYGOF, ϕ = 101.0°

CEJWIX, ϕ = 102.5°

ZEHCEU, ϕ = 89.0°

XICROQ, ϕ = 96.6 & 100.7°

XICRIK, ϕ = 86.6 & 104.3°

EWACEK, ϕ = 89.4 and 103.8°

TUWDOE, ϕ = 101.4°

NIMHIA, ϕ = 96.4°

QIHZIQ, ϕ = 93.2 and 94.1°

WADPIB, ϕ = 100.7°

YUKFEP, ϕ = 80.2 and 89.6°

Scheme 1. (*continued*)

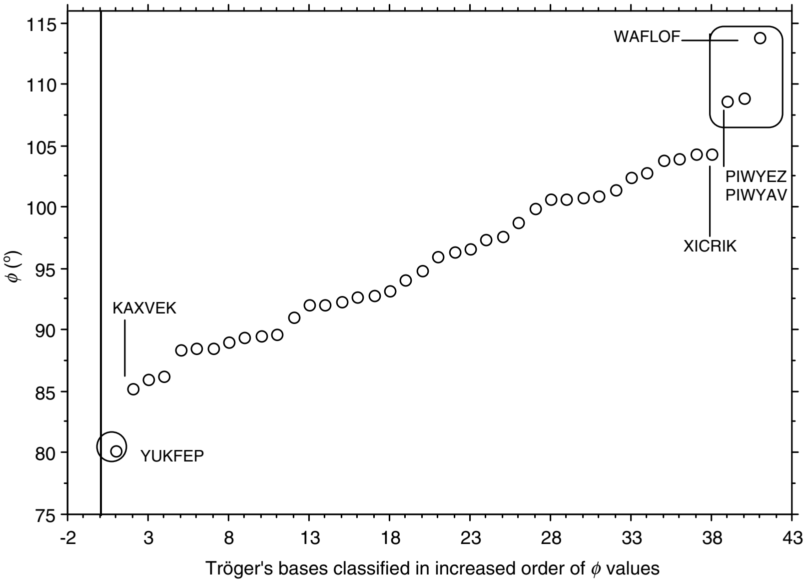


Figure 1. Variation of the ϕ angle (°) in order of increasing ϕ values for Tröger's bases of Scheme 1.

±6°. The second one is that Tröger's bases should be relatively flexible molecules because small structural variations produce significant changes in the ϕ values.

Figure 1 and Scheme 1 show that there are four 'abnormal' compounds (framed in Fig. 1). One had with a very low ϕ angle [**YUKFEP**, 80.2° (81.0°)],[8] while the other independent molecule had a 'normal' value of 89.6°. The pyrrole rings used to define the aromatic planes are very distorted in this porphyrin derivative, which can be related to the small angle; the authors limited themselves to point out that the value is somewhat smaller than the average angle in other Tröger's base analogues.[8] The three other compounds (**WAFLOF**, **PIWYAV** and **PIWYEZ**) have abnormally high ϕ angles. For the remaining ones there is a smooth variation of the ϕ angle. These last three compounds correspond to Wilcox–Diederich's molecular torsion balances that have been designed to present interactions between the lateral branch and one of the phenyl rings of the Tröger's base resulting in high ϕ values (see Fig. 2).[3,9–11]

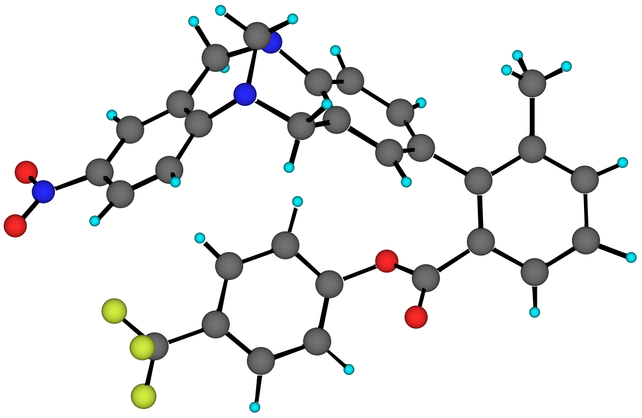


Figure 2. The molecular structure of **WAFLOF** showing the interaction responsible for the increasing of ϕ.

