Empirical Calculations of ^{1}H-NMR Shielding in Cyclophanes

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Available ring current models for the calculation of proton shifts are evaluated on the basis of cyclophanes, which provide many protons above the aromatic plane in well-defined conformations. The latter were simulated with the help of MM2 and CHARMm force fields. Agreement between calculated and observed anisotropy effects approaching $\Delta\delta_{av} = 0.17$ ppm average deviation is found for 39 signals ranging over 6.6 ppm with the Johnson–Bovey model and the parameterization of double loop geometries $p = 0.64$ Å and $r = 1.39$ Å. The calculations include cyclophanes with protons in extremely close contact with the π-surface, as reported recently by Pascal et al. and by Vögtle et al. The calculations clarify some reported discrepancies but demonstrate, in one and two cases, the presence of severe additional van der Waals (vdW) compression shifts which amount to as much as 1.6 ppm. The consequences of the extreme sensitivity of those proton locations near the shielding cone edges are discussed, in particular with respect to application to supramolecular structures or to biopolymers.

Introduction

The anisotropy effects of aromatic rings seem to be well established by many previous theoretical and empirical investigations.[1] Several reasons, however, make it timely to study the topic again on the basis of cyclophanes[2] as the most suitable models: (a) most of the early investigations concentrated on protons, occurring mainly in the deshielding plane of the arene moieties; (b) sometimes only a portion of the proton signals was used, which is not necessary since the advent of 2D NMR methods; (c) the possibility of obtaining realistic conformations from molecular mechanics calculations is now much improved; and (d) many new cyclophanes have been prepared[3] that offer new ways to check the shift calculations with well-defined, and hitherto unavailable, geometries.[4] The most important incentives for us are (e) that the previously neglected proton positions *above* aromatic planes (see (a)) are the most interesting ones for the analysis of supramolecular complexes by NMR[5] and that for similar reasons (f) such calculations may become important for the analysis of biopolymer structures.[6]

Cyclophanes provided relatively rigid models for the empirical evaluation of the most reliable ring current calculation method which would then be implemented in our SHIFT program.[7] For reasons of conformational rigidity, SHIFT was based largely on steroids, and until now, aromatic systems were not included. At the same time, we wanted to study the origin of unusual shift effects reported recently for new highly strained cyclophanes[8,9] and to make such calculations easier and more reliable.

Results

The methods published by Haigh and Mallion[1] (HM), by Johnson and Bovey[10] (JB), and by Häfelinger et al.[11] (AP) were tested with the paracyclophanes **1a**–**1e** (Chart 1). The experimental shifts reported in the literature[2,12] were substracted from those of suitable reference compounds lacking the aromatic ring (Scheme 1, supplementary material). The underlying conformations were simulated with either the MM2 field of Allinger et al.[13] or with CHARMm of Karplus et al.[14] The shielding contributions of the phenyl rings were then obtained with a new C version of our SHIFT program. The geometry factors of all equivalent or rapidly exchanging protons were averaged before comparison with the experimental shifts. Deviations from aromatic ring planarity, which were more visible in MM2 than in CHARMm simulations, were taken care of by placing a best plane through the ring atoms. The SHIFT program allows one to read

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Chart 1. Cyclophane Structures

