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Computational Chemistry

Hydrocarbon Macrocycle Conformer Ensembles and ^{13}C-NMR Spectra

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Abstract: NMR as a routine analytical method provides important three-dimensional structure information of compounds in solution. Here we apply the recently released CRENSO computational workflow for the automated generation of conformer ensembles to the quantum mechanical calculation of ^{13}C-NMR spectra of a series of flexible cycloalkanes up to $C_{20}H_{40}$. We evaluate the computed chemical shifts in comparison with corresponding experimental data in chloroform. It is shown that accurate and properly averaged theoretical NMR data can be obtained in about a day of computation time on a standard workstation computer. The excellent agreement between theory and experiment enables one to deduce preferred conformations of large, non-rigid macrocycles under ambient conditions from our automated procedure.

Conformational analysis and thereby the knowledge about preferred molecular conformations and the three-dimensional structure of molecules is of fundamental importance in chemistry.[1] It enables an in-depth understanding of reaction mechanisms,[2] molecular recognition,[3] or identification of bio-active states.[4] The investigation of flexible macrocycles already started in the early 20th century and the Nobel Prize awarded to D. Barton[5] in 1969 highlights the general interest in understanding conformationally rich cyclic compounds. Cycloalkanes represent valuable model systems for studying macrocycle conformations in solution. They meet the requirements of readily available experimental data and exist in systematically increasing ring sizes. The absence of functional groups enables unobstructed investigation of basic conformational effects and minimizes additional influences of strong interactions, e.g., hydrogen bonding. From a theoretical point of view, cycloalkanes are well suited as basic model compounds due to their relatively simple intramolecular interactions accompanied by an enormously large and rich but still explorable potential energy surface (PES). Hence, many studies on cycloalkanes were performed already in the early 1970s with important contributions by Anet, Allinger, Dale and Schleyer[6–11] to name a few. The reported data mainly consist of crystal structure information, force-field strain-energy calculations, and low-temperature NMR measurements. NMR spectroscopy presents an excellent analytical method for the study of flexible molecules and is nowadays an extremely important routine application in the field.[12–14]

Before presenting our computational approach, we briefly discuss previous works in the field of conformational analysis focusing on macrocyclic compounds in solution. From an experimental viewpoint NMR data like nuclear Overhauser effect (NOE) crosspeak volumes, ^3J scalar couplings constants and residual dipolar couplings (RDCs)[15–17] are used to analyse structural motifs. This data provides information on interatomic distances, dihedral angles and relative orientational restraints from which a molecular structure can be derived. However, often the structure identification problem is under-determined and to address this problem combined experimental and theoretical workflows like the NMR Analysis of Molecular Flexibility in Solution (NAMFIS) method have been developed.[18] Bazzo et al. proposed to compute conformer ensembles from Monte Carlo and molecular dynamics (MD) simulations, which can already in their creation process be guided by experimentally derived constraints, i.e., using ^3J dihedral or NOE distance constraints. From the ensemble NAMFIS determines relative populations of conformers that are in agreement with experimental evidence and evaluates the quality of the reproduction of the structural features, without the evaluation of theoretically determined (free) energies. This very much experimentally driven approach has been successfully applied in the investigation of flexible LSD-1 inhibitors,[19] the solution structures of cell-permeable macrocycles[20] and the folding propensities of β-hairpin peptides.[21] An improvement upon NAMFIS is the Distribution of Solution Conformations (DISCON) software, which re-implemented NAMFIS and adds a clustering algorithm and new solvers.[22–24]

More recently in 2018 Nguyen et al. introduced the conformational analysis from NMR and density-functional prediction of low-energy ensembles (CANDLE) approach.[24] It is based on an iterative generation of the ensemble through high-temperature CHARMM molecular dynamics simulations followed by energetic sorting and clustering of conformers. DFT-optimized gas-phase conformers are created from each cluster, which serve as the

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starting point for room-temperature MDs, that are then re-clustered. The final ensemble is optimized at the DFT level, energies and chemical shifts are computed and compared directly to the experiment. The authors identified the most complex task to be the exploration of the chemical space, but also noted that errors in the chemical shift calculations can hamper a comparison to experiment.

Currently, enormous efforts are being made to use macrocyclic compounds as drug leads for many difficult but highly important targets.[20,25] The main difficulty is that they are flexible and their solution ensembles and dynamics have to be taken into account, but few accurate methods exist to perform such an analysis routinely. This motivated us to study cycloalkanes as model systems and to propose a state-of-the-art method to analyze the solution conformations of flexible macrocycles.

