

FULL PAPER

Molecular Dynamics of a Schiff Base Tetramacrocycle Studied by NMR and MD Simulations

Andreas Grohmann¹, Harald Lanig², Walter Bauer³, Stefan Schmidt¹, and Frank W. Heinemann¹

¹Institute of Inorganic Chemistry, University of Erlangen-Nürnberg, Egerlandstrasse 1, D-91058 Erlangen, Germany. Fax: +49-9131-8527367; E-mail: grohmann@anorganik.chemie.uni-erlangen.de

²Computer Chemistry Center, Institute of Organic Chemistry, Nägelsbachstrasse 25, D-91052 Erlangen, Germany

³Institute of Organic Chemistry, University of Erlangen-Nürnberg, Henkestrasse 42, D-91054 Erlangen, Germany

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Abstract Schiff base condensation of the pentadentate tetrapodal amine **1** with 2,6-diformyl-4-methylphenol **2** leads in a [3 + 6] condensation to a previously not described macrocycle **3** which shows C_3 -symmetry. X-ray analysis shows a truncated cone shape for **3**. At $T \geq 100^\circ\text{C}$, the ^1H -ROESY/EXSY spectrum reveals pairwise exchange of corresponding sites, indicative of inversion of the whole molecule in an umbrella-like fashion. Molecular dynamics simulations support this hypothesis.

Keywords Macrocycle, Schiff base, NMR, Chemical exchange, MD, Proton template, ROESY, EXSY

Introduction

The terminology “template synthesis” is of fundamental importance in the field of supramolecular chemistry. Apart from the many main group and transition metal group ions used as templates [1], proton template synthesis is becoming increasingly important. Schiff base macrocycle condensations are among the more recent examples in which proton templates have shown to be effective [2]. In this paper we report on the spontaneous Schiff base condensation of a

tetrapodal pentadentate ligand with an aromatic dialdehyde, leading to a previously undescribed new kind of a tetramacrocyclic ring with interesting dynamic behavior.

