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Improved Stereochemical Analysis of Conformationally Flexible Diamines by Binding to a Bisporphyrin Molecular Clip

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Abstract: The relative stereochemistry of acyclic diamines with several stereogenic centers has been analyzed by NMR spectroscopy in combination with conformational deconvolution. Binding to a bisporphyrin molecular clip improves the stereochemical assignment significantly. The diamines were synthesized from inexpensive sugar alcohols, and their stable hydrochlorides were quantitatively converted into free bases by treatment with ion-exchange resin.

Keywords: configuration determination · conformation analysis · host–guest systems · N ligands · NMR spectroscopy

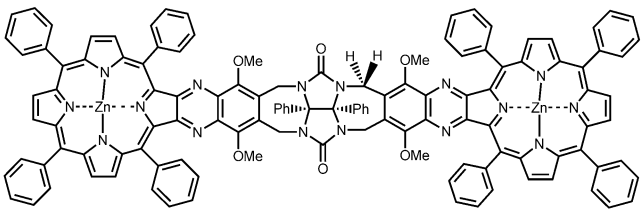
Introduction

Whenever chemical syntheses result in the formation of molecules with several stereogenic centers, it is crucial to determine their relative stereochemistry. In contrast to rigid molecules, or those with only a few conformers, this can be quite difficult to achieve for small, flexible molecules. In this situation, NMR spectroscopic parameters are obtained as population-weighted time averages and cannot truly be represented by a single conformation. To facilitate assignments under these preconditions, several methods are in common use.[1] Whereas coupling constant (*J*)-based configurational analysis assumes the data is dominated by one or a few conformers, Kishi's universal NMR database (UDB) method matches experimental spectral parameters against a library of model compounds without involving conformational analysis.[2] Computational methods for the prediction of conformer distributions and hence the resulting NMR spectroscopic parameters have to rely on a detailed knowledge of molecular interactions in solution, which might be difficult to achieve. They are therefore very successful for molecules for which a single conformation is dominant, such as proteins, but not as much for small, flexible molecules.

A different approach is used in NMR spectroscopic analysis of molecular flexibility in solution (NAMFIS), in which a complete set of conformers by matching against experimental NMR spectroscopic data is reduced to a subset, eventually obtaining a conformer population that is likely to generate the observed parameters.[3] Here, one can chose a parameter that, in contrast to scalar coupling constants (*J*) and chemical shifts (δ), is not biased by substituent effects (i.e., the nuclear Overhauser effect (NOE)). The method has been successfully applied to small and medium-sized molecules.[4]

While all these approaches handle a scenario in which the organic molecule is present free in solution, we found it tempting to investigate whether conformational restriction imposed on the flexible molecule might improve such an analysis. Diamines bound to metalloporphyrins emerged as suitable systems for this investigation, since their binding interaction has been studied extensively.[5–7] In particular, binding to bisporphyrin tweezers is responsive to a variety of molecular properties. Examples include differentiation between guests of varying size,[6] and in particular determination of the absolute stereochemistry of guest molecules, often through the circular dichroism of the formed complexes.[7] Usually, the conformations of guest molecules in these complexes are analyzed in terms of a single, dominating conformation, or are undetermined. For our purpose, we required a rigid, symmetric bisporphyrin molecular clip. Such a host would have to form host–guest complexes with diamines, have a small number of NMR spectroscopic signals, and also provide chemical-shift effects due to the diamagnetic porphyrin system, thus minimizing signal overlap between host and guest. We therefore chose the glycoluril bisporphyrin clip **1** (Schemes 1 and 2).[8]

Suitable guest molecules with known stereochemistry were prepared from two alditols by conversion into α,ω-diaminopolyolmethoxy ethers. Sorbitol was transformed into



Scheme 1. Bisporphyrin clip **1** with a glycoluril scaffold.

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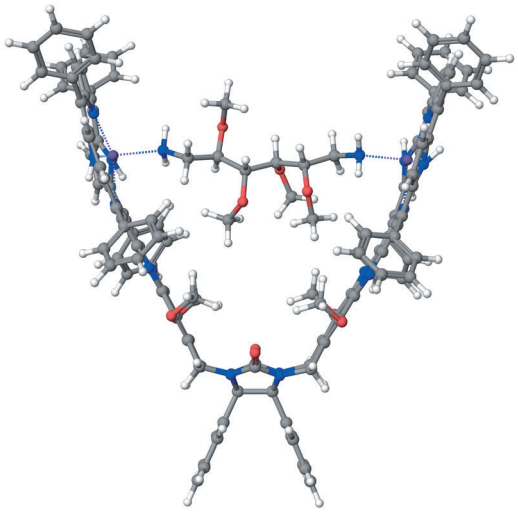
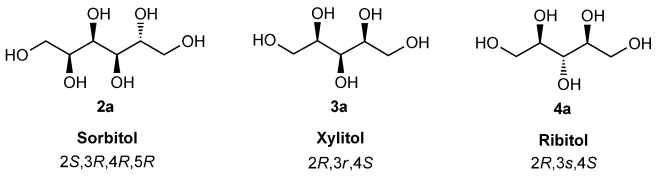


Scheme 2. The binding of (2*S*,3*R*,4*R*,5*R*)-1,6-diamino-2,3,4,5-tetramethoxyhexane (**2**) and clip **1** is illustrated.