In 2017 we proposed a theoretical protocol for the automated computation of spin-spin-coupled NMR spectra for flexible compounds.[26] Its' key aspect is the generation of a fairly complete (low-energy) conformer–rotamer ensemble (CRE) by searching on the PES of the fast semi-empirical GFN*n*-xTB[27,28] methods. The classification of the ensemble into identical isomers, conformers, and rotamers is based on electronic energy, atomic Cartesian RMSD, and purely structure-based molecular rotational constants using predefined thresholds (for more details see Ref. [28]). Subsequent refinement of geometries and free energies at a higher DFT theoretical level accurately identifies the most populated conformers for which NMR properties, i.e., shielding and spin–spin-coupling constants are calculated. Using the assembled data, the NMR parameters are properly thermally averaged, the spin Hamiltonian is solved and a fully coupled spectrum is obtained without any manual intervention which can be directly compared to experiment. The same procedure has recently been successfully applied to calculate the conformationally averaged optical rotation values of 28 large commercial drug molecules[29] as well as other properties of non-rigid compounds.[30]

Here, we investigate the series of cycloalkanes from cyclobutane to cycloicosane and their conformational behavior in $CHCl_3$ solution at 298 K. The quality of the computed conformational ensemble is investigated by comparison of theoretical and experimental ^{13}C-NMR spectra (^{1}H and ^{13}C chemical shifts are given in the Supporting Information). The high sensitivity of NMR to structural details enables a reliable benchmarking of how well theory can describe conformer populations in solution. However, for non-rigid compounds at ambient conditions, the rapid nuclei interchange typically occurring on a sub ps time scale, leads to an average of NMR parameters on the much slower time scale of the experiment which has to be considered theoretically. The relevant thermally accessible ensemble of minimum energy structures generally consists of conformers as well as rotamers (conformer/rotamer ensemble, CRE). A conformer is characterized by a distinct energy minimum, while rotamers arise from bond rotation or an inversion process leading to an interchange of nuclei and to minima with identical energies and NMR parameters.[26] For this variety of structures, an averaged NMR spectrum is measured[31] and hence the accurate computation of the CRE is a key for reliable NMR simulations of flexible compounds.

The effect of including or ignoring an ensemble average is demonstrated here for the ^{13}C-NMR spectrum of cycloheptadecane ($C_{17}H_{34}$) in Figure 1. The hypothetical spectrum of only one frozen rotamer, i.e., a single geometry depicted in Figure 1Aa) in the absence of any nuclei exchange, is shown in part B, spectrum a). Here, all 17 carbon atoms are chemically inequivalent and can be distinguished by separate signals.

As shown in Figure 1Ab) and Bb), the description improves dramatically when all rotamers belonging to one conformer are considered, i.e., correctly only a single singlet signal (ignoring spin-spin coupling as in the experiment) is obtained. For cycloalkanes, inter-conversion takes place through fast pseudo-rotation or inversion processes, whereby all methylene groups become chemically equivalent at ambient temperature.[7] However, a reasonably accurate chemical shift is obtained only by inclusion of the entire populated ensemble as shown in Figure 1B, spectrum c) and the corresponding structure ensemble presented in Figure 1Ac). This example illustrates the complexity of NMR simulations for flexible compounds even when spin–spin coupling is not involved, since all the populated conformers and rotamers of a compound and all chemically/magnetically equivalent atoms have to be identified.

To simplify the tedious task of generating fully coupled NMR spectra,[26] we have developed and tested a highly improved workflow implemented in a shell script called crenso[30] that can be used to calculate a variety of properties, e.g., NMR, optical rotation ($[\alpha]_D$), acid dissociation constants (pK_a) or partition coefficients (logP).[30]

The required steps to obtain a theoretical NMR spectrum are illustrated in Figure 2 starting from an initial three-dimensional molecule structure. First the CRE is created using the crest_combi script.[28,30] Hereby the vast chemical space is explored using meta-dynamic[32] runs at different, artificially enriched PES.[30] The huge number of associated energy and gradient calculations required in this endeavor is made possible by efficient and robust quantum mechanical methods of the GFN*n*-xTB family[27] and the GFN-FF force field.[33] Using a special principal component analysis (PCA) clustering algorithm,[34] the number of conformer candidates is efficiently condensed to the essential structures. This initial ensemble is then treated by a threshold-based algorithm termed censo, progressively optimizing according to both, lowest total Gibbs energies as well as the solution phase geometries of the conformers. After the identification of dominantly populated ones, spin–spin coupling and shielding constants are calculated by standard DFT methods. Finally, the Boltzmann weights, NMR parameters and information on chemically and magnetically equivalent nuclei are transferred to the anmr program, which averages the NMR data over the CRE, solves the spin Hamiltonian, and returns the final spectrum. Because our CRE is of high quality but not complete, i.e., the exact number of rotatmers for each conformer is not known, we assume that all conformer degeneracies are unity. By a randomized varia-