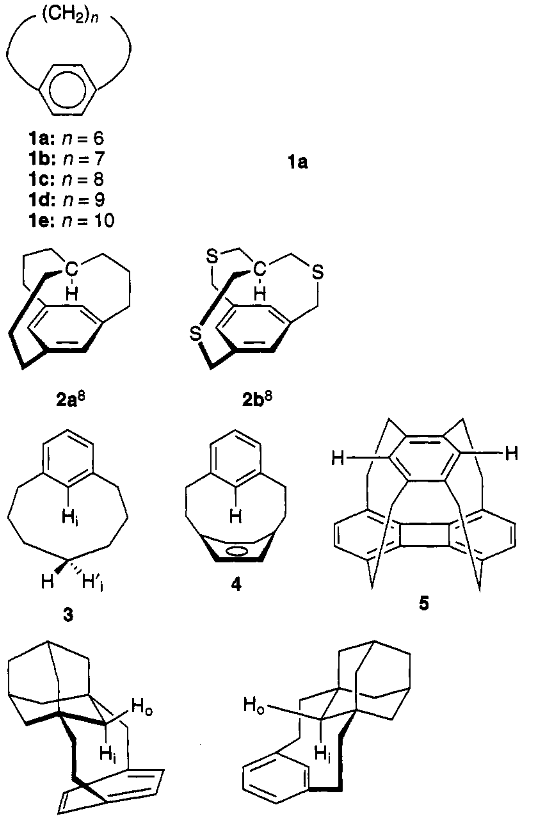

Table 1. Comparison of Shift Calculation for Paracyclophane 1a with Different Models[a]

proton	exptl	AP	HM	JBa	JBb1	JBb2	JBTab
ar	−1.37	−1.99	−1.41	−1.49	−1.51	−1.40	−1.47
α	−0.49	−1.18	−0.20	−0.57	−0.53	−0.49	−0.57
β	0.15	0.81	0.15	0.37	0.34	0.31	0.37
γ	0.94	2.10	0.39	1.16	0.99	0.91	1.16

[a] All values in ppm. Exptl: $\delta_{R1} - \delta_{TMS}$ (R1 etc.: reference compounds, see supplementary material). AP: atomic point dipole model after Häfelinger et al.[11] HM: Haigh–Maillion.[1] JB: Johnson–Bovey,[10] based on two different force field optimizations (JBa, CHARMm 3.0; JBb, CHARMm 3.21) and two different parameterizations of the Johnson–Bovey model (JB1, loop radius r = 1.39 Å, distance from plane p = 0.64 Å; JB2, r = 1.5 Å, p = 0.64 Å). JBTab: with values from Johnson–Bovey tables.[10]

in coordinates from different sources and to sum up all screening effects by functional groups upon atoms that the user has identified. As will be seen later, MM2 and CHARMm led, in most cases, to similar energy-minimized conformations and geometries, although the agreement with calculated NMR shifts was usually somewhat better with CHARMm-generated geometries. Linear electric field effects, originating, for instance, in the C–H bond dipoles of the benzene rings, were calculated to contribute <0.1 ppm (e.g., charges of 0.05 e-units at C and H, respectively).

Table 1 shows good agreement for all protons in cyclophane **1a** H, in particular with the original JB parameterization (JB1). The values change by only +0.04 ppm on average if two different CHARMm versions (versions 3.0 and 3.21) are used. Since the JB model also performed well with the other paracyclophanes (Table 2, for explicit description of all data see Table I of the supplementary material), we wanted to determine whether different results are obtained upon changing the ring current loop parameters r and p and found only slight improvement with a new set of r and p (JB2, Table 3). Therefore, the first JB (JB1) parameterization was used for all subsequent calculations. It should be noted that the agreement was always less satisfactory for the paracyclophanes with longer methylene chains (**1d**, **1e**). This is the result of the less well-defined conformational minima of these, as is evident from the improved agreement obtained with more rigid cyclophanes. Discrepancies reported earlier (e.g., for the [10]paracyclophane[4a]) between experiment and ring current calculations were, in view of our results ($\Delta\delta_{av}$ = 0.06 ppm), likely due to computational inadequacies.

Table 2. Average Deviations $\Delta\delta_{av}$ of Calculated and Experimental Shifts for *p*-Cyclophanes 1a–1e with Different Models[a]

	AP	HM	JB1	JBTab
1a	0.22	0.39	0.10	0.10
1b	0.58	0.57	0.16	0.11
1c			0.06	
1d	0.43	0.33	0.19	0.18
1e	0.36	0.26	0.17	0.17

[a] See footnotes to Table 1; other local minima conformation of **1c** give, e.g., with AP, 0.63; HM, 0.33; JB1, 0.30; and JBTab, 0.26 ppm.

