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Theoretical study of conformation and dynamic behaviour of [3.3]orthocyclophane and heterocyclic analogues

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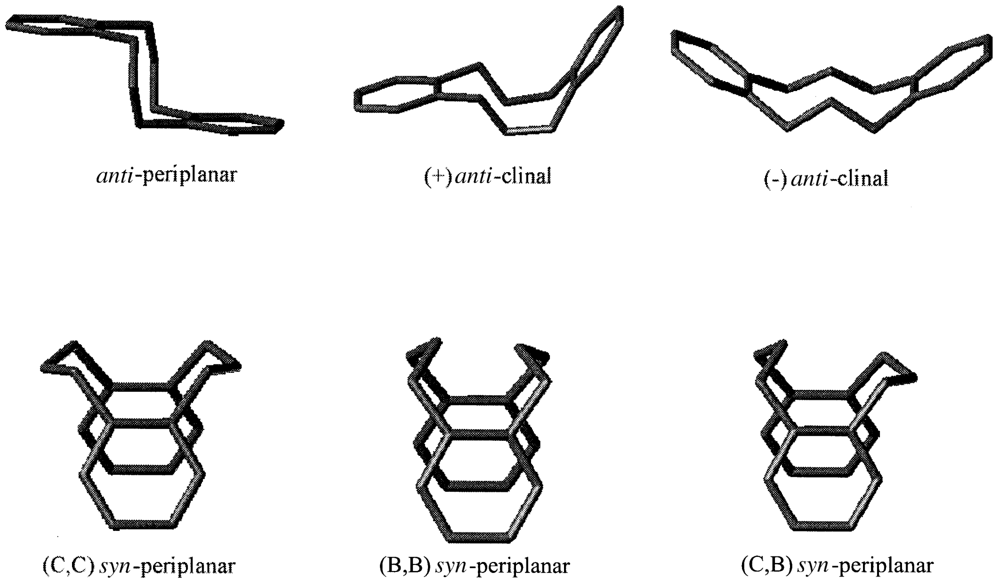
Abstract—Both the conformational equilibria and the dynamic behaviour of *N*,*N*′-di-substituted 3,12-di-aza-[3.3]orthocyclophane (R = H, $COCH_3$, COPh, tosyl) were calculated by the semi-empirical PM3 method and at the ab-initio level of theory (HF 6-31G*) in the light of inconsistent previous experimental results. The preferred conformer proved to be generally the *chair* form (*anti-periplanar*) and the exchange phenomena, which could be studied by dynamic NMR spectroscopy, result from the ring interconversional process and the restricted rotation about the *exo*-cyclic partial C,N double bond. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

[3.3]Orthocyclophane can exist in a number of *syn-periplanar*, *anti-periplanar* and *anti-clinal* conformations (cf. Scheme 1); also *twisted* alternatives to the latter could be possible. Fukazawa et al.[1] studied [3.3]orthocyclophane **1** and its 3,12-all-deutero-substituted derivative **2** (cf. Scheme 2) both in solution and in the solid state and assigned the most stable conformer to be the *chair*-like *anti-periplanar* conformation by employing (in addition to dynamic NMR spectroscopy to freeze the present conformational equilibrium at lower temperature) quantitatively the aromatic ring current model[2] together with accompanying molecular mechanics calculations.[2] The same author found the dioxa analogue **3** also in an *anti* conformation but having the two benzene rings in (−)*anti-clinal* orientation[3] employing the same methods;[2] the corresponding ring interconversional process was investigated by Kleinpeter et


anti-periplanar

(+)*anti*-clinal

(-)*anti*-clinal

(C,C) *syn*-periplanar

(B,B) *syn*-periplanar

(C,B) *syn*-periplanar

Scheme 1.

Keywords: 3,12-di-aza-[3.3]orthocyclophanes; ab-initio MO calculations; NMR; conformational equilibria; ring interconversion; restricted rotation.