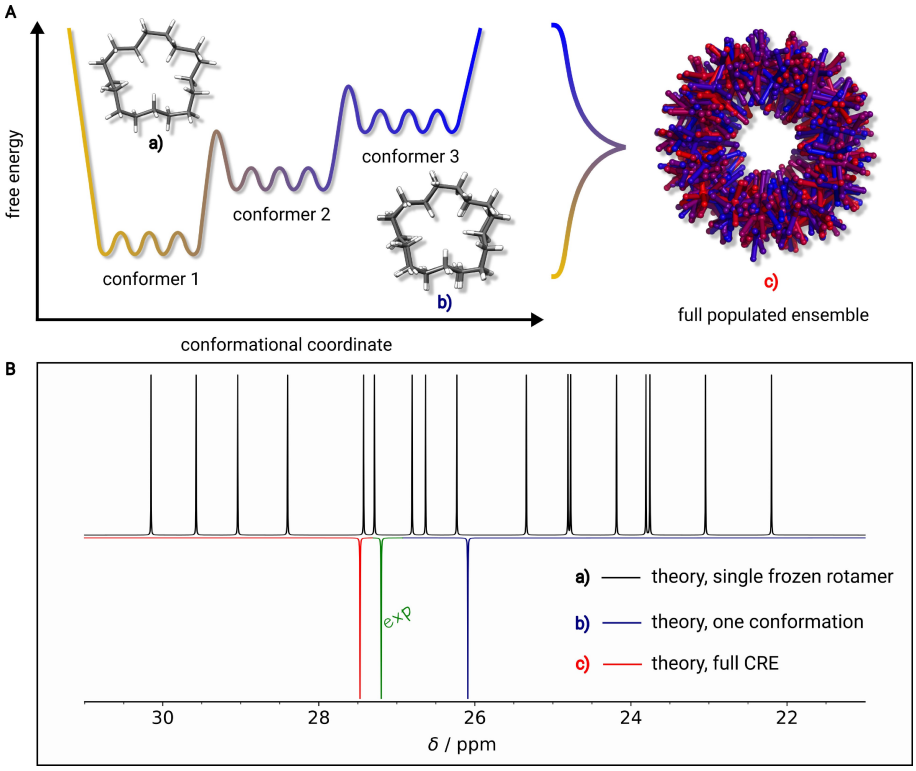


Figure 1. A) represents a schematic potential energy surface (PES) of cycloheptadecane with three conformers and some energetically degenerate rotamers. B) Theoretical ^{13}C-NMR spectra of cycloheptadecane $C_{17}H_{34}$ in $CHCl_3$ at 298 K obtained for: a) without rotamer averaging, b) including a single (lowest) conformer with all its rotamers and c) including all significantly populated conformers (168) in the ensemble (the colors in the overlay visualize the diversity of contributing conformers). The experimental reference chemical shift is shown in green (see Table S1).

tion of populations (explained in the caption of Figure 3) we checked that that this approximation is valid and leads only to insignificant changes of the average (see gray confidence band in Figure 3). More relevant is the proper consideration of the molecular symmetry of each conformer in the thermostatistical evaluation of the free energy (molecular rotation/symmetry number) which is in some cases crucial for determining reliable Boltzmann factors (an extreme example is cyclononane,[35] see Figure S4).

All DFT calculations were conducted with Turbomole 7.5.1.[36] The COSMO-RS[37] solvation contribution to the Gibbs energy was calculated with COSMOtherm19[38] (*BP_TZVP_19.ctd* parameterization). To save computation time, these calculations use the electron density and energy from the corresponding respective DFT level within the censo program. Geometries were optimized with implicit solvation at the r^{2}SCAN-3c/DCOSMO-RS[39,40] level of theory. r^{2}SCAN-3c shows good performance for general thermochemistry and yields highly accurate conformational energies making this efficient composite density functional an ideal choice.[39] The final Gibbs energies were calculated as the sum of r^{2}SCAN-3c electronic energy (E), COSMO-RS solvation free energy ($\delta G^{T}_{\mathrm{solv}}(\mathrm{CHCl_3})$) and the thermostatistical correction (G^{T}_{mRRHO})[41] at GFN2-xTB/ALPB-($\mathrm{CHCl_3}$)[42] level. NMR parameters (shielding constants) are calculated at the PBE0/def2-TZVP[DCOSMO-RS][43,44] level. The entire workflow can be called by simple UNIX commands, e.g., crenso -nmr chc13 -13 and for further details and technical settings see Supporting Information and Ref. [29,30].