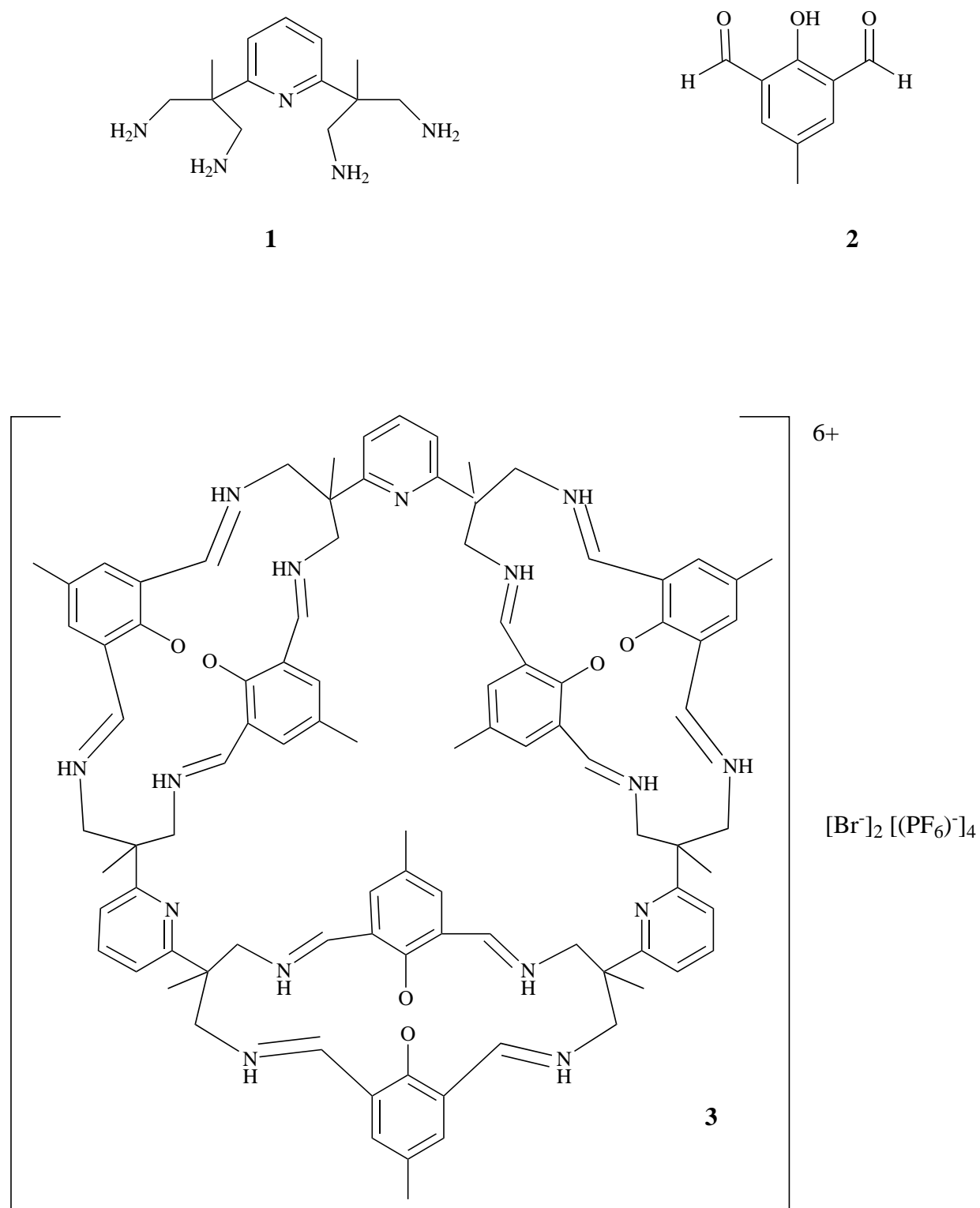
Results and discussion

The reaction of tetraamine **1** and dialdehyde **2** (see Scheme 1) in a 1:2 stoichiometric ratio in refluxing methanol and in the presence of two equivalents of HBr resulted in the formation of a red precipitate. After anion exchange (ClO_4^- or PF_6^- for Br^-), red crystals were obtained.

To our surprise, the X-ray analysis revealed a Schiff base condensation product where three units of **1** and six units of **2** are fused to form a cyclic [3 + 6]-species **3**. The molecular structure of the macrocycle in **3** is shown in Figure 1 [3].