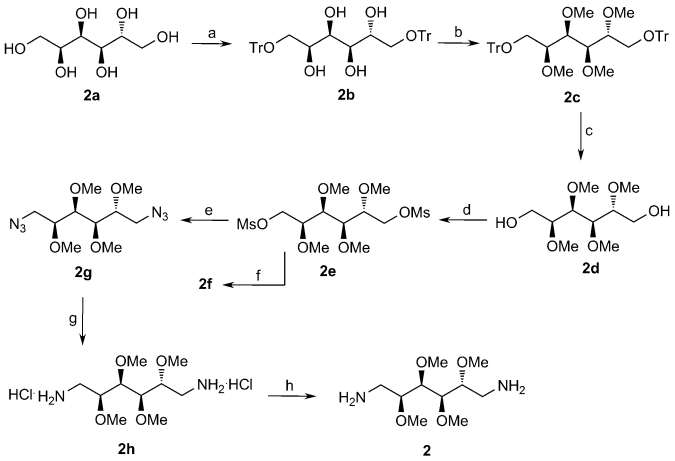
compound **2**, which has no symmetry elements, and xylitol provided *meso* compound **3**. In these guests, methoxylation of the hydroxy groups was expected to prevent the conformational equilibria to be dominated by hydrogen-bonding interactions.

Results and Discussion

Synthesis of diaminopolyol methoxy ethers: Diaminodideoxyalditols constitute an interesting group of monomers for the preparation of biodegradable polymers from renewable starting materials.[9,10] In a previously published synthetic route starting from a 1-benzyl hexopyranoside,[11] a sequence of methylation with MeI, debenzylation, reduction, mesylation, nucleophilic substitution, and subsequent reduction of the diazide to diamine afforded the title compounds in seven steps. One peculiar observation was the formation of cyclic ethers from the mesylated intermediates.[10,11] Initially, a series of alternative, apparently simpler synthetic routes was considered. Thus, oxidation of the alditol to aldaric acids, followed by methylation, ammonolysis to the diamides, then followed by reduction to diamines yielded a complex product mixture.[12] Sulfonylation of an alditol[13] followed by azidation gave a mixture of products in low yield. Therefore, we devised a strategy related to the one by Galbis et al.[11] but starting from alditols (Schemes 3 and 4).



Scheme 3. Alditol starting materials.

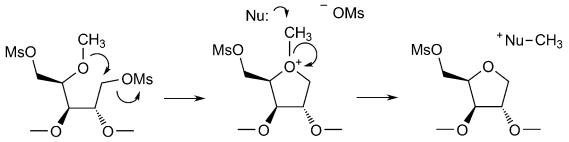


Scheme 4. Synthesis of 1,ω-diaminodideoxyalditol methyl ethers (here starting from sorbitol). a) TrCl, pyridine, 100 °C, 69 %; b) MeI, DMF, NaOH, 77 %; c) *p*-TSA monohydrate, MeOH/CH_2Cl_2, 77 %; d) Et_3N, MsCl, 99 %; e) NaN_3, DMF, 70 °C, 70 %; f) chromatographic materials, 70 %; g) $LiAlH_4$ (**1**), HCl (**2**), 0 °C, 89 %; h) Amberlite IRA-400, MeOH, quantitative.

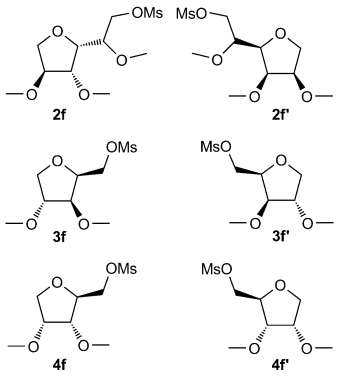
Sorbitol **2a** was tritylated at the terminal positions with tritylchloride/pyridine (69 %), and the resulting tetraol **2b** was methylated with iodomethane to afford the tetramethyl ether **2c** (77 %). Detritylation (*p*-TsOH in MeOH/CH_2Cl_2) yielded the tetramethylated sorbitol **2d** (77 %). Mesylation with mesyl chloride afforded **2e** (crude yield from NMR spectroscopy integration 99 %). Reaction of **2e** with sodium azide gave the diazide **2g** (yield 70 %). Reduction of **2g** with $LiAlH_4$ produced the diamine, which after treatment with dry hydrogen chloride was obtained as the hydrochloride **2h** (yield 89 % from diazide). Total yield from **2e**: 62 %. In an analogue synthesis, xylitol was converted into the (2*R*,3*R*,4*S*)-1,5-diamino-1,5-dideoxy-2,3,4-tri-*O*-methylxylitol dihydrochloride (**3**), 39 % yield from mesylate **3e** (see the Supporting Information for details).

Deprotonation: Hydrochloride salts are the derivative of choice for storage of amines without decomposition. However, quantitative deprotonation of the dihydrochlorides **2h** and **3h** by the addition of various bases was difficult to achieve with satisfactory purity due to the solubility of the protonated species in both water and organic solvents. On the other hand, Amberlite IRA-400 resin was found to provide a fast, convenient, and clean method to convert **2h** and **3h** into the free amines **2** and **3**, by using MeOH as solvent to prevent formation of emulsions, in quantitative yields. This deprotonation also works equally well for very basic chelating diamines such as bispidine derivatives and for terminal diamines with long (up to 20 carbon atoms) alkyl chains.[14] This method has previously been used for the deprotonation of base-sensitive oligosilsesquioxane amine hydrochlorides.[15]

Formation of cyclic byproducts: During workup, the mesyl methyl ethers **2e** and **3e** but not **4d** were found to undergo



Scheme 5. Proposed mechanism for demethylative cycloetherification of **3e**.