The workflow described in Figure 2 is applied to cycloalkanes containing 4–20 carbon atoms, starting from smiles strings or PubChem geometries. A comparison of theoretical and experimental chemical shifts in $CHCl_3$ is shown as a function of ring size in Figure 3. The experimental values refer to the fundamental work by Fritz et al.[45,46] Since experimental data in chloroform is not available for cyclononane and cycloheptadecane, their reference values are extrapolated from the next larger and smaller homologous, respectively. This extrapolation is considered appropriate because experimental data measured in other solvents result in significant inconsistencies if the trend over a series of compounds is of main interest.

The conformers of lowest free energy are displayed in Figure 4 and since the chemical shifts and structures are interrelated, they are discussed together hereafter. As recommended by Lodewyk et al.,[48] calculated DFT shielding constants $\sigma_{\mathrm{DFT,raw}}$ are corrected globally by linear regression to eliminate systematic discrepancies between theory and experiment[48] using the formula $\delta_{\mathrm{DFT,corr.}} = 0.942 \times (186.156 - \sigma_{\mathrm{DFT,raw}})$ where $\delta_{\mathrm{DFT,corr.}}$ is the corrected shift discussed in the following. The linear regression parameters have been determined from a database of small organic molecules with experimental carbon

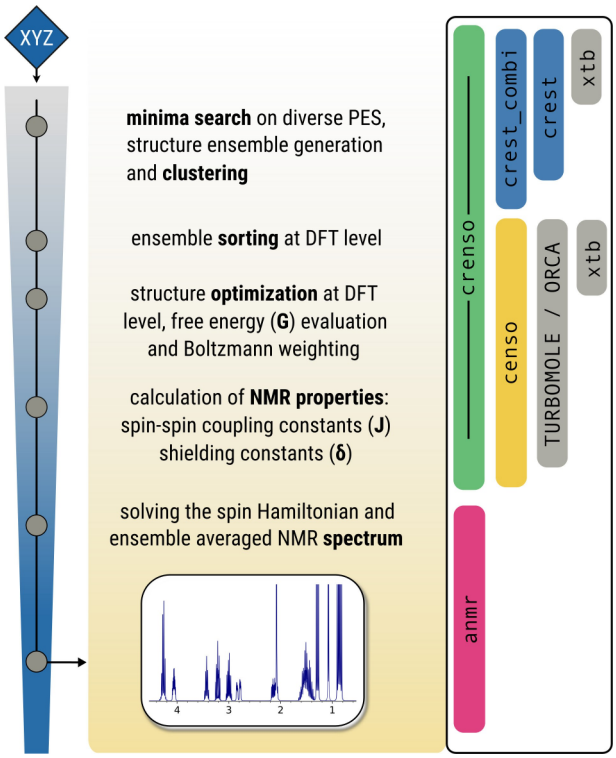


Figure 2. Computational workflow for the automated computation of NMR spectra and therein employed computer codes and scripts. The colored boxes indicate codes that are directly accessed and contain relevant thresholds for generating and sorting the CRE or are related to the generation of the NMR spectrum/properties. The gray colored boxes indicate the necessary infrastructure relevant to the QM description of the model.

and proton shifts, accessible at the chemical shift repository[49] (see Supporting Information for details).

The variation of the ^{13}C chemical shift for the investigated cycloalkanes is relatively small with ≈6 ppm. However, because their chemical structure is very similar, the observed subtle changes for different ring sizes suggest that conformational effects play a major role and that their account is theoretically challenging. In fact, a fully automated QM-based study of this type has never been performed for the NMR spectra of such large and immensely flexible systems with hundreds of contributing conformers. The proton spectra of the cycloalkanes studied (see Figure S1) show only minor changes for the larger cycloalkanes, and thus only the more informative carbon spectra will be discussed.

Cycloalkanes and their properties are usually categorized into small, common, medium and large rings.[50] Cyclobutane is classified as a small ring showing large deviations from the usual tetrahedral angles with corresponding high angle- and torsion-strain, resulting in a low chemical shift.[51] Significantly populated conformers are shown in the Supporting Information, along with a discussion of conformers identified from previous experimental or computational studies (see Supporting Information, section 8). Common rings with 5 to 7 carbon atoms exhibit outside facing hydrogens, small deviation from the tetrahedral bonding angle and cyclohexane is usually referred to as a strain-free.[52] These common rings in $CHCl_3$ exist in a single conformation at room temperature (cf. Figure 4). The reduced strain (see Figure S5 in the Supporting Information) compared to the small rings is evident in the increased shifts reaching a maximum for cycloheptane. For medium-sized rings from octane to undecane, steric interaction occur due to hydrogens facing inside, called transannular interaction. Cyclononane is the first compound with more than a single dominantly populated conformer and the lowest free energy triangular [333] conformation with D_3 symmetry is populated by only 47.1 %. Cyclodecane with an even number of ring atoms can be superimposed on a diamond lattice indicating nearly ideal tetrahedral angles and therefore low strain. However, some transannular interaction between competing inward facing hydrogen atoms can be observed. The cyclododecane conformations are exposed to less stress than in cycloundecane and therefore it exhibits the largest high-field shift within the medium-sized rings (see Figure S5 in the Supporting Information). Large rings with more than 12 carbon atoms slowly start to resemble their open-chain alkane analogues.[46] This is also reflected in the geometries of the highly populated conformers, which, for example in $C_{16}H_{32}$ and $C_{20}H_{40}$, adopt rectangular structures and thus the inner methylene groups adopt geometries similar to linear *n*-alkanes. The population of cyclododecane is strongly dominated by the square [3333][10] conformation with D_4 symmetry, while other conformers are significantly higher in free energy. Except for the small rings, cyclododecane represents the system with the strongest high-field shift of all investigated compounds. From cyclotridecane on, a trend towards low-field chemical shifts can be observed, which is only significantly interrupted by cyclotetradecane in its preferred rectangular, diamond-lattice type conformation.[10]