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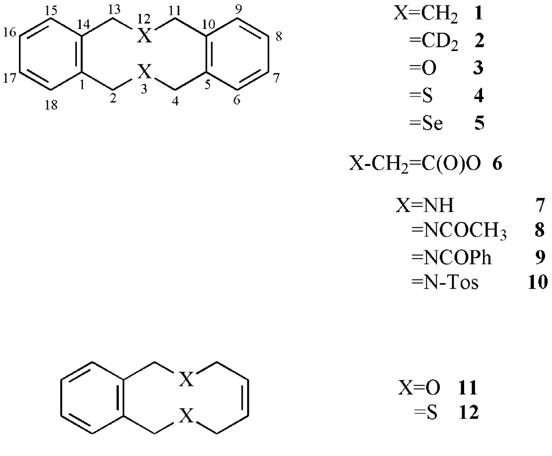


X=CH_2 **1**
=CD_2 **2**
=O **3**
=S **4**
=Se **5**

X-CH_2=C(O)O **6**

X=NH **7**
=$NCOCH_3$ **8**
=NCOPh **9**
=N-Tos **10**

X=O **11**
=S **12**

Scheme 2.

al.[4] The same (−)*anti-clinal* conformation was found for **6** in solution.[5] In the solid state, however, the same conformer proved to be twisted.[5]

The preferred conformer of the dithia **4** and the diselena analogues **5** is again the *chair*-like *anti-periplanar* conformer,[6] supported by Hopf et al.[7,8] Previously, **4** was assigned to prefer the (*C*,*C*)*syn-periplanar* conformer;[9] the same authors investigated also the ring interconversional process by dynamic NMR spectroscopy.[9]

The *N*,*N′*-di-substituted 3,12-diaza-[3.3]orthocyclophanes **7–10** (cf. Scheme 2), finally, have been studied by Kleinpeter et al.;[4] in the cases of **7–9** (X=H, $COCH_3$, COPh) also the *chair*-like *anti-periplanar* conformation proved to be the preferred conformer. In the case of **10** (X=Tos), however, these authors found the (*C*,*B*)*syn-periplanar* conformer dominating this conformational equilibrium due to extremely high field shifts of the aromatic protons of the orthocyclophane moiety.[4] In addition, the dynamic behaviour of **7–10** was investigated by dynamic NMR spectroscopy.[4] Both the barriers to rotation about the exo-cyclic partial C,N double bond of **8–10** and the barriers to ring interconversion of **1–7** (as far as available) are given in Table 1.

Later,[10] for **10** also the *chair*-like *anti-periplanar* conformer proved to exist in the solid state, and therefrom it was concluded on the conformational equilibrium existing in solution; two conformers **10A**$\leftrightharpoons$**10B** (ca. 50%:50%), found at lower temperatures, were assigned to be the preponderant conformers, and the dynamic process, studied by dynamic NMR spectroscopy at the same time, was assigned to be the restricted rotation about the N–S bond.[10]

Because of the latter inconsistency of the experimental results, both the conformational equilibria and the dynamic behaviour of the *N*,*N′*-di-substituted 3,12-di-aza-[3.3]cyclophanes **7–10** has been studied theoretically by employing the semi-empirical PM3 method. The geometries thus obtained were refined by ab-initio HF/6-31G* calculations. Beside the di-aza analogueous *6-10-6 systems* **7–10** also the heteroanalogueous *6-10-0 systems* **11** and **12** (cf. Scheme 2) were included in this study because of also being involved in Ref. 4. It is the major objective of this paper to report on the theoretical results obtained in the light of previous experimental studies of these compounds.

