Supramolecular Chemistry, Part 97[+]

The Use of Complexation Induced Proton NMR Chemical Shifts for Structural Analysis of Host–Guest Complexes in Solution

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Abstract: Proton shielding variations in supramolecular complexes contain a wealth of information on complex geometries in solution that has been until now mostly neglected. We describe herein ways for such analyses with five cyclophane and two cyclodextrin complexes in water, by using a program SHIFT which is based on and parametrized with the analyses of over 300 *intra*molecular proton shift variations in well defined molecular frameworks such as steroids or cyclophanes. The *inter*molecular shift changes in the host–guest complexes at 100% complexation (CIS values) are calculated as sum of anisotropy effects $\Delta\chi$ from aromatic ring currents and linear electric field effects LEF, based on force field generated geometries. The conformations with the best agreement between calculated and observed CIS values are at least for non-charged guest compounds close to those obtained from molecular mechanics and/or MD calculations and intermolecular NOEs (where available), noticeably without adjusting the complex geometries to the experimental CIS. Through-space electrostatic field effects LEF, which have been until now often neglected, can be sizeable also for non-charged systems; best agreement between experiment and calculation is observed with Gasteiger atomic charges.

Keywords: anisotropy effects · complexation induced NMR shifts · NMR spectroscopy · supramolecular chemistry

Introduction

Methods: Proton NMR shifts reflect in a particularly sensitive way through-space interactions between different molecules or between parts of a larger molecular entity. For this practical reason proton NMR chemical shift titrations have become the most important tool to characterize supramolecular complexes in solution. Until now, however, most reports are restricted to the extraction of association constants from the corresponding isotherms; the use of the simultaneously obtained shift changes (CIS values, at 100% complexation) is usually based on only qualitative interpretations or often only on guesswork. The ring-current induced shift changes seen with complexes of aromatic guest molecules with cyclodextrins[1]or cyclophanes[2] have been used quite early for the conformational analyses of such supramolecular systems. It was shown early, however, that neglect of charge-induced linear electric field effects in these early calculations can lead to wrong conclusions.[3] The advent of two-dimensional NMR methods provides a routine application to obtain CIS values also for signals masked in simple one-dimensional NMR titration; this and the now available convenient assignment techniques should provide a new incentive to make better use of the wealth of numerical information regarding the underlying supramolecular structures. It has been stated, that the chemical shift compares infact favourably with other NMR parameters such as NOEs, coupling constants or relaxation times in terms of dispersion of parameters and of their accuracy, contrary to its less common use for example in protein chemistry.[4, 5]

Application of NMR-shielding variations to the elucidation of biopolymer structures poses quite similar problems and promises as application to host–guest complexes, but has been recently more advanced.[4] Besides quantum chemical approaches[6] the most successful method for larger systems are based either on strictly empirical correlations[4] or in particular on the application of classical, semiempirical equations introduced decades ago by McConnell,[7] Zürcher,[8] and Pople[9] et al. The corresponding calculations of anisotropy and electric field effects and their later developments are documented in many NMR textbooks and reviews;[4] they are also the basis of our approach to analyze CIS values in supramolecular complexes,[3, 10] which are the focus of the

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present paper. Comparable in force field applications the reliability of quantitative NMR shielding analyses depends essentially on the correctness of the underlying equations. In particular the extensive work by Abraham et al.[11] has always been based on comparison of experimental and calculated shifts in *intra*molecular frameworks. Advanced programs for shift calculations in biopolymers[4] such as that by Williams et al.[12] are to a large extent based on comparison of experimental shieldings in proteins. Notably, however, the use of biopolymer data as training set for shielding calculations is limited by the accuray of the underlying structural coordinates, which is usually limited to some tenths of an Angstrom at best. Model calculations show that, for example, the displacement of an hydrogen atom by only 0.15 Å can lead to shift differences of up to 0.7 ppm, if the observed proton happens to lie close to the edge of the shielding cone generated by an aromatic ring current.[13]