Overall, the characteristic experimentally determined shift profile for different ring sizes is almost perfectly reproduced by our theoretical workflow. This is particularly impressive for the larger cycloalkanes where up to almost 1000 conformers are initially considered and many structures contribute to the average. To illustrate the difficulty in the correct description of the ^{13}C-NMR spectrum of larger rings, the range of chemical shifts within the final ensemble is shown by gray error bars in Figure 3, spanning a range of ≈7 ppm which is similar to the overall variation with ring size. Thus, a randomly chosen structure will most likely not yield a satisfactory result, and the need for an extensive and reliable conformer search becomes apparent. Furthermore, our data suggest that the sole consideration of the lowest-lying conformer (represented by green crosses) in Figure 3 is also insufficient, which highlights the influence of higher lying conformers in the CRE. Evidently, smaller (high-field) shifts are regularly obtained for rings with an even number of methylene groups than for odd-numbered ones. This also indicates a conformational effect and it can be deduced from the structure ensembles that the odd-numbered homologous exhibit increased bond-, angle- and torsion strain due to unfavorable positioning of the additional methylene group.

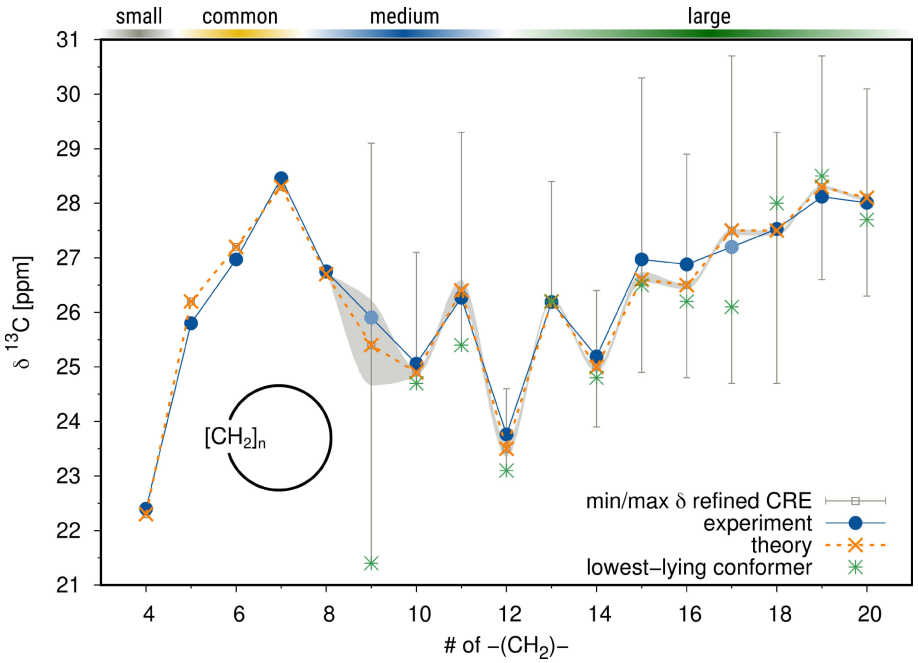


Figure 3. Experimental[46] (dark blue points) and theoretical (orange crosses) ^{13}C chemical shifts of cycloalkanes in $CHCl_3$ are plotted against their ring size. Error bars represent the smallest and largest chemical shift computed for the populated structures in the ensemble. Light blue points show extrapolated reference values of systems for which no experiment was available. Green crosses depict values of the highest populated conformer. The gray confidence band represents estimated changes in the shifts when the Boltzmann factors of randomly selected conformers in the CRE are adjusted by changing their free energy by up to 0.4 kcal mol^{-1}, which is a reasonable error estimate for our treatment (see for example the relative conformer energies test sets ICONF, ACONF, MCONF, and SCONF in the GMTKN55 thermochemistry benchmark[47]). The connecting lines are only drawn for visual guidance.