2. Results and discussion

2.1. Conformational equilibria

The conformations given in Scheme 1 were developed using the TRIPOS force field and energy optimized by the semi-empirical PM3 method. Finally, employing ab-initio MO calculations (HF/6-31G*), they have been energy optimized at this level of theory. The following results for the [3.3]orthocyclophanes **3** and **7–12** have been obtained and are given as relative energies of formation Δ*E* (kcal/mol) in Table 2. In all cases the *chair*-like *anti-periplanar* conformer (cf. Scheme 1) proved to be the most stable one. This result is in complete coincidence with the experiment.[4,10]

For the dioxa analogue **3** the conformational equilibrium could not be frozen;[4] as in the case of the other [3.3]orthocyclophane derivatives, the *chair*-like *anti-periplanar* conformation was calculated to be the most stable one. However, two other conformers [(−)*anti-clinal* and (*C*,*B*)*syn-periplanar*] proved to be of similar energy. In the solid state the twisted (−)*anti-clinal* conformer was found only;[3] in solution both the ^{1}H- and ^{13}C NMR spectra could corroborate the participation of the *anti-periplanar* and the (−)*anti-clinal* conformers in the conformational

Table 1. Barriers to ring interconversion and restricted rotation about *exo*-cyclic partial double bonds of the heterocyclic [3.3]orthocyclophane derivatives **2–10**

Compounds	Studied nuclei	Coalescence temperature T_c/K	Chemical shift differences $\Delta\nu/H$ at T_c	Barriers ΔG_c^*/kJ mol	References
2 (X=CD_2)	CH_2	313	–	64	1
3 (X=O)	CH_2	<165	–	–	4
4 (X=S)	CH_2	225	21.6 (*J*=14.7)	46.1	9
6 [X–CH_2=C(O)O]	CH_2	<183	–	–	7
7 (X=NH)	CH_2	189	35	38.2	4
8 (X=N–$COCH_3$)	CH_2	343[a]	15.4[a]	74.2[a]	4
		199	99	39.0	
9 (X=N–COPh)	CH_2	325[a]	22[a]	69.2[a]	4
		256	410	47.8	
10 (X=N–Tos)	CH_2	210	415	38.9	4
			–	43.2–43.5[b]	10

[a] Restricted rotation about the *exo*-cyclic partial C,N double bond.
[b] Result of a complete line shape analysis.

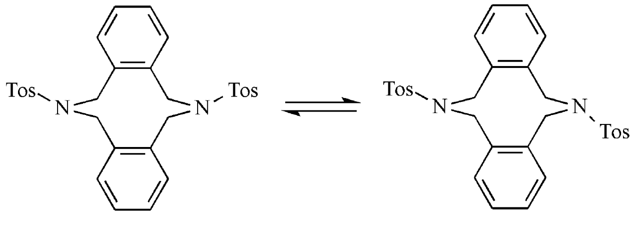
Table 2. Relative energies of formation ΔE (kJ/mol) of the various conformations of **3** and **7–12** as ab-initio calculated (HF/6-31G*level of theory)

Conformer/Compound	*anti-periplanar*	(+)*anti-clinal*	(−)*anti-clinal*	(*C*,*C*)*syn-periplanar*	(*C*,*B*)*syn-periplanar*	(*B*,*B*)*syn-periplanar*
3	0	27	2	34	4	46
7	0	19	13	46	25	81
8	0	–	69	46	52	–
9	0	49	94	42	69	–
10	0.0/0.8	–	34	–	53	–
11	0	59	5	32	14	75
12	0	–	64	38	74	–

In case of values not given $\Delta E>10$ kcal/mol (1 kcal/mol=4.184 kJ/mol) or conformation not obtained.

equilibrium of **3** which is still fast on the NMR time scale at lowest temperatures. The presence of the (*C*,*B*)*syn-periplanar* conformer, however, can be only very minor in solution as could be concluded from the low field position of the aromatic cyclophane protons.[4]