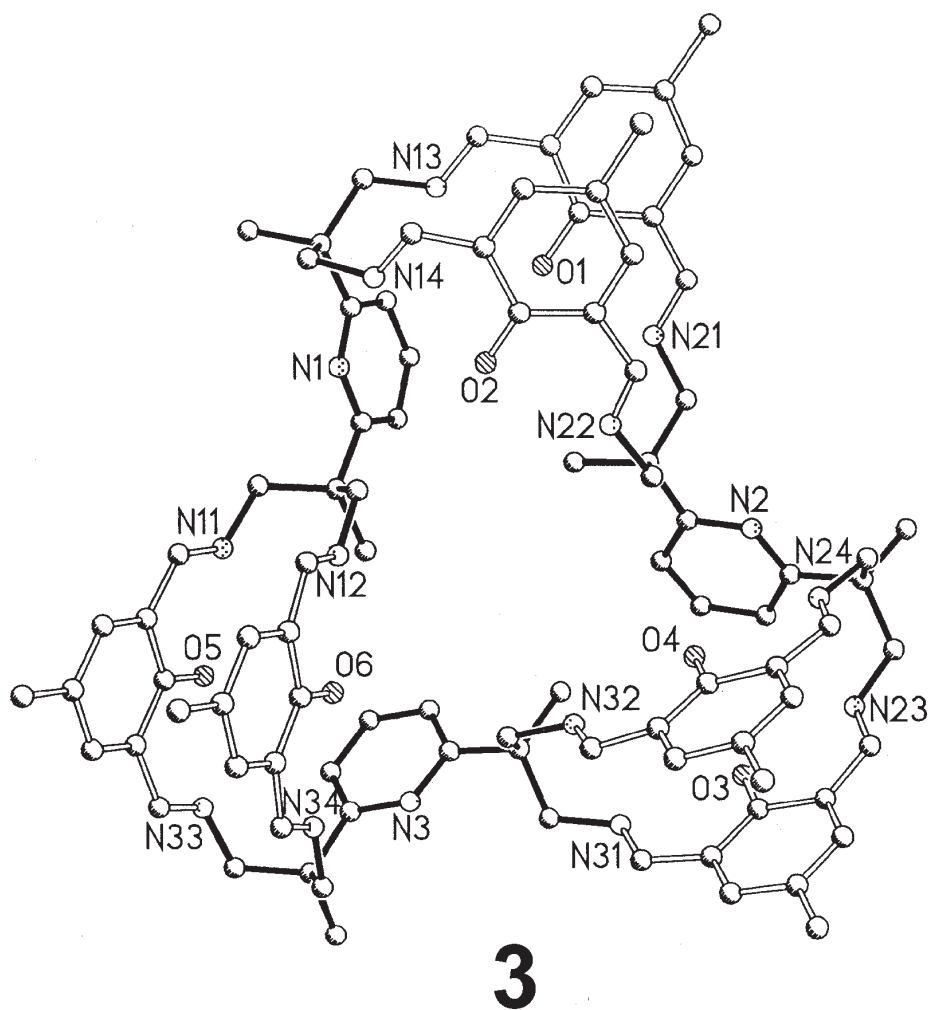
Correspondence to: A. Grohmann

Dedicated to Professor Paul von Ragué Schleyer on the occasion of his 70th birthday and in appreciation of his outstanding contributions to experimental and theoretical chemistry



Scheme 1 Schematic representation of the pentadentate tetrapodal amine **1**, 2,6-diformyl-4-methylphenol **2** and the Schiff base tetra-macrocycle **3**

Figure 1 Molecular structure of the tetramacrocycle **3**, obtained from the condensation of polyamine **1** (solid bonds) and dialdehyde **2** (open bonds) in the presence of acid. Hydrogen atoms at carbons and anions ($\text{Br}^-/\text{PF}_6^-$) have been omitted for clarity



Double strand moieties formed by the phenyl rings alternate with single strand moieties of the pyridines.