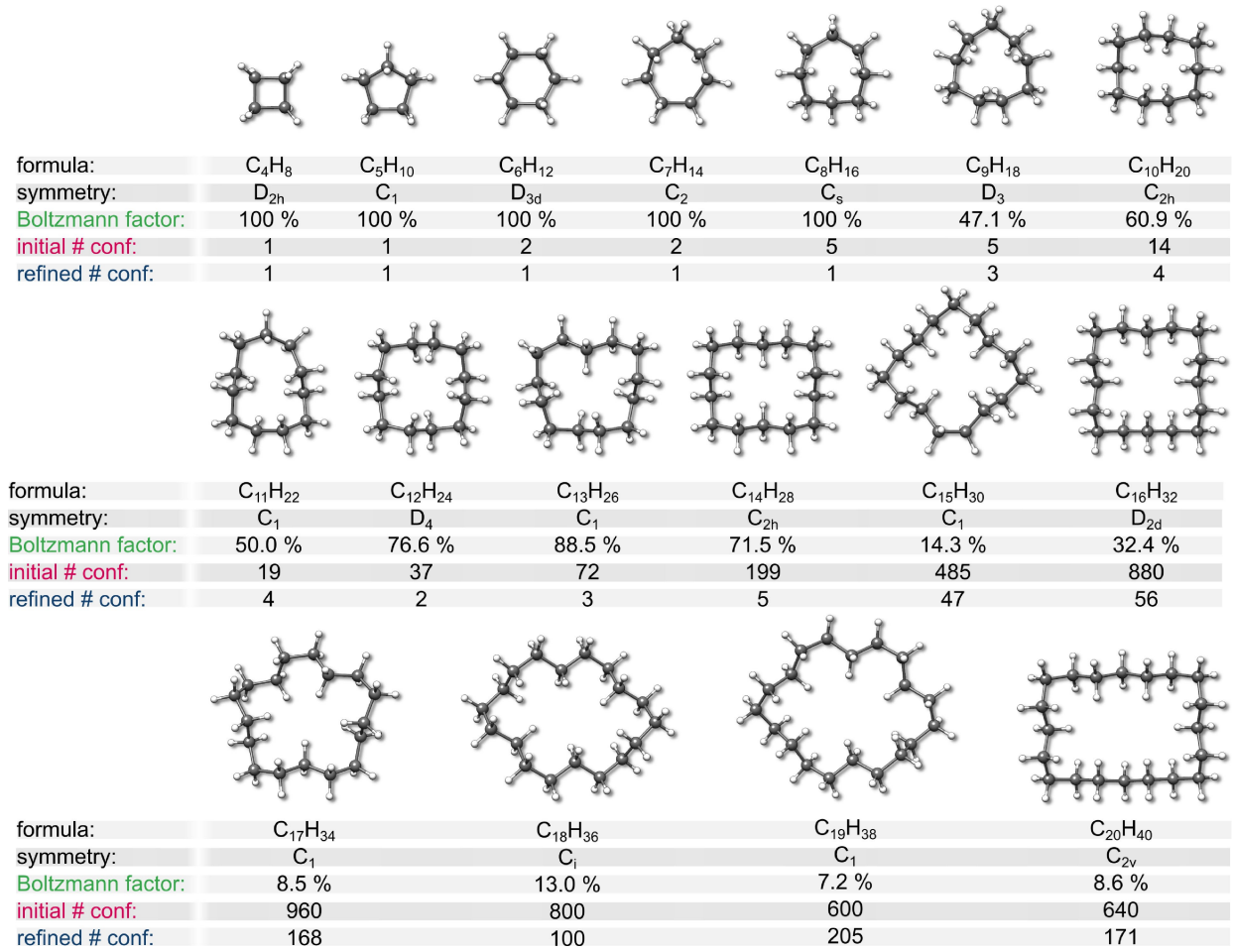
From cyclopentadecane on, with 47 low-lying conformations, an increasing number of significantly populated conformers is observed, reaching a maximum of 205 structures at cyclononadecane. In such cases, the spectrum is no longer determined by a single or few dominant structures but rather by an ensemble with dozens of similarly populated minima. In 1990 Saunders et al.[53] compared the results of several conformational space exploration methods for cycloheptadecane and by combining all search results they identified 262 gas-phase conformers within an energy window of 3 kcal mol^{-1}.[53] This is in good agreement with the 168 populated solution phase conformers found here within a free energy threshold of 2.5 kcal^{-1}.