With increasing energy, for the 3,12-diaza analogue of [3.3]orthocyclophane **7** next to the most stable *anti-periplanar* conformer come the two *anti-clinal* conformations [(−) +1.3 kcal/mol; (+) +1.9 kcal/mol]; from a theoretical point of view, participation of the two latter conformers in the conformational equilibrium of **7** cannot be excluded. As the least stable conformations, the three *syn-periplanar* conformers were found (being at least 2.5 kcal/mol less stable) and for this reason, most probably, not participating in the conformational equilibrium of **7**.[4] In the *N*,*N*′-diacetyl and *N*,*N*′-dibenzoyl-substituted derivatives of **7** only the *chair*-like *anti-periplanar* conformer should participate in the corresponding conformational equilibria.[4] As the next stable conformers, the *boat*-like (*C*,*C*)*syn-periplanar* conformations were found (being at least 4.2 kcal/mol less stable); due to intramolecular steric hindrance the two (+/−)*anti-clinal* conformations proved even less stable.



10 A **10 B**

Scheme 3.

For the *N*,*N*′-ditosyl derivative of **7**, finally, which was reported differently with respect to the present conformational equilibrium,[4,10] beside the most stable *chair*-like *anti-periplanar* conformer only the (+)*anti-clinal* and the (*C*,*B*)-*syn-periplanar* conformers were found, the latter 5.3 kcal/mol less stable than the *chair* conformers, hereby proving the incorrect assignment in Ref. 4. Obviously, the authors incorrectly assigned the preferred conformer due to the enormous high field shifts in the ABCD spectra of the aromatic protons in the [3.3]orthocyclophane derivative (which are actually a result of the ring current effects of the tosyl substituents — vide infra) and because of not recognizing the presence of two preferred conformers (being actually ca. 50%:50%). These two *cis*/*trans-anti-periplanar* conformers (cf. Scheme 3) have also been calculated to be of similar energy (the *cis-anti-periplanar* conformer being 0.8 kcal/mol less stable) in complete coincidence with Ref. 10.

Similar conformational behaviour was obtained for the *6-10-0 systems* **11** and **12** studied. For the di-oxa analogue a rather complex conformational equilibrium has been calculated (cf. Table 2): beside the most stable *chair*-like *anti-periplanar* conformer, also the (+)*anti-clinal* conformer (>0.5 kcal/mol) and the (*C*,*B*)-*syn-periplanar* conformer (>1.4 kcal/mol) could participate in the conformational equilibrium of **11** in solution; only the *anti-periplanar* conformer was found experimentally.[4] However, because the low field position of the aromatic protons had been used as the major criterion of assignment, the results of the present calculations cannot completely exclude the participation of the (+)*anti-clinal* conformer.

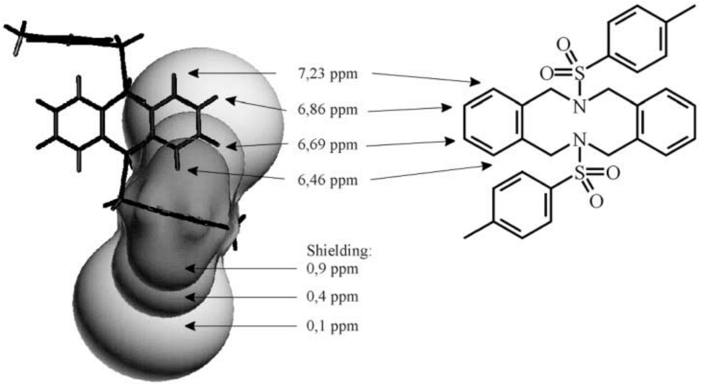


Figure 1. Visualization of the ring current effect of the tosyl aromatic moieties on the aromatic proton chemical shifts of the [3.3]orthocyclophane systems.