The cyclophanes **2a** and **2b** reported by Pascal et al.[8] are most attractive for the shielding evaluation of a proton that approaches an aromatic π-center as closely as possible (a situation also expected in supramolecular and edge-to-face benzene complexes). The previous authors, however, concluded that force field as well as MNDO calculations give too large a distance d between the in-proton H$_i$ and the aryl ring when compared to X-ray structure and recent ab initio calculations and therefore would be in disagreement with distances taken from JB tables. On the other hand, we obtain excellent agreement with our tested JB SHIFT calculations based on CHARMm-simulated geometries (Table 4), which suggests that the distance d is indeed 1.91 Å for **2a** and 1.96 Å for **2b** and that the X-ray-derived values of 1.66 and 1.69 Å, respectively, may fall systematically short. The apparent discrepancy may also originate in high-order compression shifts,[15] as they are discussed below for **7**, although H$_i$ in **2a** is exposed to a more isotropic and "soft" interaction. Similar agreement was obtained for the metacyclophanes **3** and **4**. For **5**, the ring current effect **on** benzene protons was evaluated by comparing the experimental shift to either a parent-substituted benzene ($\Delta\delta_{av}$ = 0.7 ppm) or to cyclohexadiene, with evaluation also of the ring current effect of the benzene itself ($\Delta\delta_{av}$ = 0.28 ppm).

The largest known anisotropy effect generated by a benzene ring is visible in adamantophanes like **6** and **7**, reported recently by Vögtle and Lemmertz.[9] For **6** we obtain, by subtraction of 1.3-dimethyladamantane shifts as reference (see supplementary material), 5.39 ppm for the proton closest to the phenyl ring and, for **7**, 2.84 ppm. However, the shift calculation for **7** actually predicts 1.24 ppm. Such a large deviation was not observed with the other cyclophanes. Since the geometry factors for such anisotropy effects are extremely dependent on the basic conformations (see below, and refs 4a and 7), a conformational search was undertaken to test whether slight

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(15) This possibility is supported by remarkable effects on infrared compressed frequencies of the C–H$_i$ stretching modes. See ref 8, Pascal, R. A.; Grossman, R. B.; Engen, V. D. *J. Am. Chem. Soc.* **1981**, *109*, 6878 and references cited therein.

Table 3. Shift Calculations with Different Parameters of the Johnson–Bovey Model[1] with 1a[a]

r/p	0.0/0.0	1.0/0.64	1.0/1.0	1.39/0.0	JB1 1.39/0.64	1.39/1.0	1.5/0.0	JB2 1.50/0.64	1.5/1.0	exptl
H_{ar}	−3.50	−2.09	−0.95	−2.52	1.51	−0.68	−2.34	1.40	−0.63	−1.37
H_α	−0.77	−0.74	−0.67	−0.56	−0.53	−0.48	−0.52	−0.49	−0.45	−0.49
H_β	0.51	−0.47	0.40	0.37	0.34	0.29	−0.34	0.31	0.26	0.15
H_γ	1.26	1.37	1.53	0.91	0.99	1.10	−0.84	0.91	1.02	0.94
$\Delta\delta_{av}$	0.75	0.50	0.36	0.36	0.10	0.25	0.81	0.06	0.24	

[a] See footnotes to Table 1.