Scheme 6. Possible products from ring closure of dimesyl-*o*-methyl derivatives **2e**, **3e**, and **4e**. Only compounds **2f** and **3f/3f'** were formed.

a slow demethylation to form cyclic ethers (Schemes 5 and 6). Such a demethylation has previously only been reported by Galbis et al. (also for **3e**).[11] The analogous debenzylative cyclization is a fairly common reaction of benzylated polyols with good leaving groups,[16] and its dependence on stereochemistry has been discussed by Defaye and Horton.[17] The mechanism involves anchimeric assistance of a benzyloxy group in the δ position to a good leaving group by means of the formation of a cyclic oxonium ion.[16a] Since this side reaction reduces yield and purity of the mesyl methyl ethers, we found it worthwhile to look into the conditions for this reaction to occur.

Formation of cyclic compounds occurred during the preparative workup of **3e** from a synthesis performed in a nonnucleophilic solvent such as CH_2Cl_2. The reaction was facilitated by the presence of chromatographic materials (SiO_2, basic Al_2O_3, neutral Al_2O_3, and Florisil). Contrary to previous observations,[11] we found **3e** to be stable in room-temperature solutions in the absence of such materials. In the same manner the cyclic byproduct **2f** was isolated after column chromatography of **2e**. To check the impact of stereochemistry, the ribitol analogue **4e** was synthesized. When tested, **4e** did not form any cyclic byproduct (i.e., **4e** remained intact after column chromatography and after standing in solution over silica for 12 h). As for the impact of the stereochemistry, it was confirmed that cyclization only occurs when the ring alkoxy groups are in a *trans* position, such as in **2f** and **3f/3f'** as opposed to **4f**.

Binding studies of guests 2 and 3 with clip 1: Binding between clip **1** and diamines **2** and **3**, respectively, was indicated by UV/Vis and by ^{1}H NMR spectroscopy. Thus, a redshift of the Soret band by 7 nm was obtained at 1:1 ratios.[7e] NMR spectroscopic titration of the diamines with **1** resulted in the expected chemical-shift change of guest signals to lower values, with a maximum change for 1:1 molecular ratios. Ditopic binding was also indicated by the number of observed NMR spectroscopic signals, which were in accordance with the diamines being positioned on the inside of the clip and binding to both porphyrin walls. Furthermore, protons closest to the amino groups showed the largest chemical-shift change upon binding. At lower temperatures, some signal broadening was observed. This indicates residual dynamics at higher temperatures, which eventually ceases upon cooling (Figures S38–41 in the Supporting Information).

The ^{1}H NMR spectra of **2** and **3** are first order, with signals within a narrow chemical-shift range. Upon binding to clip **1**, signals become thoroughly separated (Figure 1) as is commonly observed for organic molecules that bind to porphyrin hosts.

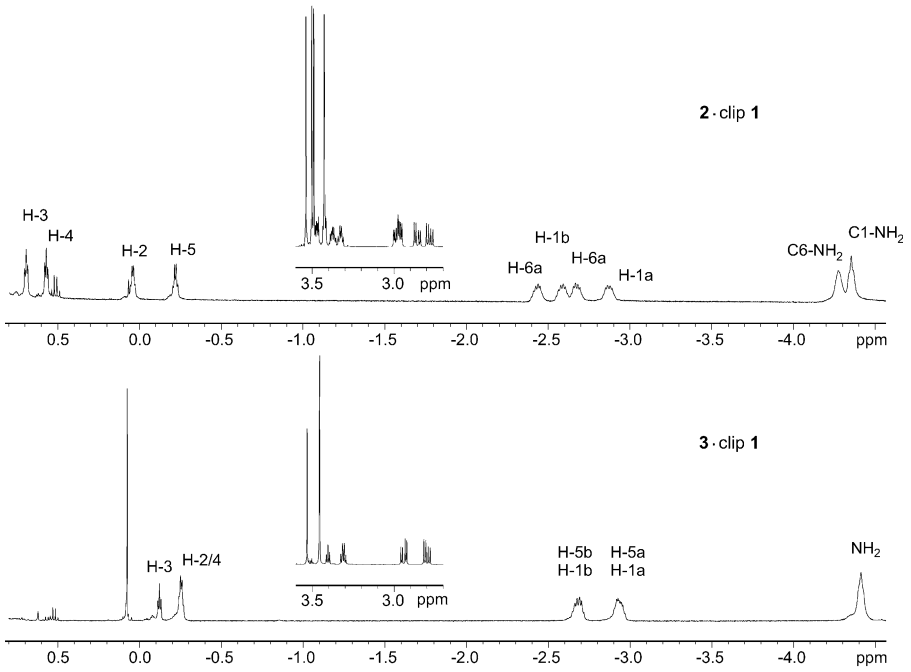
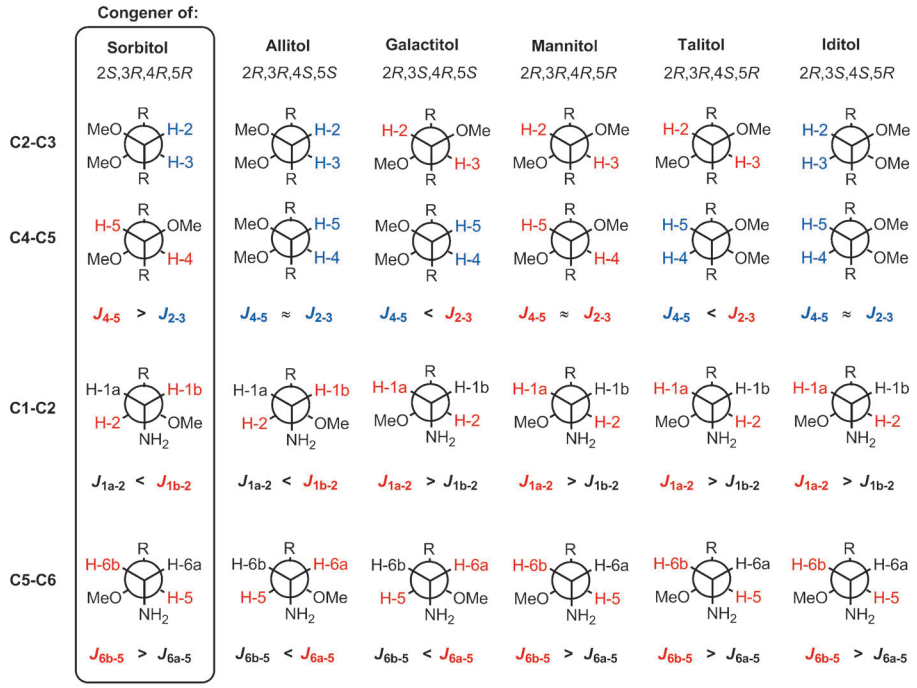