The computation time strongly depends on the number of relevant conformers and is mostly spent for geometry optimization (see Supporting Information Figure S3). For the most flexible cyclononadecane, the initial conformer search took about two hours and the refinement including NMR property calculation required about 50 hours computation time on 28 cores (Intel(R) Xeon(R) CPU E5-2660 v4 @ 2.00GHz). Most of the calculations for more rigid structures finish within a day or even a few hours computation time.

When comparing our CRENSO workflow to other approaches such as NAMFIS or CANDLE, the main focus is also on generating the most complete (low-energy) conformer ensemble possible. However, unlike NAMFIS, our conformer search explores the SQM/FF PES without experimental constraints that could spuriously influence the search results and the final Boltzmann weights of the solution ensemble are computed ab initio and not determined from a fit to experimental data. Similar to CANDLE, we need the experimental chemical shifts of protons or carbon atoms only for the final comparison step, which is more convenient than a full spectral assignment required for NOE or RDCs. With CRENSO, we try to model all relevant physical processes on a as high as computationally possible level and quantum mechanical basis, while maintaining an automated workflow with low computational cost. Thus, structures are optimized with implicit solvation, we accurately account for all free energy terms including (intramolecular) London dispersion, and properly describe the chemical shifts. This work extends the toolbox of existing analytical methods for non-rigid macrocycles in solution and in principle these methods can complement each other, i.e., by combining and further completing differently generated ensembles or employing the created ensemble in a NAMFIS like evaluation.

In this communication we propose a robust, automated approach of identifying populated hydrocarbon macrocycle conformations in chloroform solution. The workflow is generally applicable to more complicated compounds with typical functional groups or other solvents.

As a proof of principle this is demonstrated here (see Figure 5) for a cyclic peptide PGLGF,[54] and the two natural products lobophytolins A[56] and (−)-dactylolide.[57] The



formula:	C_4H_8	C_5H_{10}	C_6H_{12}	C_7H_{14}	C_8H_{16}	C_9H_{18}	$C_{10}H_{20}$
symmetry:	D_{2h}	C_1	D_{3d}	C_2	C_s	D_3	C_{2h}
Boltzmann factor:	100 %	100 %	100 %	100 %	100 %	47.1 %	60.9 %
initial # conf:	1	1	2	2	5	5	14
refined # conf:	1	1	1	1	1	3	4

formula:	$C_{11}H_{22}$	$C_{12}H_{24}$	$C_{13}H_{26}$	$C_{14}H_{28}$	$C_{15}H_{30}$	$C_{16}H_{32}$
symmetry:	C_1	D_4	C_1	C_{2h}	C_1	D_{2d}
Boltzmann factor:	50.0 %	76.6 %	88.5 %	71.5 %	14.3 %	32.4 %
initial # conf:	19	37	72	199	485	880
refined # conf:	4	2	3	5	47	56

formula:	$C_{17}H_{34}$	$C_{18}H_{36}$	$C_{19}H_{38}$	$C_{20}H_{40}$
symmetry:	C_1	C_i	C_1	C_{2v}
Boltzmann factor:	8.5 %	13.0 %	7.2 %	8.6 %
initial # conf:	960	800	600	640
refined # conf:	168	100	205	171

Figure 4. r^{2}SCAN-3c/DCOSMO-RS geometries of the highest populated conformers given with Boltzmann weight of all investigated cycloalkanes up to cycloicosane. The initial number of conformers equals the number of conformers provided by crest_combi at the GFN-FF/GFN2-xTB level while the refined number refers to the final ensemble obtained from censo at DFT level. The symmetry of the lowest free energy conformer is provided in Schoenflies notation.

results are discussed in more detail in the Supporting Information and show impressive overall agreement expressed by the mean absolute deviations between the experimental and theoretical carbon chemical shifts ranging from 1.0–2.4 ppm. In addition, the experimentally identified structures are found in the final CRENSO ensembles as lowest free energy conformers in all three cases highlighting the accuracy and generality of our approach. Cyclic hydrocarbons were solely chosen as model systems mainly because good experimental reference data are available and the intramolecular interaction motifs are treated reliably even by low-level theoretical methods. For more complicated, e.g., polypeptide or drug structures with more complex PES, the initial search step at the lowest theoretical level becomes crucial which is a topic of ongoing research. Nevertheless, this and a related study[29] provide strong evidence that our methods can accurately explore the conformational space of very flexible macrocycles. This is convincingly shown here by comparison of computed and experimental solution phase ^{13}C-NMR spectra. Herein our recently published CRENSO workflow efficiently samples the PES, refines the structure ensemble and automatically performs all NMR property calculations. We showed that identifying conformer ensembles with dominant populations is essential for an accurate prediction of NMR spectra, and that considering only random or even the lowest lying conformer is insufficient. In turn, the excellent agreement between theory and experiment enables to deduce the preferred conformations under ambient measurement conditions. The calculations with our sophisticated mostly quantum chemical workflow can be performed on a normal workstation computer within hours with minimal user input and all our codes are freely available. This opens a route for highly accurate NMR simulations for more diverse and challenging macrocycles in the future.