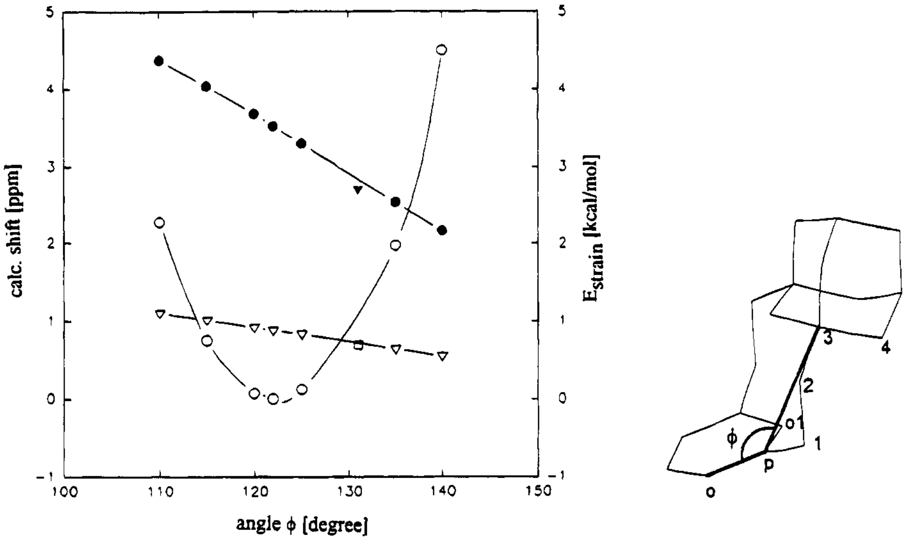

Figure 1. Strain energy E (kcal/mol) and SHIFT-calculated shielding of H_i and H_o in cyclophane **7**[9] as a function of the angle $\phi(C_o{-}C_p{-}C_3)$ (C_{2v} symmetry with the same angle ϕ on the opposite side; changes at only one ϕ leads to slightly higher energies).

Table 4. Calculations for Protons above the Plane for Cyclophanes 2–5[a]

	d	$\Delta\delta_{calc}$[e]	$\Delta\delta_{exp}$[f]
2a	1.906[b]	5.14	5.05
2a	1.658[c]	6.60	5.05
2b	1.959[b]	4.96	4.90
2b	1.739[c]	6.14	4.90
2b	1.690[d]	6.54	4.90
3 H_i		−1.50	−1.63
3 $H_{i'}$		2.53	2.60
4		0.31	0.43
5		0.13	−0.15

[a] See footnotes to Table 1. [b] Distances (Å) between C–H and aromatic ring center from CHARMm. [c] As in b, but from ab initio (3-21G(*)) calculations.[8] [d] As in b, but from X-ray[8] results. [e] With parameterization JB1 (see Table 3). [f] $\delta_{exp} = \delta_{R2a/2b} - \delta_{TMS}$.

Table 5. Calculations for Protons H_o and H_i in Cyclophanes 6 and 7 with Different Geometries[a]

	6		7	
compd proton	H_o	H_i	H_o	H_i
CHARMm I	1.92	5.39	0.69	2.84
CHARMm II	2.99	3.52	0.45	3.47
MM2	1.67	6.52	0.93	3.93
X-ray	1.16	7.26		
exptl	2.12	5.20	1.06	1.24

[a] See footnotes to Table 1. CHARMm II represents a second local minimum conformation with a strain energy higher by 6 kcal/mol compared to CHARMm I.

geometry changes might be responsible for the observed discrepancy in this case. Figure 1 shows that the minimum energy conformation is rather well defined, in contrast to more flexible geometries where similar analyses have yielded many conformations with small energy, but large NMR coupling constant differences.[7] The 10-membered ring formed between the adamantane and the benzene adopts a chairlike conformation with a slightly bent aryl ring. As expected, the H_o shift changes less with the angle defined in Figure 1 than does the shift of H_i, which is closest to the phenyl ring. Other possible geometries, generated by small torsional angle changes at the adamantane moiety (torsional angle 1–2–3–4), show smaller energy differences and would not explain the observed discrepancy for the H_i proton (see supplementary material).