Figure 1. ^{1}H NMR spectra of diamines **2** and **3** bound to clip **1**. Inset (plotted at same scale): free diamines (500 MHz, $CDCl_3$ solution, 25 °C).

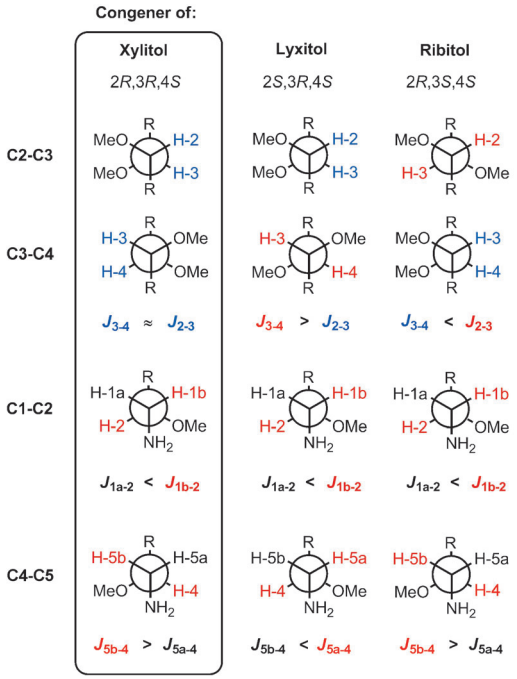


Scheme 7. Newman projections along C–C single bonds in the proposed main rotamer of **2** (box) and its diastereomers, identified by their parent alditol. The proton pair generating the largest J value when comparing J(H-2,H-3) to J(H-4,H-5), J(H-1a,H-2) to J(H-1b,H-2), or J(H-6a,H-5) to J(H-6b,H-5) is marked in red.

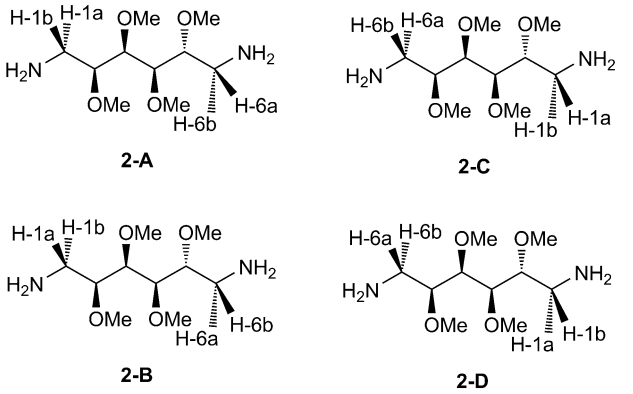
Signal assignment: Initial signal assignment was achieved by using J-based arguments. Whereas the sequential connectivity of H-1 through H-6 is unequivocal, it is still necessary to distinguish between the signals of H-1a/b versus H-6a/b. If we assume an all-*trans* carbon chain to represent the main conformer, we can identify substituent arrangements about each C–C single bond with the largest substituents in *anti* positions (Scheme 7, sorbitol stereochemistry). The diastereomers of sorbitol are included in the analysis to illustrate that these J-based arguments would not clearly single out one stereoisomer if the stereochemistry of the investigated compound were unknown. Here, when looking at sorbitol for the assignment of **2**, the dihedral angle between the two protons H-2 and H-3 is 60°, and for H-4 and H-5 this angle is 180°. Therefore, J(H-4,H-5) would be expected to be larger than J(H-2,H-3). Of the two alternative coupling constants, we therefore assigned J(H-4,H-5) = 5.2 Hz and J(H-2,H-3) = 2.7 Hz, respectively. This then results in the assignment of H-1 through H-6. Clearly, the difference in the coupling constants is small, and we cannot be certain that the rotamer shown in Scheme 7 is the dominant one.