Supporting Information

Supporting Information is available for this paper containing additional computational details.[59]

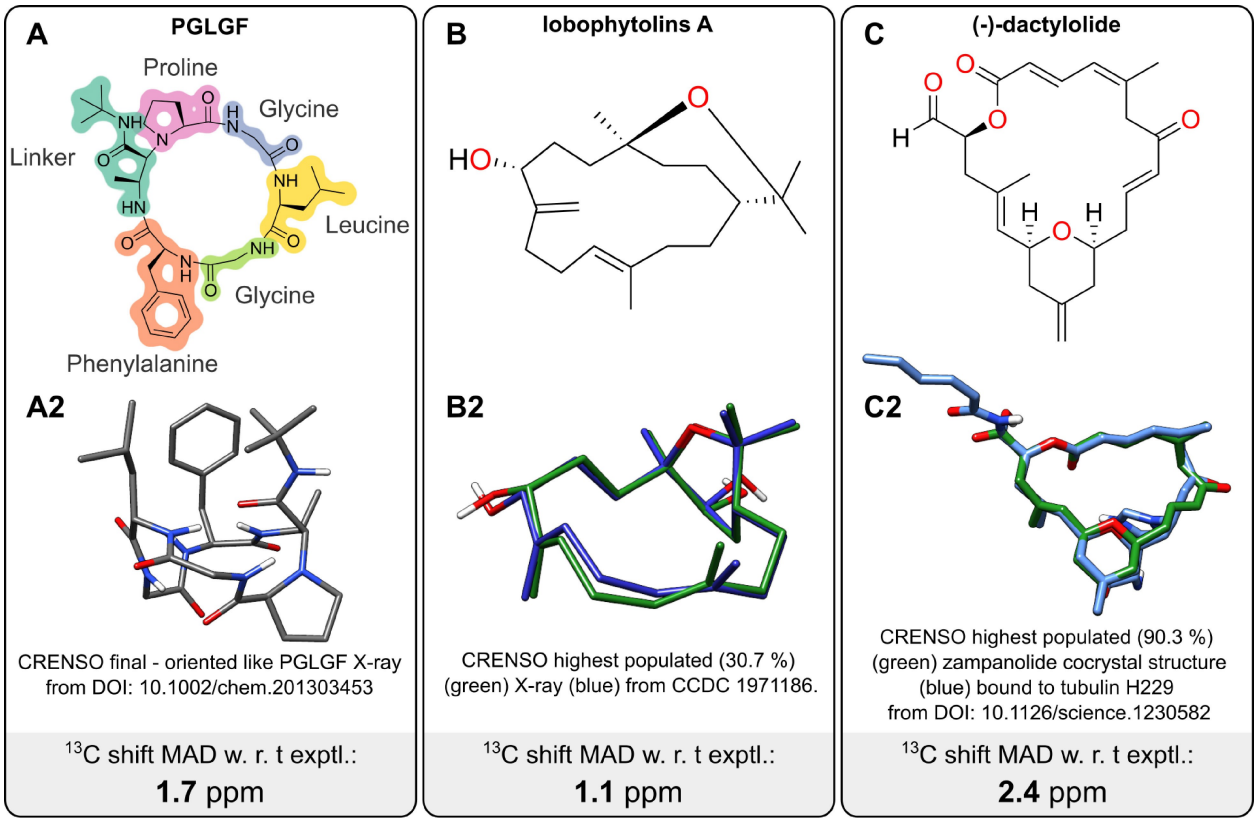


Figure 5. The results of the CRENSO workflow on three macrocyclic compounds containing functional groups. A) The cyclic peptide PGLGF[54] whose highest populated conformer is shown in A2 and visually corresponds to the crystal structure of PGLGF from Ref. [55]. B) Lobophytolin A,[56] which has 20 populated conformers and the overlay of the lowest lying conformer and the crystal structure is shown in B2. C) The Lewis structure of (−)-dactylolide[57] and C2 includes the overlay of the highest populated conformer and the cocrystal structure of the related natural product zampanolide.[58] For all systems, the mean absolute deviation of the carbon chemical shifts with respect to the experiment is reported, which shows good overall agreement.

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Conflict of Interest

The authors declare no competing interests.

Keywords: Computational Chemistry · Macrocycle · NMR-Spectroscopy · Structure Elucidation

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[59] The xtb program package, CRENSO and all used scripts are available free of charge for academic use via the GrimmeLabs Github page: https://github.com/grimme-lab.

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