Another approach uses the difference $\Delta\delta$ between calculated and experimental shifts for adjusting parameters in a corresponding pseudopotential, which is implemented into a force field, similar to the common usage of NOE constraints.[14] Naturally, the agreement $\Delta\delta$ between calculated and observed shifts is better with this method, which we illustrate also with one example using a GRID-SHIFT procedure with the complex between CP44 and *p*-toluenesulfonic acid (TsOH), see below. In this approach, however, experiment and calculation are mixed; the use of NOEs for this purpose is less problematic as it is commonly used only as a cut-off constraint, and in principle only depends on a single distance relationship. NMR shifts are always a mixture of several, more complex screening mechanisms; in view of sizeable long distance effects, which for example for LEF has been even observed with non-charged steroids over 8 Å,[15] NMR shifts lend themselves less for cut-off constraints than NOEs do.

Abstract in German: *Die Variation von Protonen-NMR-Verschiebungen in supramolekularen Komplexen enthält eine bisher meist vernachlässigte Vielzahl an Informationen über deren Geometrie in Lösung. Wir beschreiben Wege zu einer entsprechenden Analyse mit fünf Cyclophan- und zwei Cyclodextrin-Komplexen in Wasser: Die Grundlage ist ein Programm SHIFT, welches auf der Analyse von mehr als 300 intramolekularen Verschiebungsvariationen in geometrisch gut definierten Gerüsten wie Steroiden oder Cyclophanen beruht. Die intermolekularen Verschiebungsänderungen in Wirt–Gast-Komplexen bei 100% Komplexierung (CIS-Werte) werden berechnet als die Summe von Anisotropieeffekten $\Delta\chi$ aus aromatischen Ringströmen und von linerearen Feldeffekten LEF, jeweils auf der Grundlage von kraftfeldberechneten Modellgeometrien der Komplexe. Die Konformation mit der besten Übereinstimmung zwischen berechneten und experimentellen CIS-Werten gleichen zumindest für nichtgeladene Systeme denen, die aus Molekülmechanik- und/oder aus Moleküldynamik-Rechnungen bzw. aus intermolekularen NOE-Effekten (soweit verfügbar) resultieren. Hervorzuheben ist, dass dies ohne Anpassung der Komplexgeometrien an die experimentellen CIS-Werte erreicht wird. Die durch den Raum wirkenden elektrostatischen Feldeffekte (LEF), welche bisher meist vernachlässigt wurden, sind erheblich, auch bei ungeladenen (nicht-ionischen) Systemen; die beste Übereinstimmung zwischen Experiment und Rechnung wird erhalten mit Hilfe von Gasteiger-Atomladungen.*

We have developed the program SHIFT on the basis of more than 300 *intra*molecular proton shift variations analysed in conformationally well-defined cyclohexanes,[16a] steroids,[16b] decalins[16c] and cyclophanes.[13] High-resolution structures of these frameworks, obtained from molecular mechanics calculations, and comparison with selected X-ray analyses, served as a basis for the evaluation and parametrization of classical equations describing anisotropy effects $\Delta\chi$ and linear electric field effects (LEF). Important effects such those of square electric fields or of steric distortions can also be calculated, particularly for example for the ^{13}C nuclei, but in view of strain energy are fortunately small in typical host–guest complexes; they are therefore neglected in the present work. Other than the early approaches[8] SHIFT provides for time averaged shifts in multiple conformations, for example protons of methyl group can be calculated separately and then averaged.