Finally, amongst the diastereotopic methylene protons on C-1 and C6, H-6a/H-6b are distinguished by realizing that H-6a should have a smaller coupling with H-5 (60° dihedral angle) than H-6b (180° dihedral angle). Likewise, H-1a (60° dihedral angle) should have a smaller coupling than H-1b (180° dihedral angle) with H-2. The same argument is used for the other diamino derivative **3** (Scheme 8) as well as intermediates **2b–h**, **3b–h**, and **4b–e**. Although this analysis makes it likely (although not certain) that of the four alternative assignments in Scheme 9 the one labeled **2-A** is the correct one, it should be emphasized that a J-based analysis would not be sufficient to distinguish between **2** and all of its diastereomers, or between **3** and its diastereomers.

Signal assignment using conformational deconvolution of NMR spectroscopic parameters: The four alternatively assigned structures **2-A** through **2-D** were subjected to a NAMFIS-type analysis[3] (i.e., a set of NMR spectroscopic parameters was fitted against varying populations of possible conformations). This conformational deconvolution was carried out by using DISCON software, which expresses the quality of fit in terms of root–mean–square (RMS) values.[18] These RMS values are calculated by comparing the experimental parameter values (NOEs and J) with those calculated for the chosen population of conformations. For the free diamine **2**,



Scheme 8. Newman projections along C–C single bonds in the proposed main rotamer of **3**, **4**, and diastereomer, identified by their parent alditol. The proton pair generating the largest J value when comparing J(H-2,H-3) to J(H-3,H-4), J(H-1a,H-2) to J(H-1b,H-2), or J(H-5a,H-4) to J(H-5b,H-4) is marked in red.



Scheme 9. Alternative directional assignments of the C1–C6 chain, and of the diastereotopic protons Ha/Hb of diamine **2** derived from sorbitol.

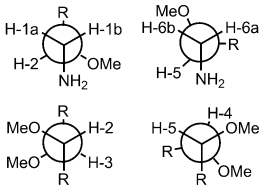
the analysis resulted in a small variation of RMS values (derived from NOEs and *J* values) with **2-A** providing the best fit (Table 1). The same result was obtained for the bound diamine. It should be noted that the dominant conformation of the bound **2** was not all-*trans*, but *gauche* interactions

Table 1. Assignment analysis of diamine **2** by conformational deconvolution.

Assignment (Scheme 9)	free diamine[a]	NOE distance RMS bound diamine all-*trans* conformer[b]	population[c]
2-A	0.31	0.43	0.32
2-B	0.42	0.71	0.45
2-C	0.47	0.59	0.46
2-D	0.44	0.66	0.46

[a] Population from unrestricted conformational search reduced by redundant conformation elimination. NOEs and *J* values were used in the analysis. [b] Only NOEs were used in the analysis. [c] Population of conformations with the N–N distance restricted to 4–9 Å. Only NOEs were used in the analysis.

were present (Figure 2 and Scheme 10). Most likely, these are a result of suboptimal fitting between the diamine and the cavity provided by the clip **1**. As expected, trying to fit the data to a single, all-*trans* conformation, which in the analysis corresponds to approximately 25% of the population, resulted in increased RMS values and a modified order of best fit assignment. Thus, conformational deconvolution provided the correct signal assignment without requiring presumptions about conformational preferences. It must be



Scheme 10. Newman projections along C–C single bonds in the dominant conformation of bound **2**.

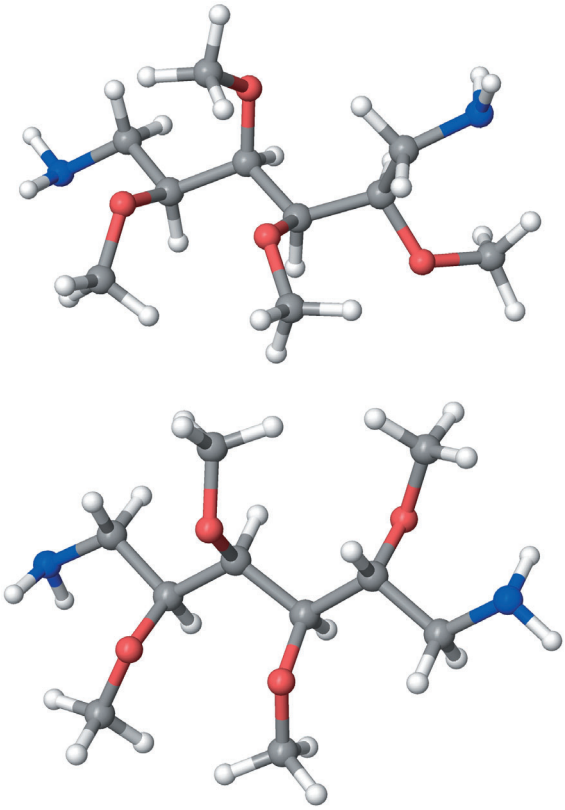


Figure 2. Main conformations of **2** bound to clip **1**. Top: Dominant conformation (≈75%). Bottom: All-*trans* conformation (≈25%).

stressed, however, that a comparison of RMS values is meaningful only within the same series of isomeric structures, since different series might have this parameter derived from different parameter numbers and experimental data.

Conformational analysis: The free diamine **2**, due to its high flexibility, is expected to adopt a multitude of conformations in solution. Thus, conformational deconvolution yielded four main families of conformations (Figure 3) with a molar ratio of approximately 1:1:1:2 (RMS 0.31).

In contrast, the free symmetric diamine **3** derived from xylitol was not a suitable candidate for this analysis due to the chemical equivalence of several protons (i.e., H-2/H-4, H-1a/H-5a, H-1b/H-5b, and MeO-2/MeO-4). By signal averaging on the NMR spectroscopic timescale, these protons, although being nonequivalent in the various conformations, become degenerate in chemical shift. Therefore the experimental data is indeterminate for the analysis and no acceptable matching of conformers can be obtained.