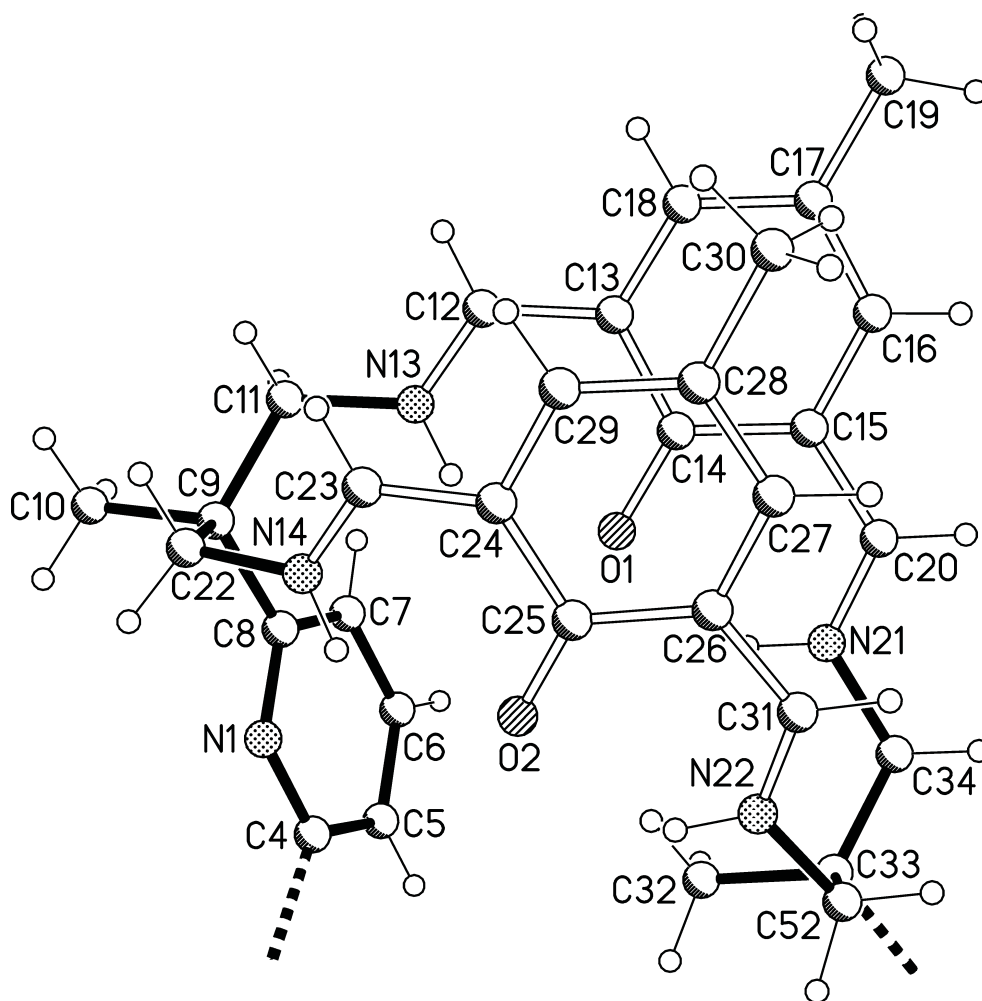
Macrocycle **3** is chiral and has C_3 -symmetry. A side view is reminiscent of a truncated cone where the narrow orifice is at the site of the phenyl oxygens and the wide orifice at the site of the phenyl methyl groups. Due to π -stacking forces, the phenyl rings are pairwise co-planar, with an average interplanar distance of 3.7 Å. All phenolbis(alimine) units are planar because of hydrogen bonding in the $\text{N}\cdots\text{H}\cdots\text{O}\cdots\text{H}\cdots\text{N}$ arrangements, which involve two aldimine nitrogens and one phenol oxygen.

The formation of macrocycle **3** is remarkable: in a high-yield (> 90%) single batch reaction a total of 12 new bonds are formed, leading to a cyclic oligomer with an unprecedented structure. We suggest that the reaction is driven by proton templates in the same way as in the [2 + 2]-condensation of 1,3-diaminopropane with 2,6-diformyl-4-methylphenol [4]. The role of bromide during macrocycle formation presumably is of minor influence since bromide may be removed completely by anion exchange. Detailed studies on the reaction mechanism are underway.

The ^1H - and ^{13}C -NMR spectra of dissolved crystals of **3** in DMSO-d_6 are completely in agreement with the X-ray structure. Due to the inherent threefold symmetry of the molecule the spectra reduce to the "monomeric" unit shown in Figure 2. The numbering therein is adopted from the X-ray analysis. Numbers of protons in the following refer to the parent carbon- or nitrogen atoms. All ^1H - and ^{13}C -resonances have been assigned by a combination of standard 1D/2D-methods [5] (COSY, HETCOR, HMQC, HMBC, COLOC, ROESY) as well as by the newly developed pulse sequence DPFGE-ROE [6].