As all NMR-based structure evaluations SHIFT requires as input three-dimensional model conformations, for which shielding effects $\Delta\chi$, LEF etc using the above-mentioned classical equations are then calculated and added to underlying shifts δ_0. For *intra*molecular effects the δ_0 values must be taken from parent compounds, from NMR shift tabulations, from empirical increments, or from calculations with related[11] programs. In order to analyze *inter*molecular shielding effects, which are the focus of the present work, the δ_0 values are simply, and exactly available from measurements of the isolated compounds, such as the host and guest, under the same conditions as the complex. A detailed description of the program and its application to *intra*molecular shielding effects is available elsewhere.[16–18] In the simplest version of the program the user compares the experimentally observed shift changes (CIS values) of user-selected protons with those calculated by SHIFT for different conformations; if the agreement $\Delta\delta$ between calculated and observed shifts is significantly better for one particular conformation, this conformation can be considered to represent the most important present. The present paper describes for the first time the comprehensive application of the program for the structural evaluation of host–guest complexes, with a validation which in contrast to earlier reports[3, 10b, 14c] is based on the analyses of many complexes and on widely tested parameters for the underlying equations. Where possible (i.e., with the cyclophanes) not only the effects of guest on the host, but also the inverse effects on the guest molecule was analysed.

Results

Cyclophane complexes: Application of SHIFT to complexes of benzene as the guest in cyclophane **CP44** with either $^{+}NH_2$ or $^{+}NMe_2$ corner groups (**CP44(NH$_2$)** or **CP44(NMe$_2$)**) showed a very good agreement between calculated and observed shifts (Table 1) for CHARMm-generated[19] geometries (Figure 1).

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Table 1. Results from SHIFT calculations with cyclophane CPnn complexes.[a]

Host	Guest	Proton	Arom. $\Delta\chi$	LEF	$\Sigma\Delta\chi$ + LEF	exptl
CP44(NH_2)	benzene	–	−1.45	0.36	−1.09	−1.12
CP44(NMe_2)	benzene	–	−1.04	0.16	−0.88	−0.96
CP44	+ *p*-TsOH	H2	−2.36	0.03	−2.33	−1.02
	(CHARMm-	H3	0.04	0.02	0.06	−1.33
	optimized)[b]	Hx	−0.51	−0.02	−0.53	−0.53
CP44	+ *p*-TsOH					
	(Grid-Proced.)[c]				$\Delta\delta_{av} = 0.13$[c]	
CP66	benzene	–	−0.74	0.06	−0.68	−0.71
CP66	naphthalene[d] eq	H1	−0.55	0.00	−0.55	−0.95
		H2	−1.65	0.02	−0.61	−1.02
	pseudoaxial ps	H 1	−1.18	−0.01	−1.19	
		H 2	−0.60	−0.01	−0.61	
	axial ax	H 1	−1.24	−0.01	−1.25	
		H 2	−0.38	−0.01	−0.39	
	mixture eq + ax	H 1	−0.90	−0.01	−0.90	
		H 2	−1.02	0.01	−1.01	

[a] All values refer to complexation induced shifts (at 100% complexation) in ppm; aromatic ring current induced shifts, arom. $\Delta\chi$; linear electric field effetcs, LEF; sum of both, $\Sigma\Delta\chi$ + LEF; experimental data exptl CP44(NH_2): cyclophane with protonated nitrogen atoms, all others with permethylated nitrogen atoms. [b] For single conformer as obtained form CHARMm enegry minimization. [c] Obtained with a Grid procedure which selects the closest to the observed CIS values out of 1098 conformations, see text; [d] Naphthalene insertion modes either equatorial, eq; pseudoequatorial, ps; axial ax; or 50:50 mixture of eq + ax.

the NMR data yields mostly several structures which are in fast equilibrium; nevertheless in all cases numeric evidence for the intracavity inclusion can be found.