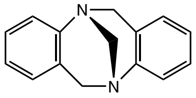
Excluding these four compounds, 37 ϕ values remain, the mean being 95.3°, the minimum value 85.2° (**KAXVEK**) and the maximum 104.3° (**WOKNUF** and **XICRIK**) (see Fig. 1). Wilcox et al.[12] from a series of seven ϕ values, reported a range of 88–104°. There are no significant differences between benzenes (31 compounds, 95.1°) and five-membered heterocycles (six compounds, 95.9°), but between neutral (31 compounds, 96.5°) and cations or metal complexes (six compounds, H$^+$, R$^+$, metals, 91.9°) there seems to be a significant decrease of the ϕ angle (4.6°).

Since the crystal structures are unsuitable for studying the influence of the substituents on the geometry of Tröger's bases, we decided to carry out DFT calculations to avoid phase effects. We calculated four Tröger's bases differing only in the position of the methyl group, including the original Tröger's base, 2,8-dimethyl-6*H*-12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine. The following ϕ angles were calculated: 1,7-dimethyl 103.8°, 2,8-dimethyl 101.4°, 3,9-dimethyl 101.5° and 4,10-dimethyl 105.4°. The 2,8-dimethyl derivative was compared with **AXAGEL** (102.8°) and **DILLEP** (92.9° and 97.4°) the calculated value, 101.4°, is much closer to the (+)-enantiomer (Scheme 1). Due to the fact that the calculated geometry of an isolated molecule is more similar to that of the enantiomer, than to that of the racemic, no consequence can be drawn: the differences in geometry in the crystals are due to packing effects that actually are quite different in **AXAGEL** and **DILLEP**.

The presence of methyl groups close to the diazocine ring increases the ϕ angle 2.4° in 1,7 and 4.0° in 4,10 with regard to the 2,8- or 3,9-derivatives. There are two compounds with methyl groups in 4,10: **FUPKUW** 104.0° and **EKOPOJ** 100.8°, but the effects, as expected, are blurred by the packing.

We then examined the flexibility of the skeleton, that is, the effect of ϕ on the energy by carrying out B3LYP/

6-31G* calculations on model **2**. In the minimum energy conformation, the angle ϕ amounts to 101.33°.



2 $\phi = 101.33°$

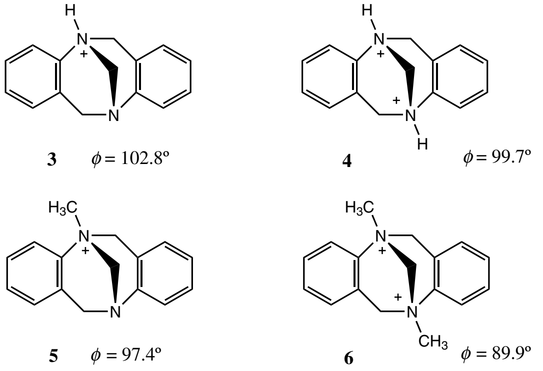
The variations of the energy with the ϕ angle are reported in Table 1 and Figure 3.

The results of Table 1 confirm the flexibility of Tröger's bases and the flat nature of their potential curves (Fig. 3).

We have carried out calculations on some charged species (Scheme 2) to check the observation, which previously reported, that cations and metal complexes have lower ϕ values (4.6°, see above) than neutral TBs. The results show that quaternary ammonium salts have ϕ angles about 5° lower than protonated cations (that duplicates in double salts). Mono-protonation alone is not sufficient enough to modify ϕ (compare **2** and **3**). In fact if one compares the neutral **DILLEP** (92.9° and 97.4°) with the mono-protonated derivative **SIVTOG** (97.6°) and the mono-quaternary salt **DEGRIQ** (86.2°), the quaternary salt has a ϕ value 11.4° lower that the protonated cation, which is similar to that of the neutral molecule.