Thus, the calculated H_i shielding variations (Figure 1) do not account for the discrepany with the observed shielding, which is 1.6 ppm lower than expected. We therefore considered the possibility that this proton suffers from high-order compression effects which generate deshielding by deformation of the electron clouds.[16,17] Such effects have been observed, e.g., with phenanthrene, in which the inner protons 4 and 6 are deshielded by 0.9 ppm. These protons are separated by 2.21 Å (CHARMm simulation), which corresponds to a value of 92% of the sum of the van der Waals radii. For the cyclophane **7**, we calculate a distance of 2.14 Å between H_i and the carbon o1-C, as the closest atoms, which corresponds to 72% of the vdW radii sum (the next closest hydrogen atom is at a distance of 2.56 Å). Although the larger polarizibility of the π-electron cloud will diminish the compression effect by a C compared to a H atom, it is clear that there is substantial deformation, which must be responsible for the observed discrepancy. Such deviations are barely observed for the inner proton H_i in cyclophane **6**, since this proton points symmetrically to the center of the benzene ring where the electron density is reduced. The CHARMm calculated distance of 2.33 Å here corresponds to 97% of the summarized vdW radii.

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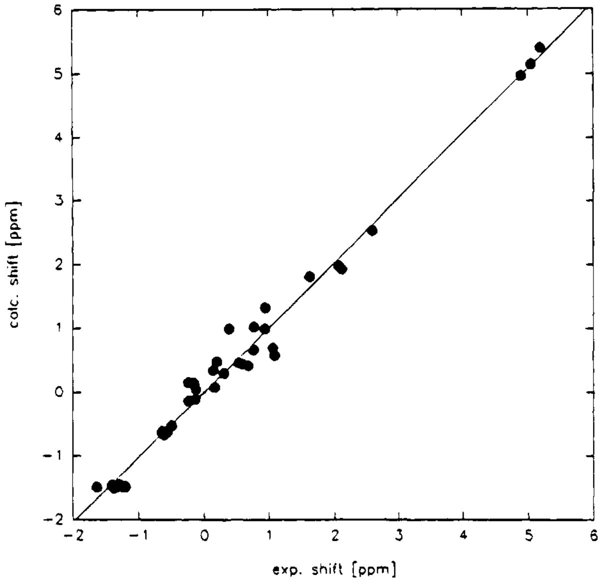

Figure 2. Comparison of SHIFT-calculated and experimental NMR shifts for all cyclophanes. The points with larger deviations are from cyclophanes **1d** and **1e** which due to the large ring size have less well-defined minima.

Conclusion

With the exception of the single proton H_i in **7** and perhaps H_i in **2a**, which suffer from compression effects, all 39 observed proton shifts in the 12 cyclophanes **1**–**7** correlate very well with the anisotropies calculated on the basis of the JB1 parameterization (Figure 2). The close agreement between experiment and calculation for such a large range of structures and protons in conformational space makes it difficult to justify explicit consideration of other factors like aromatic plane deviation, local anisotropies,[4a] or electric field effects. We believe our analysis to be the most comprehensive check of such benzene ring current effects to date. The largest deviations may obviously occur with protons close to the edge of the shielding cones where the sign changes from + to −. This necessary consequence of the induced ring current is illustrated in Figure 3, which shows the extreme sensitivity of the anisotropy effect on the exact location of protons approaching the benzene ring with $p = 0$ Å and $z = 1.4$ Å. For such protons, a cartesian coordinate inaccuracy of, e.g., 0.14 Å will lead to shift changes of 0.67 ppm! For this reason, the evaluation of any shifts of nuclei around such locations requires great caution. For an attempt to adjust a cyclophane geometry to calculated ring current effects, see Ogata et al.[4c] For biopolymers,[6] where errors of ±0.5 Å and more are quite common, and which we also therefore believe to be a poorer basis for the parameterization of NMR shift calculation programs, the solution might be to omit such nuclei. As mentioned in the introduction, however, the interaction of charged and/or aromatic groups with aromatic rings is a frequent structural motif in proteins.[17]