Due to the double-cone-shaped structure of **3**, the phenyl rings forming the "inner" and the "outer" cone are non-equivalent, resulting in two separate ^1H - and ^{13}C -singlets for methyl groups C19 and C30. In addition, based on the threefold molecular symmetry, ring positions C27 and C29 are diastereotopic. Similar considerations apply for other corresponding pairs of positions (e.g., $\text{N13} \neq \text{N14} \neq \text{N21} \neq \text{N22}$; $\text{C5} \neq \text{C7}$; etc.). All geminal pairs of hydrogen atoms at C11, C22, C34 and C52 are diastereotopic. Since these carbon positions are diastereotopic themselves, a total of eight proton chemical shifts for these hydrogen positions result (Fig-

Figure 2 “Monomeric” unit in **3**. The proton numbers follow the numbers of their parent carbon or nitrogen atoms



ure 3a). Each pair of geminal protons at the above positions shows a doublet and a double doublet (apparently a triplet). This is due to the positions relative to the protons at the adjacent N-atoms: hydrogens *gauche* to NH show no coupling with NH (and, hence, only a doublet due to coupling with the geminal proton) whereas the hydrogens *anti* to NH reveal both geminal (2J) and vicinal (3J) couplings (Karplus equation [7]).

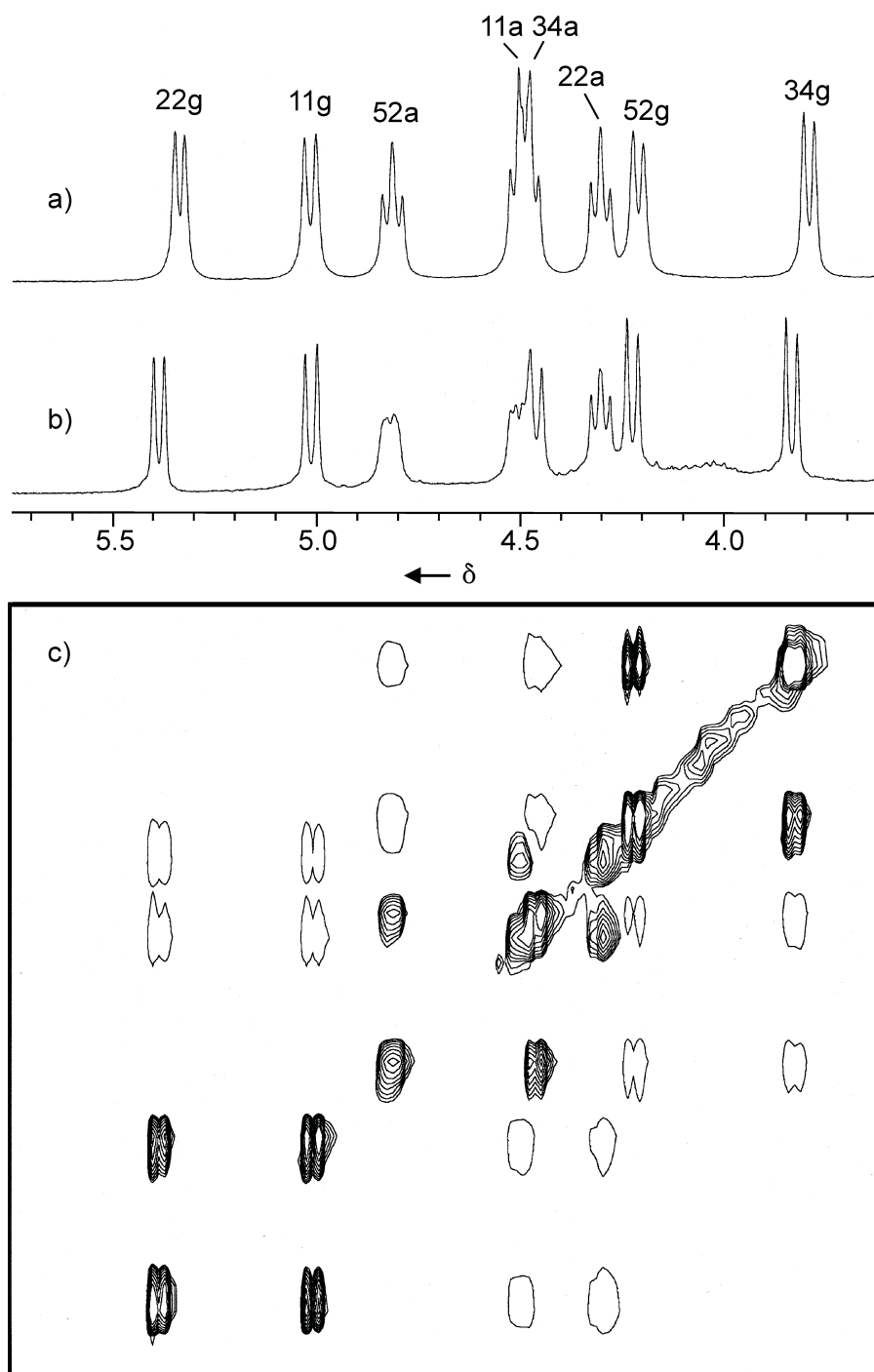
Interesting dynamic phenomena are observed at elevated temperatures (Figures 3b and 3c). At +70°C, the ROESY/EXSY-spectrum indicates chemical exchange of the NH-protons, not unusual for iminium hydrogen atoms. However, at still higher temperatures ($\geq 100^\circ\text{C}$) pairwise chemical exchange of the proton positions of the dialdehyde-derived aromatic rings is observed, i.e. the “inner” rings of the cone exchange with their “outer” counterparts. Additional exchange is observed for the imine CH-protons, e.g. H12 \leftrightarrow H23. Moreover, of the geminal CH₂-protons, each “inner” proton exchanges with its “outer” counterpart, e.g. H11(*gauche*) \leftrightarrow H22(*gauche*); H11(*anti*) \leftrightarrow H22(*anti*). We interpret these observations as a dynamic process in which the entire molecule changes conformation in an umbrella-like fashion, lead-