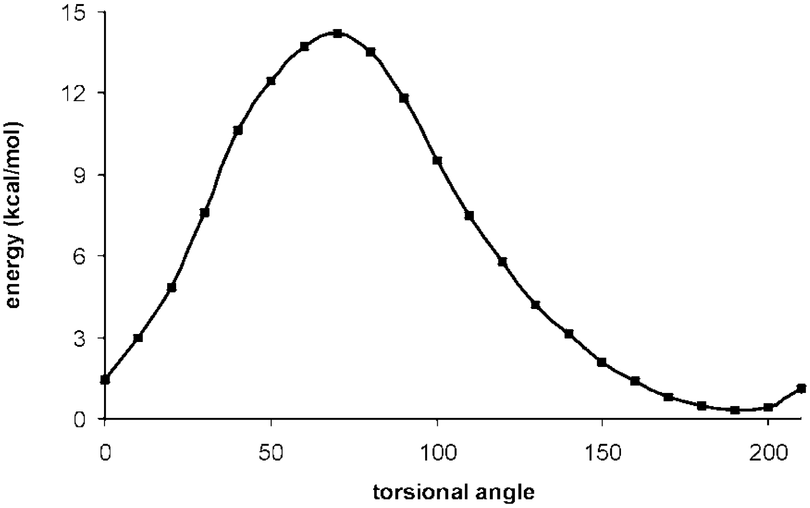


Figure 2. Reaction coordinate of the restricted rotation about the partial C,N double bond in *N*,*N*′-di-acetyl-3,12-di-aza[3.3]orthocyclophane **8**.

The ab-initio MO calculation of the dithia analogue **12** proved to be more in line with the experimental result: next to the most stable *chair*-like *anti-periplanar* conformer only the (*C*,*C*)-*syn-periplanar* conformer (>3.8 kcal/mol) was found, probably not participating in the corresponding conformational equilibrium. As further conformers of **12**, only the (+)*anti-clinal* conformer (>6.4 kcal/mol) and the (*C*,*B*)-*syn-periplanar* conformer (>7.4 kcal/mol) could be realized; stable (*B*,*B*)-*syn-periplanar* and (+)*anti-clinal* conformers were not obtained.

2.2. Ring current effect on ^{1}H chemical shifts of 3,12-di-tosyl-*N*,*N*′-diaza[3.3]orthocyclophane

In Ref. 4 the ring current effects of the tosyl substituents were not taken into account to assign the ^{1}H NMR spectra obtained; only the ring current effects of the [3.3]orthocyclophane aromatic moieties were considered. Now the tosyl ring current effects, present in the most stable conformer of **10**, the *chair*-like (*trans*) *anti-periplanar* conformer (cf. Scheme 3), have been calculated employing the GIAO method[11] on the basis of the corresponding HF/6-31G* optimized structure. The corresponding ring current anisotropy cones are visualized in Fig. 1; both the high field position and the ABCD nature of the [3.3]orthocyclophane aromatic protons becomes fully explainable: these protons are positioned in the 0.9–0.1 ppm shielding areas of the adjacent tosyl aromatic ring systems and here become adequately high-field-shifted to 6.45, 6.69, 6.86 and 7.23 ppm respectively.[4] This ring current effect, now calculated quantitatively,[12] proves both the result of the present ab-initio MO calculation with respect to the preferred conformer of **10** but also the reason for the enormous high field position of some of the [3.3]orthocyclophane aromatic protons in the ^{1}H NMR spectrum of **10** to be correct.[4]

2.3. Intramolecular mobility

At lower temperatures both the ^{1}H and ^{13}C NMR spectra of the studied compounds broaden and resolve after coalescence to several sets of signals; in the case of **8** and **9** two coalescence temperatures were obtained. The low temperature dynamic phenomena in the cases of **7**–**12** were assigned to the *interconversion of the 10-membered ring system* (cf. Table 1).[4] In the case of the *N*,*N*′-diacetyl and *N*,*N*′-dibenzoyl aza-derivatives of [3.3]orthocyclophane, a second dynamic process, the *restricted rotation about the partial C,N double bond* had been assigned (see also Table 1).[4] Contradicting these results, in Ref. 10 the only dynamic process obtained in **10** at lower temperature was assigned to the sterically restricted rotation about the N—S bond.