In complex with **1**, diamine **2** exists in a 1:3 molar ratio of two dominant conformations (RMS = 0.32). Of these, the all-*trans* conformer (25%) had an N–N distance of 8.9 Å. In contrast, the most dominant conformation (75%) exhibits a carbon chain with a *gauche* conformation about one of the C–C bonds (Figure 2 and Scheme 10) and an N–N distance of only 7.6 Å.

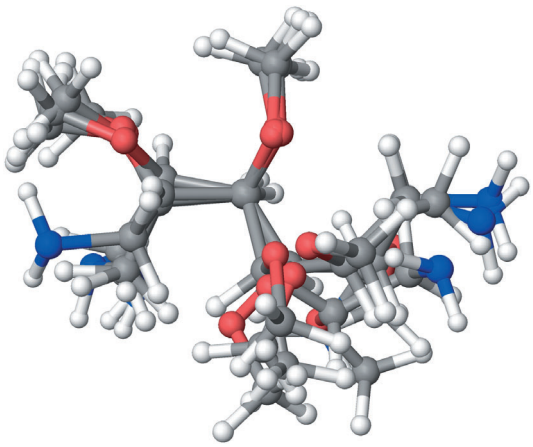


Figure 3. Ensemble of the four main conformations of free diamine **2**.

When diamine **3** is bound to **1**, there are three best matching conformers (1:1:2 molar ratio, RMS = 0.48), one of which (with ratio 2) is completely all-*trans* (Figure 4). Within these, N–N distances are 5.6, 6.6, and 7.6 Å (all-*trans*), thus indicating some flexibility of the clip **1**, which

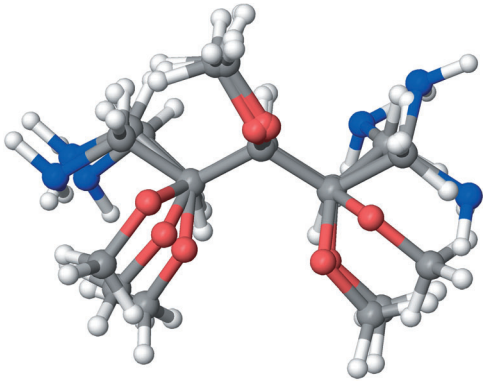


Figure 4. Dominant conformations of bound **3**.

can adjust the wall-to-wall (Zn–Zn) distance depending on the bound diamine. Previously, the equilibrium distance between Zn atoms in clip **1** was found to vary from approximately 7.0 to 12.4 Å depending on the size of the ligand. Considering a Zn–N bond length of typically 2.03 to 2.23 Å,[19] this would correspond to ligand N–N distances between 3.0 and 8.4 Å being able to fit into the clip.

Distinction of stereoisomers: To investigate if different diastereomers of a flexible molecule such as **2** could be distinguished from each other, we subjected its diastereomers to a similar conformational deconvolution analysis (Table 2). Conformational searches were performed for **2** and all of its diastereomers (identified in Table 2 by the corresponding parent alditols), excluding enantiomers. For the fitting procedure, experimental NOE or ROE values measured for free **2** were used. The lowest RMS error was obtained for

Table 2. Conformational deconvolution analysis of free and bound **2** and its diastereomers.

Isomer derived from[a]	Stereochemistry[b]	RMS, free diamine[c]	RMS, bound diamine[d]
sorbitol	2*S*,3*R*,4*R*,5*R*	0.31	0.37
allitol	2*R*,3*R*,4*S*,5*S*	0.38	0.49
galactitol	2*R*,3*S*,4*R*,5*S*	0.38	0.50
mannitol	2*R*,3*R*,4*R*,5*R*	0.39	0.69
talitol	2*R*,3*R*,4*S*,5*R*	0.40	0.57
iditol	2*R*,3*S*,4*S*,5*R*	0.66	0.49

[a] Stereochemistry indicated by the corresponding alditol. [b] Assignment in the order used for **2**. [c] Population from unrestricted conformational search. [d] Single all-*trans* conformers.

the diamine derived from sorbitol, which is identical to the actual isomer **2**. However, the RMS variation is very small (ΔRMS = 0.07–0.09, with the exception of the iditol congener with ΔRMS = 0.35). Therefore, it is debatable if this would be considered sufficient to confirm the stereochemistry of **2**. On the other hand, for the bound diamines, there is a more pronounced difference between the RMS for the correct isomer (i.e., the sorbitol congener) and its diastereomers (ΔRMS = 0.13–0.32), thereby resulting in a more convincing identification.

A more substantial gain by binding is obtained when matching diamine **3** derived from xylitol against its diastereomers. Here, the data for the free diamine were too degenerate to allow any analysis. For the bound diamine, which was matched against experimental data for **3** bound to clip **1**, a significant difference of RMS values was obtained, with **3** having the lowest value (**3** (2*R*,3*R*,4*S*) = 0.39, lyxitol congener (2*S*,3*R*,4*S*) = 0.69, ribitol congener (2*R*,3*S*,4*S*) = 0.71). We suggest that this is mostly an effect of conformational rigidification of the bound molecules.

To summarize, these results indicate a significant improvement in the stereochemical analysis on the basis of conformational deconvolution by restricting the number of relevant conformations through binding to a molecular clip.