ing to its enantiomer. Consistent with this assumption, the relative positions of the methyl groups of the pyridine spacers do *not* change: C10 remains pointing “outward”, irrespective which enantiomer is present, C32 remains pointing “inward”. As deduced from the chemical shift differences of pairwise exchanging sites, the umbrella inversion of the molecule must proceed with a barrier of $\Delta\Delta G^\ddagger > 18 \text{ kcal mol}^{-1}$. This estimation is based on the well-known equation (1) and the Eyring equation. The smallest number of the chemical shift difference of exchanging proton pairs has been employed for this calculation (H11a \leftrightarrow H22a; $\Delta\nu = 103 \text{ Hz}$). Additional dynamic effects are observed for some of the protons *anti* to NH in Figure 3b. We attribute this to differences in the exchange rates of the NH-protons which causes coalescence for the involved CH₂-protons.

$$k_{\text{exch}} = \pi \Delta\nu / (2)^{1/2} \quad (1)$$

To explore the conformational behavior of the molecule, Molecular Dynamics simulations at different equilibration temperatures were performed. The common starting geometry was obtained by minimizing the X-ray geometry using Allinger’s MM3 force field (see details in the experimental

Figure 3 (a) $^1\text{H-NMR}$ spectrum of **3** in $\text{DMSO-}d_6$, $+100^\circ\text{C}$; resonance region of the geminal CH_2 protons H11, H22, H34, and H52. The numbering is based on the numbering of the parent carbon atoms in Figure 2. Symbols a and g denote anti and gauche positions relative to the vicinal NH proton; (b) Same as (a), at $+100^\circ\text{C}$; (c) ROESY spectrum of **3** ($\text{DMSO-}d_6$, $+25^\circ\text{C}$). Cross peaks with more than one contour are positive (same sign as diagonal peaks) and are due to chemical exchange. Cross peaks with only one contour are negative and originate from NOE