Table 1. Conformational analysis of compound **3** calculated at the B3LYP/6-31G* level

Angle ϕ	Energy (hartree)	Relative energy (kJ mol^{-1})
85.00	−689.515450	5.09
90.00	−689.516508	2.31
95.00	−689.517120	0.70
100.00	−689.517381	0.02
101.33	−689.517388	0.00 (minimum)
105.00	−689.517282	0.28
110.00	−689.516844	1.43



Scheme 2. Calculated ϕ angles (B3LYP/6-31G* level) for models of mono and dications.

2.2. NMR chemical shifts

To briefly summarize the situation, in general (including compound **1**) the *endo* protons appear more shielded than the *exo* ones, but in some acridine derivatives the opposite happens.[13] The GIAO approximation was used to calculate the absolute shieldings (see Computational details) because we have obtained good linear correlations between experimental δ values and calculated σ absolute shieldings of the type $\delta = \delta_0 + a\sigma$, where δ_0 is close to the value of the reference.[14,15] In Table 2, we have summarized the experimental chemical shifts from one of our previous works,[16] together with the absolute shieldings (GIAO/B3LYP/6-311++G(d,p)//B3LYP/6-31G*).

By taking into account that TMS has $\sigma = 32.075$ ppm (^{1}H) and 183.15 ppm (^{13}C) while nitromethane has σ^{15}N = −340.4 ppm, the following equations were obtained:

$$\delta(^1\mathrm{H}) = (30.7 \pm 0.6) - (0.96 \pm 0.02)\ \sigma(^1\mathrm{H}),\quad n = 8,\ r^2 = 0.997 \tag{1}$$

$$\delta(^{13}\mathrm{C}) = (173.8 \pm 0.9) - (0.951 \pm 0.009)\ \sigma(^{13}\mathrm{C}),\quad n = 10,\ r^2 = 0.999 \tag{2}$$

$$\delta(^{15}\mathrm{N}) = -154.5 - 0.97\sigma(^{15}\mathrm{N}) \tag{3}$$

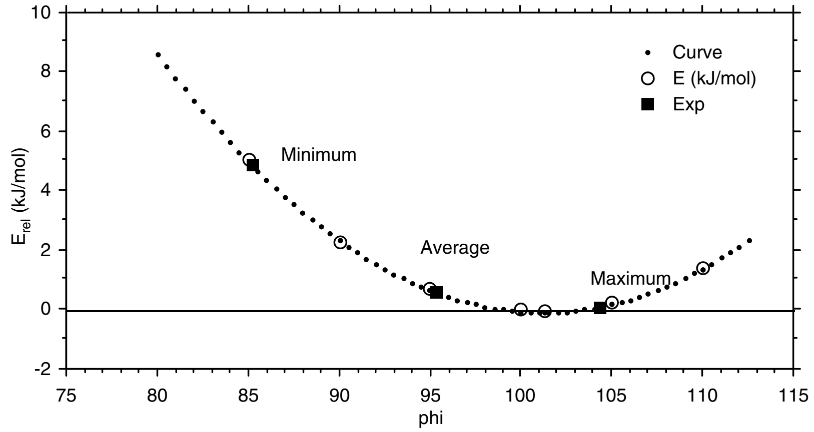
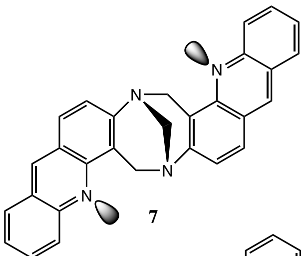


Figure 3. Variation of the relative energy with the angle ϕ: white circles correspond to Table 1 values; black squares to the experimental minimum (**KAXVEK**), mean ($\phi = 95.3°$) and maximum values (**WOKNUT** and **XICRIK**). The curve corresponds to the equation $E_{\mathrm{rel}} = 197.71 - 3.908\phi + 0.0193\phi^2$.