Conclusion

We have shown how the structural assignment of conformationally flexible molecules with several stereogenic centers by NMR spectroscopy can be improved by binding to a symmetric, semirigid bisporphyrin molecular clip with two binding sites. An additional advantage of this host, besides rigidification of the guest molecule, is the separation of host signals, which otherwise might overlap in the ^{1}H NMR spectrum. Furthermore, we also have devised a modified synthetic strategy for the preparation of 1,ω-diaminodideoxyalditol methyl ethers, starting from inexpensive alditols. Initially formed dihydrochlorides are quantitatively transformed into the free bases by use of ion-exchange resin. The formation of cyclic ethers by demethylative cyclization can be avoided by minimizing the contact with typical chromatographic stationary phases.

Experimental Section

Starting materials were purchased from commercial suppliers and were used without purification. Room temperature (RT) refers to 20–22 °C. Column chromatography was performed using Merck silica gel 60 (40–63 μm), Fisher Florisil (60–100 μm), or Merck basic aluminum oxide (60–200 μm). Thin-layer chromatography (TLC) was performed by using aluminum sheets precoated with silica gel 60 F_{254} (0.2 mm, E. Merck). Chromatographic spots were visualized by UV and, if required, by one of the following stains: a solution of ninhydrin (2%) in ethanol, a solution of H_2SO_4 (10%) in ethanol, or a basified solution of $KMnO_4$ in H_2O. MS-ESI data were obtained using a Waters Micromass ZQ systems, EI, 70 eV; compounds were dissolved in methanol prior to analysis. High-resolution mass spectra were recorded using a Waters GCT Premier, CI (methane), 70 eV, with a direct insertion probe. NMR spectra were recorded using Varian Unity Inova 500 MHz (^{1}H 499.9 MHz, ^{13}C 125.7 MHz), Varian Unity 400 MHz (^{1}H 399.5 MHz, ^{13}C 100.6 MHz), or Varian Mercury Plus 300 MHz (^{1}H 300.0 MHz, ^{13}C 75.5 MHz) spectrometers. Chemical shifts are referenced indirectly to tetramethylsilane through the residual solvent signals (^{1}H: $CHCl_3$ at $\delta = 7.26$ ppm, HDO at $\delta = 4.79$ ppm, ^{13}C: $CDCl_3$ at $\delta = 77.0$ ppm). Signal assignments were derived from ^{1}H, ^{13}C, COSY,[20] PE COSY,[21] gHSQC,[22] gHMBC,[23] ROESY,[24] and TOCSY[25] spectra. For NMR spectroscopic titrations, aliquots of ligand solution were added to a solution of clip **1** in an NMR spectroscopy tube. The relative stereochemistry of the synthesized compounds was determined using 2D NMR spectroscopy and *J*-based configurational analysis.[1] Melting points were determined in open capillaries using a Stuart Scientific SMP10 melting-point apparatus and are uncorrected. Specific optical rotations were measured using a Perkin–Elmer 241 polarimeter. Elemental analyses were performed by Eurofins Mikrokemi AB, Uppsala, Sweden.

Conformational analysis: Coupling constants were extracted from first-order multiplets in ^{1}H NMR spectra. NOE buildup experiments were performed using NOESY[26] experiments with six different mixing times (see the Supporting Information). NOE peak integrals were measured as an average of both symmetry-related cross-peaks after thorough baseline and phase corrections and normalized against both diagonal peaks. For bound ligands, ROESY[24] experiments were performed with the same strategy. Unrestricted conformational searches for each compound were performed in MacroModel 9.9 with the OPLS-2005 force field and $CHCl_3$ as solvent to generate conformations that represented the entire conformational space. This set of conformations was reduced by a redundant conformer elimination using ConfGen[27] and/or manual elimination of similar conformations to result in a set of 5–15 structures. For comparison of diastereoisomers in all-*trans* mode, the structure of **2** was built and minimized, then chirality was inversed to create the other isomers from the same base structure. For ligands bound to clip **1**, an N–N distance restraint of 4 to 9 Å was applied in a series depending on the ligand and then combined. For the NAMFIS[3] analysis, DISCON[18] software was utilized, using the goodness-of-fit expressed as an RMS deviation as an indicator for agreement between calculated population of conformations and experimental data, with lower values meaning better fit.

For the synthesis of **2a–h**, **3a–h**, and **4a–e**, see the Supporting Information.