The calculation of ring current effects should become a tool of increasing importance for the analysis of supramolecular and biological complexes in solution. It will be greatly helped by the availability of rigorously tested models and computerized approaches. (For readers who may still want to use numerical data as such, we provide a nomogram based on the tested JB1 parameterization with coordinates more conveniently measured in Å from the center of the benzene ring, Figure 3b.) Applications to supramolecular complexes, including azoniacyclophanes, have already shown promise with calculations of *inter*molecular shielding[5b] but, however, **only** if linear electric field effects exerted by charges are taken into account.

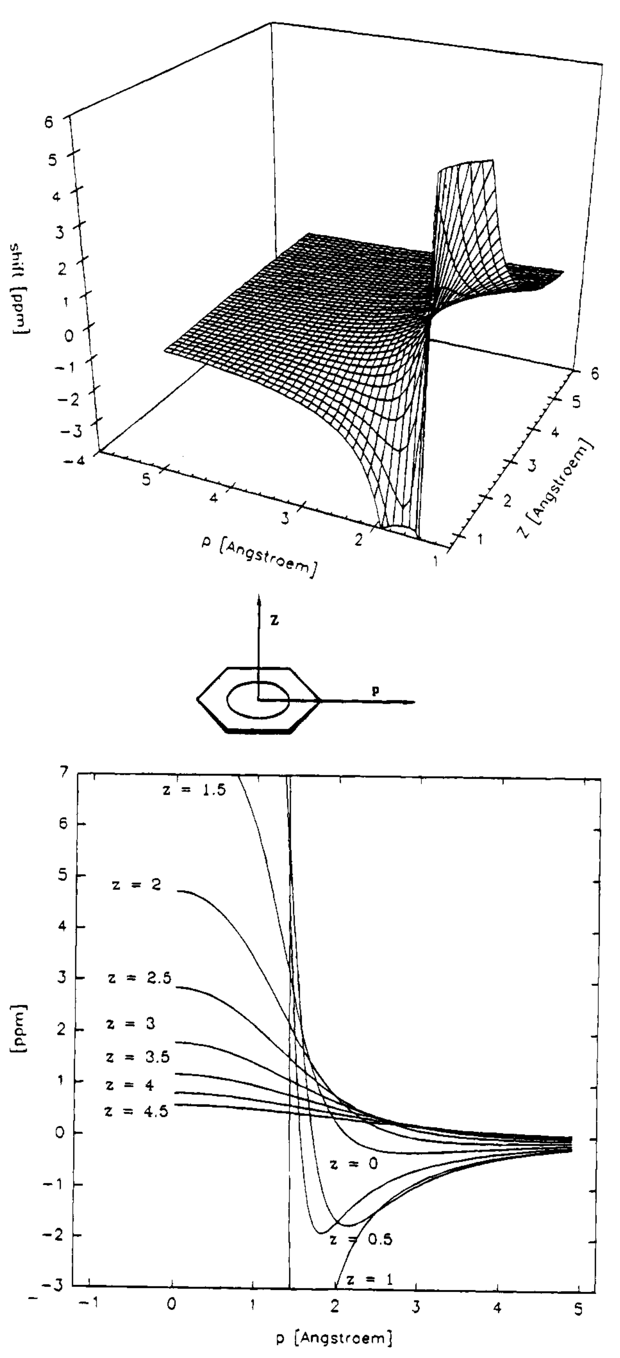

Figure 3. The shielding cone for a benzene ring as a function of the coordinates z and p (Å), measured from the benzene center, calculated with JB1 parameterization: (a) 3D visualization; (b) nomogram.

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Supplementary Material Available: Reference compounds, shift calculations for **1a**–**1e**, anisotropy effects for **2a**, strain energy, and shielding in **7** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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