Table 2. Experimental chemical shifts and calculated absolute shieldings (both in ppm) of Tröger's base **1**

Atom	Chemical shift (experimental)[16]	Absolute shielding (calculated)	Atom	Chemical shift (experimental)[16]	Absolute shielding (calculated)
H-1	6.721	25.2346	C-1	127.26	50.9887
CH_3	2.231	29.6255	C-2	133.42	43.1795
H-3	6.792	24.7341	CH_3	20.81	160.8032
H-4	7.045	24.7374	C-3	128.11	50.0740
H-6 *endo*	4.121	27.7728	C-4	124.77	51.8651
H-6 *exo*	4.666	27.2060	C-4a	145.37	27.8086
CH_2-13	4.320	27.6822	C-6	58.66	118.9786
N	−340.4		C-6a	127.48	46.8785
			C-13	67.05	112.8295

The most important result is that the *endo* and *exo* protons of the methylene group at the 6-position are predicted exactly as found experimentally. We then calculated a model of acridine Tröger's base **7** where the terminal benzene rings have been deleted (the quinoline derivative **8**).



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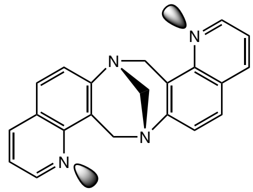
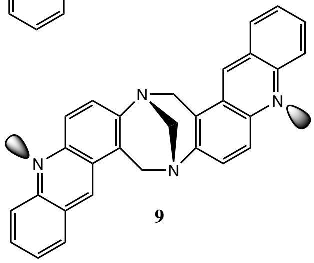


8 $\phi = 102.6°$



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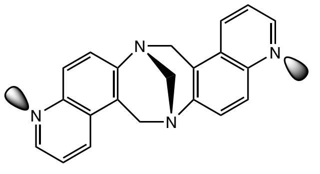

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For **8**, the *exo* proton of the 6-position is calculated at $\sigma = 26.6680$ while the *endo* one is calculated at $\sigma = 26.7161$. Using Eq. 1, the following chemical shifts are predicted, 5.17 (*exo*) and 5.13 (*endo*), the experimental values for **7** being 5.11 (*exo*) and 5.12 ppm (*endo*),[13] thus the calculations are able to explain why a clear difference of 0.55 ppm for **1** becomes almost null for acridines. Note that compounds **9**[17] and **10**[18] that have the lone pair removed from the methylene at the 6-position present *endo*/*exo* signals such as **1**.

2.3. Absolute configuration of Tröger's base 1

The absolute configuration (AC) of Tröger's base **1** was first incorrectly assigned by Mason et al. using the analysis of the circular dichroism (CD) by means of the exciton coupling method.[19,20] The X-ray analysis of a diastereomeric salt allowed Wilcox et al. to prove that the original AC assignment was erroneous and that the correct AC is (+)-(5*S*,11*S*) [(−)-(5*R*,11*R*)].[21] Indeed, application of the exciton chirality method to Tröger's base has led to a wrong assignment because the direction of polarization of the considered transitions has not been correctly established. The specific rotation of Tröger's base **1** is $[\alpha]_D^{20} = +280$ (*c* 0.5, hexane)[22] and $[\alpha]_{589}^{25} = +287$ (*c* 0.29, hexane).[21] Some of the structures reported in Scheme 1 correspond to pure enantiomers, such as **AXAGEL** [**1**-(+)-5*S*,11*S*][23] and **DEFQAG**.[24]

In a series of remarkable papers, Devlin et al. established that the Wilcox assignment is the correct one by calculating the VCD (vibrational CD) and OR (optical rotation) of **1** (Fig. 4) by means of the DFT/GIAO approximation.[25–27]

It is important to understand that there are two OR values: the $[\alpha]_D(0)$ at zero frequency (static) and the $[\alpha]_D$ (dynamic).[27,28] The second one is the value that has to be compared with the experimental result, but it is usually computationally prohibitive.[29]

The calculated $[\alpha]_D$ for **1** (5*R*,11*R*) is −341.5 (aug-cc-pVDZ) and −319.8 (6-311++G(2s,2p)) [the calculated $[\alpha]_D(0)$ are −242.3 and −224.2, respectively[27]]. The 319.8 value is in good agreement with the experimental results (287 and 307).[21] Giorgio et al.[29] have tried unsuccessfully to use small basis sets with **1**, only to have a moderate success with an acridine derivative similar to **NIHMEW**: experimental $[\alpha]_D = 4800$,[23] calculated (6-31G*) $[\alpha]_D = 2384$.[29]

Using the computational level recommended [B3LYP/6-311++G(2s,2p)] we first calculated the $[\alpha]_D(0)$ value for compound **1** (−220.2, lit.: −224.2)[27] and then calculated a series of related molecules (Scheme 3).