(2*S*,3*R*,4*R*,5*R*)-1,6-Diamino-1,6-dideoxy-2,3,4,5-tetra-*O*-methyl sorbitol (2): Amberlite IRA-400 resin (chloride form, Sigma–Aldrich, 0.5 cm^3) was rinsed with H_2O (5 mL), NaOH (1 M, 8 mL), and H_2O (5 mL) again, upon which an $AgNO_3$ test for Cl^- was performed to verify complete conversion of the resin to the OH^- form. This resin was rinsed with MeOH (3 mL) and transferred into a 1 mL vial. (2*S*,3*R*,4*R*,5*R*)-1,6-Diamino-1,6-dideoxy-2,3,4,5-tetra-*O*-methyl sorbitol dihydrochloride (**2h**; 9 mg, 0.03 mmol) was dissolved in MeOH (0.5 mL) and poured over the resin. The mixture was left to stand for 30 min under an argon atmosphere and then filtered through a glass wool plug. Evaporation of the solvent afforded **2** as a clear oil (7.1 mg, 0.03 mmol, 100%). $[\alpha]_D^{20} = 31.9$ ($c = 8$ in CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): $\delta = 3.53$ (s, 3H; OCH_3-4), 3.50 (s, 3H; OCH_3-2), 3.48 (s, 3H; OCH_3-3), 3.47 (dd, ^3J(H,H) = 5.6, 3.4 Hz, 1H; H-3), 3.42 (s, 3H; OCH_3-5), 3.42 (dm, ^3J(H,H) = 3.4 Hz, 1H; H-4), 3.37 (ddd, ^3J(H,H) = 6.6, 6.6, 4.0 Hz, 1H; H-5), 3.33 (ddd, ^3J(H,H) = 5.6, 5.4, 3.6 Hz, 1H; H-2), 2.99 (dd, ^3J(H,H) = 13.5, 3.6 Hz, 1H; H-1a), 2.96 (dd, ^3J(H,H) = 13.2, 4.0 Hz, 1H; H-6a), 2.85 (dd, ^3J(H,H) = 13.5, 5.4 Hz, 1H; H-1b), 2.78 ppm (dd, ^3J(H,H) = 13.2, 6.6 Hz, 1H; H-6b); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): $\delta = 83.6$ (C-2), 82.5 (C-5), 81.4 (C-4), 79.6 (C-3), 60.8 (OCH_3-4), 60.5 (OCH_3-3), 59.3 (OCH_3-2), 57.6 (OCH_3-5), 42.4 (C-6), 40.8 ppm (C-1); HRMS (CI): *m*/*z* calcd for $C_{10}H_{24}N_2O_4$ [M^+]: 237.1818; found: 237.1814.

Diamine 2 bound to clip 1: Clip **1** (3.1 mg, 0.0016 mmol) was dissolved in Alox-filtered $CDCl_3$ (0.6 mL) in an NMR spectroscopy tube. Aliquots of **2** dissolved in $CDCl_3$ were added in small portions until a clip **1/2** molar ratio of 1:0.8 was reached. ^{1}H NMR ($CDCl_3$, 500 MHz, 25 °C): $\delta = 1.67$ (s, 3H; Me-4), 1.48 (s, 3H; Me-3), 1.43 (s, 3H; Me-2), 1.17 (s, 3H; Me-5), 0.69 (m, 1H; H-3), 0.57 (m, 1H; H-4), 0.04 (m, 1H; H-2), −0.22 (m, 1H; H-5), −2.43 (m, 1H; H-6b), −2.58 (m, 1H; H-1b), −2.67 (m, 1H; H-6a), −2.87 (m, 1H; H-1a), −4.27 (br s, 2H; NH_2-C6), −4.35 ppm (br s, 2H; NH_2-C1); UV/Vis (CH_2Cl_2): $\lambda_{max} = 428$, 582, 672 nm.

(2*R*,3*R*,4*S*)-1,5-Diamino-1,5-dideoxy-2,3,4-tri-*O*-methyl xylitol (3): Amberlite IRA-400 resin (chloride form, Sigma–Aldrich, 0.5 cm^3) was rinsed with H_2O (5 mL), NaOH (1 M, 8 mL) and H_2O (5 mL) again, upon which an $AgNO_3$ test for Cl^- was performed to verify complete conversion of the resin to the OH^- form. This resin was rinsed with MeOH (3 mL) and transferred into a 1 mL vial. (2*R*,3*R*,4*S*)-1,5-Diamino-1,5-dideoxy-2,3,4-tri-*O*-methyl xylitol dihydrochloride (**3h**; 12 mg, 0.045 mmol) was dissolved in MeOH (0.5 mL) and poured over the resin. The mixture was left to gently stir for 30 min under argon atmosphere and then filtered through a glass wool plug. Evaporation of the solvent afforded **3** as pale yellow oil (8.5 mg, 0.044 mmol, 99%). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): $\delta = 3.53$ (s, 3H; OCH_3-3), 3.46 (s, 6H; OCH_3-2 + OCH_3-4), 3.40 (dd, ^3J(H,H) = 4.8, 4.8 Hz, 1H; H-3), 3.31 (ddd, ^3J(H,H) = 6.2, 4.8, 4.8 Hz, 2H; H-2 + H-4), 2.94 (dd, ^3J(H,H) = 4.8, 13.3 Hz, 2H; H1-b + H5-b), 2.80 ppm (dd, ^3J(H,H) = 6.2, 13.3 Hz, 2H; H1-a + H5-a); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): $\delta = 83.0$ (C-3), 81.9 (C-2 + C-4), 60.8 (OCH_3-3), 58.9 (OCH_3-2 + OCH_3-4), 42.3 ppm (C-1 + C-5); HRMS (CI): *m*/*z* calcd for $C_8H_{20}N_2O_3$ [M^+]: 193.1541; found: 193.1539.

Diamine 3 bound to clip 1: Clip **1** (3.2 mg, 0.0016 mmol) was dissolved in Alox-filtered $CDCl_3$ (0.6 mL) in an NMR spectroscopic tube. Aliquots of **3** dissolved in $CDCl_3$ were added in small portions until a clip **1/3** molar ratio of 1:0.8 was reached. ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 1.1$ (s, 6H; Me-2 + Me-4), 1.09 (s, 3H; Me-3), −0.12 (dd, ^3J(H,H) = 4.8, 4.8 Hz, 1H; H-3), −0.26 (dm, ^3J(H,H) = 4.2 Hz, 2H; H-2 + H-4), −2.69 (m, 2H; H-1b + H-5b), −2.94 (m, 2H; H-1a + H-5a), −4.41 ppm (br s, 4H; NH_2); UV/Vis (CH_2Cl_2): $\lambda_{max} = 428$, 582, 672 nm.

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