In order to prove also these different results, published previously, both the rotation about the C,N bond in **8** and **9** and about the N—S bond in **10** were also calculated by both the semi-empirical PM3 method and at the ab-initio HF/6-31G* level of theory. The torsional angles $C^2—N^3—S—C$ and $C^2—N^3—C{=}O$, respectively, were frozen and the molecules optimized with respect to the energy in this conformation; the relative energies, obtained hereby, were plotted vs the frozen dihedral angle and visualized in Figs. 2 and 3.

In Fig. 2 the reaction coordinate of the restricted rotation about the partial C,N double bond of the *N*,*N*′-di-acetyl-3,12-di-aza-[3.3]orthocyclophane **8** has been visualized. The typical behaviour was obtained: upon rotating the acetyl group from the common plane of delocalization with the lone pair at the ring nitrogen atom (at ca. 190°), this delocalization becomes increasingly hindered thereby raising the energy of the system. Near to the perpendicular conformation (at ca. 75°), this delocalization is interrupted and the highest point on the reaction coordinate is achieved. Further twist stabilizes the molecule again. The calculated highest and lowest points on the reaction coordinate were not exactly at 90 and 180°, respectively, but slightly different. The reason for this proved to be the interplay of delocalization of the nitrogen lone pairs and steric hindrance of the *N*,*N*′-acetyl substituents with the rest of the molecule, which both influence the total energy of the molecule studied. The barrier to rotation, thus obtained for **8** at the HF/6-31G* level of theory, is 59.5 kJ/mol (in rather good coincidence with the experimental value of 74.2 kJ/mol). A

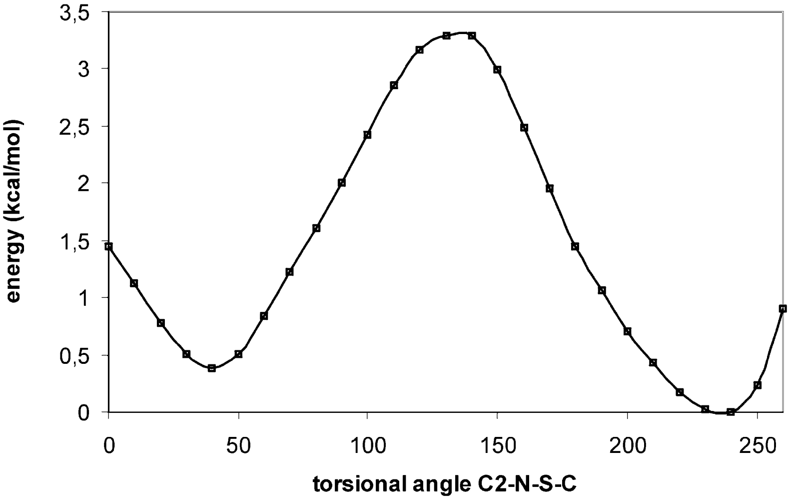


Figure 3. Reaction coordinate of the sterically hindered rotation about the *exo*-cyclic N–S bond in *N,N′*-di-tosyl-3,12-di-aza[3.3]orthocyclophane **10**.

similar plot for the *N,N′*-dibenzoyl analogue **8** has been obtained with the barrier to rotation slightly reduced (58.2 kJ/mol; exp. 69.2 kJ/mol).

The barriers to rotation about the partial C,N double bond have been calculated to be lower than those obtained experimentally. The reason for these theoretical results should be that both the solvent influence and the electron correlation were not taken into account. For this dynamic process, these two influences on the calculationed result, if taken into account, will increase the corresponding barrier to rotation by at least 10–12 kJ/mol.[13] In this light, the theoretical results obtained for the C,N barrier to rotation proved to be excellent.