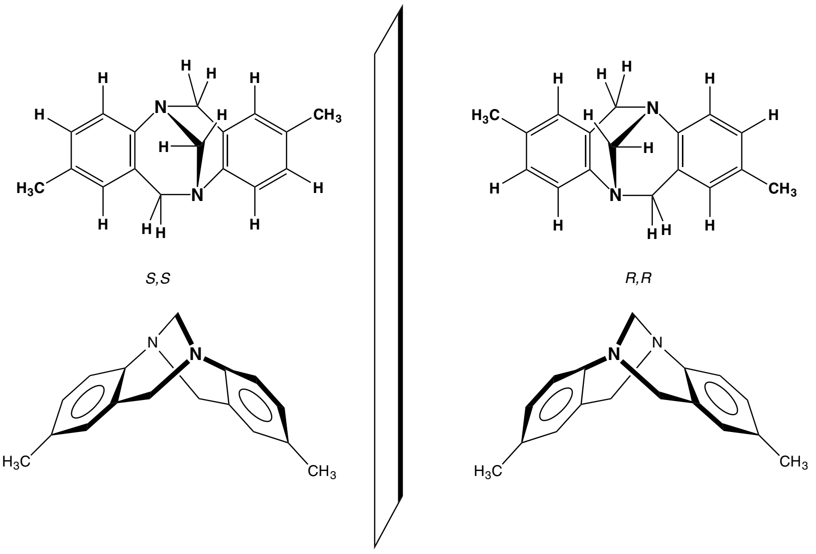
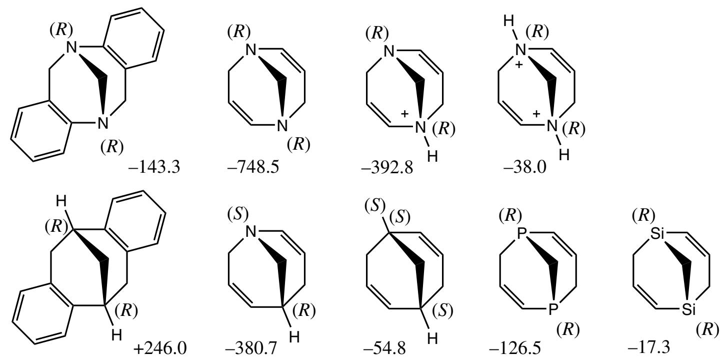


Figure 4. The enantiomers of Tröger's base **1**.



Scheme 3. Calculated specific rotation values.

It should be noted that in some cases, the changes in the *R*/*S* notation, all the molecules of Scheme 3 have similar structures and the inversion of sign of $[\alpha]_D$ when compound (*R*,*R*)-**2** (−143.3) is compared with the corresponding carbocycle (+246.0). Although it has been postulated that the high $[\alpha]_D$ values of TBs are related to both the skeleton rigidity and the presence of aromatic rings,[29] it is clear that the aromatic rings are not necessary (compare −143.3 with −748.5).

3. Computational details

The geometry of the molecules were optimized with the Gaussian 03 package[30] at the B3LYP/6-31G* computational level.[31,32] The minimum nature of the structure was confirmed by frequency calculations at the same computational level. These geometries were used to evaluate the optical rotation and the absolute shieldings (within the GIAO approximation)[33] at the B3LYP/6-311++G(d,p)[34] (absolute shieldings) and B3LYP/6-311++G(2d,2p) [optical rotation, $[\alpha]_D(0)$] computational level.[34] This level of theory was recommended as the minimum to obtain reliable optical rotation values in the literature.[28,35]

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