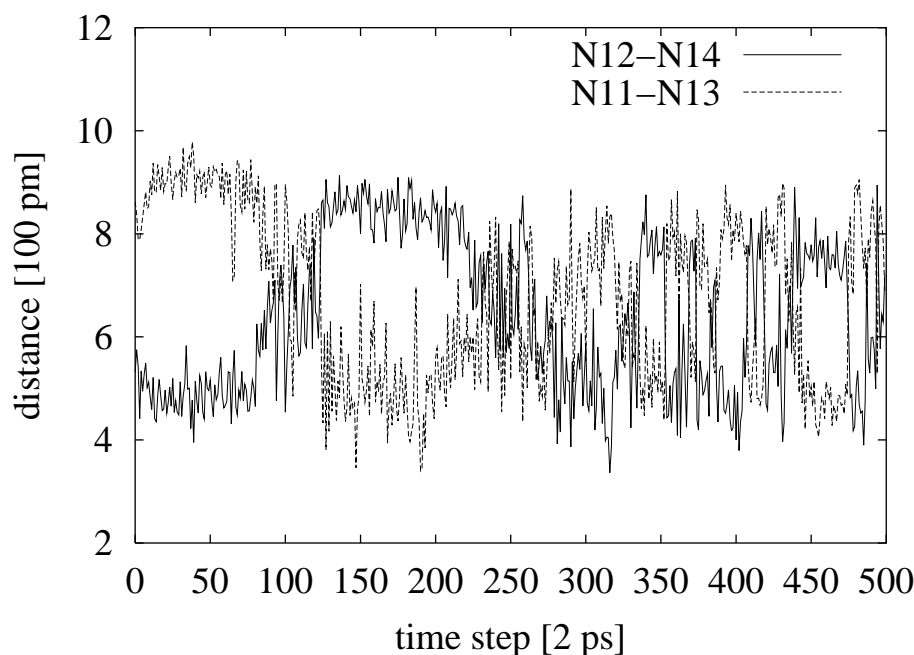
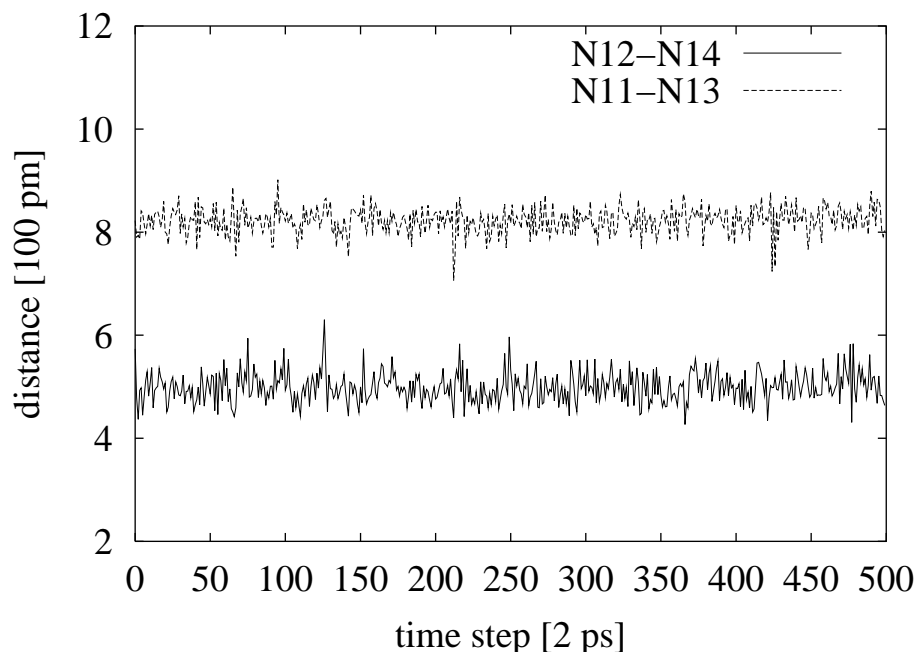


section). It is important to note that the overall conical shape of the molecule was maintained during the minimization. However, the exact parallel orientation of the phenol subunit could not be maintained because of the neglect of explicit π - π stacking interactions and, not to be underestimated, by the absence of crystal packing effects within a gas-phase simulation. To comprehend and quantify a possible inversion of the whole structure during the MD simulation, for every snapshot the distances between (a) the inner and outer phenolic

oxygen atoms and (b) the inner and outer adjacent Schiff base nitrogen atoms were calculated.