Completely different from this behaviour, consider the restricted rotation about the N—S bond in **10**. The present calculation proves steric hindrance dominates the reaction coordinate, which is visualized in Fig. 3. The lowest point was found at 45° torsional twist; the highest point at 135°. Both conformations are determined by the amount of repulsive interaction between the tosyl aromatic moiety and the aromatic [3.3]orthocyclophane protons H-6,9,15,18. The corresponding barrier to rotation thus obtained, amounts to 13.8 kJ/mol only, too low to be in charge of the dynamic phenomena found along the previous dynamic NMR study (38.9 kJ/mol[4] and 43.2–43.5 kJ/mol[10]). As a result of this theoretical study it can be concluded finally that also in the *N,N′*-ditosyl-3,12-di-aza[3.3]-orthocyclophane **10** (as found for the [3.3]orthocylophane **1** and **2** and the other heterocyclic analogues **3–9**, **11** and **12**) the dynamic process, which could be studied by dynamic NMR spectroscopy at lower temperatures, proves to be the *ring interconversion of the 10-membered [3.3]orthocyclophane ring system* as published previously,[4] but incorrectly reassigned in Ref. 10.

3. Conclusions

Both the conformational equilibria of the heterocyclic [3.3]orthocyclophane derivatives **3** and **7–12**, and the restricted rotation about the C,N and S,N bonds, respectively, in **8–10** have been calculated at the HF/6-31G* level of theory. The *chair*-like *anti-periplanar* conformer proved to be the most stable conformer in coincidence with previous experimental studies.[3,4,10] In the cases of **3** and **11** the additional participation of the (−)*anti-clinal* conformer in the present conformational equilibria cannot be excluded. For *N,N′*-ditosyl-3,12-di-aza[3.3]-orthocyclophane **10** the *cis/trans* isomers **10A** and **10B** have been confirmed to be the preferred conformers[10] and not the (*C,B*)*syn-periplanar* conformer, as incorrectly assigned previously.[4]

The ring interconversional process of the heterocyclic analogues of [3.3]orthocyclophane had been studied already by dynamic NMR spectroscopy[4] and was found in the range of 38–48 kJ/mol; the dynamic phenomena studied in both the ^{1}H and ^{13}C NMR spectra of **10** could be assigned to the same process excluding the alternative restricted rotation about the N,S bond as another of this theoretical study.

The restricted rotation about the partial C,N double bond in the *N,N′*-disubstituted 3,12-diaza[3.3]orthocyclophane derivatives **8** and **9** has also been calculated and proved to be in good agreement with the barriers to rotation, experimentally determined.

4. Experimental

The quantumchemical calculations were performed on SGI O2 and a SGI Origin 2000 computers at the University of Potsdam. Molecular dynamics simulations were carried out using the Tripos Force Field implemented in the Sybyl 6.6[14] program package; geometry optimizations were performed with the semiempirical method PM3[15,16] and at the HF 6-31G* level of theory[17] using the program GAUSSIAN 94.[18]

To investigate the conformational space of the compounds, the molecules were allowed to move freely at 1000 K over a time period of 1 ns. Every 20 fs a conformation was stored yielding a set of 50000 snapshots for each compound studied. Afterwards, the family algorithm was used to subdivide these conformations into groups containing the conformations which will reach the same local energy minimum along the geometry optimization. For this clustering six of the eight torsional angles within the 10-membered ring system were used; the grid width was choosen to be 30°. From each family one conformation was used for geometry optimization with the semiempirical PM3 method; the final refinement of the geometry was calculated by employing ab-initio HF calculations with the HF 6-31G* basis set.

For the calculation of the shielding/deshielding cones of the ring current effects of the tosyl-substituents in **10**, the global minimum structure of **10** was set into a grid of ghost atoms ranging from −10.0 to +10.0 Å.[12] The chemical shielding/deshielding at every point of that grid was calculated with the GIAO method[11] and visualized as iso-chemical shift surfaces (ICSS).[12]

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