Figure 4 shows two representative examples of a plot of the distances N12-N14 and N11-N13 during the simulation for several temperatures. In every frame, a distance of an inner atom pair (N12-N14) is plotted together with the corresponding outer pair (N11-N13), named according to the situation in the starting geometry (minimized X-ray coordinates). The direct comparison of the inner and outer atom pair dis-

Figure 4 Time evolution of the distances N12-N14 (inner) and N11-N13 (outer) during the 1 ns trajectory for several simulation temperatures. The terms inner and outer correspond to the situation inside or outside the cone within the starting geometry. (a): $T = 400$ K. (b) As the temperature reaches 600 K the antipodal oscillations indicate an inner/outer inversion of the corresponding phenyl fragments



tances belonging together allows the identification of structural inversion in that area.

At temperatures higher than 500 K, oscillations in the plotted distances can be found. This value should not be compared quantitatively to the experimental result, because of the limited simulation time (which requires higher, often unrealistic temperatures) and the lack of environmental effects like periodic boundaries or explicit solvent molecules. However, the corresponding inner/outer pairs behave oppo-

sitely. This observation is important, because the parallel phenol subunits of the starting geometry are not coupled in their movement by stacking interactions or especially introduced interaction parameters. The oscillating behavior is the same for all Schiff base nitrogen distances and also, with a larger amplitude, for the inner and outer phenolic oxygens (not shown). It is therefore reasonable to argue that these oscillations describe an inner/outer inversion of the molecule.

Visual inspection of selected snapshot geometries is not as revealing as expected, because the geometries are hot (trajectory is in equilibrium at the desired temperature) and so strong geometrical distortions are introduced. This is true even after applying a Simulated Annealing protocol to selected structures to remove the excess energy (data not shown).

Experimental

NMR spectra were recorded on a JEOL Alpha500 spectrometer (11.7 T) in DMSO- d_6 solution. For the spectra shown in Figure 3, an inverse probehead has been used. Spectral parameters of the ROESY spectrum (Figure 3c) were: 1024 data points in t_2 , spectral width in f_2 and f_1 7740 Hz, acquisition time 0.1323 sec, 32 scans per t_1 -increment, recycle delay 2 sec, 256 t_1 -increments, spin lock time 1000 ms, temperature 100°C; Figure 3 shows the cutout of the region of the geminal CH_2 protons.

In order to explore the conformational behavior of the compound, we performed Molecular Dynamics simulations according to the following procedure. To obtain a reasonable starting geometry without internal strain, the X-ray coordinates were first minimized by a conjugate-gradient algorithm using Allinger's MM3 force field [8] until the energy gradient was smaller than $0.01 \text{ kcal mol}^{-1} \text{ \AA}^{-1}$. During all simulations, no explicit Coulomb potential was introduced, electrostatic interactions were treated by bond dipoles applying a dielectric constant of 1.5 for the environment (parameterization default value). The structure obtained served as starting geometry for all subsequent dynamics simulations.

First, the molecule was heated to the desired temperature by applying a Berendsen coupling [9] to an external bath using a coupling time of 0.1 ps. As integration method for the Standard Newtonian dynamics, the Velocity Verlet procedure with a time step of 1 fs was used. No distance cutoffs or periodic boundaries were applied to the energy function. Every two picoseconds of the ongoing trajectory (length 1 ns), the conformation was saved, resulting in an ensemble of 500 snapshots. Because the primary intention was to explore

the dynamical behavior of the molecule and not possible minimum-energy conformations, no subsequent quenching of the snapshots by minimization or Simulated Annealing protocols was added. All calculations were performed using the Tinker Molecular Modeling Package.[10]

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