The shielding effects exerted by an aromatic guest molecule inside a cavity *on* the host protons are also large and informative with respect to the complex geometries (Schemes 1, 2); this is illustrated with the results in Table 3, as well as the approximate agreement to be reached with the SHIFT program. Here the total of seven shifts can be used which indicate a preferred axial orientation ($\Delta\delta_{av} = 0.19$) of naphthalene sulfonic acid within the

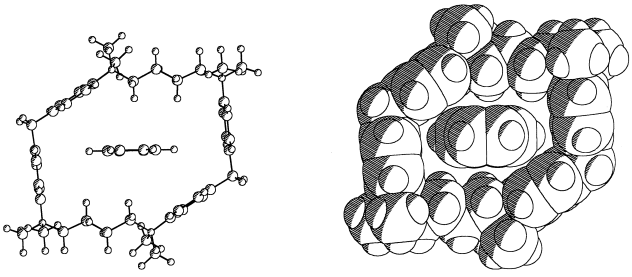


Figure 1. CHARMm-simulation of the complex between CP44(NMe_2) and benzene.

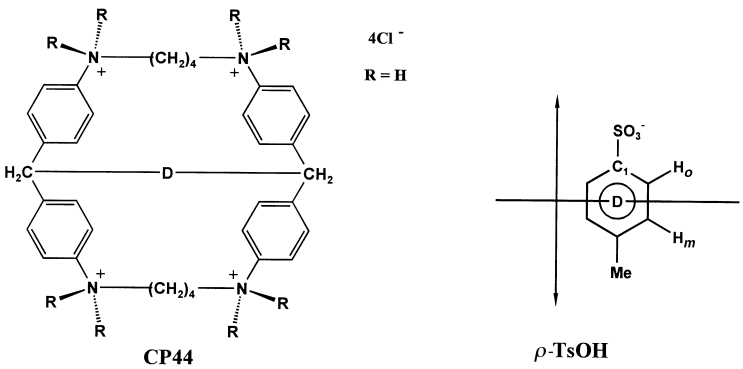
Experimental CIS values in some related complexes change little with the solvent composition; this indicates that solvent effects may be small on the inclusion geometry.[20] The hithertoo often neglected electric field effect exerted by the permanent positive host charges contribute up to one third of the total calculated shielding. With *p*-TsOH the CHARMm-generated conformations showed only approximate agreement (Table 2). Only after applying an automatted GRID search, by which 1098 structures were generated and compared with the experimental CIS values, an average agreement of $\Delta\delta = 0.13$ for all three TsOH signals was observed with one of these structures (Table 1); this is in contrast to the best value of $\Delta\delta = 0.3$ obtained by moving the guest within the host cavity without simultaneously adjusting to the observed CIS values.

The larger **CP66** host can accomodate benzene in a variety of conformations; the force field optimized single conformation agrees well with $\Delta\delta_{av} = 0.03$ with the SHIFT calculation. Naphthalene can be complexed within this larger cavity in a axial (ax), equatorial (eq), pseudoeqatorial (pseudo-eq) conformation, or in a mixture of eq and ax geometries. The calculations show satisfactory agreement with $\Delta\delta_{av} < 0.5$ (Table 2) only for an assumed 50:50 mixture of both eq and ax complex structures. However, as a result of the time averaging

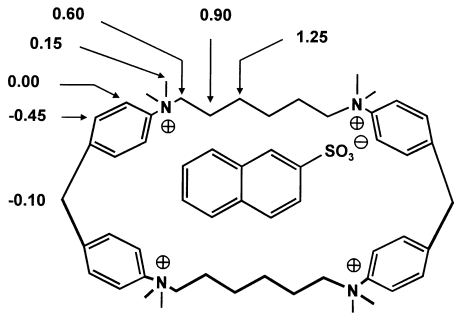
Table 2. CIS values calculated for the complex CP44 and *p*-toluenesulfonic acid with different depth of immersion.[a]

d[a]	Guest Proton	Eff_{arom}	Eff_{LEF}	Eff_{calcd}	$\Delta E = Eff_{calcd} - E_{exptl}$
1.02	H_o	2.75	−0.11	2.64	1.07
	H_m	0.66	−0.43	0.23	−1.68
	Me	0.13	−0.22	−0.09	−0.74
0.89	H_o	2.13	−0.32	1.81	0.24
	H_m	1.68	−0.43	1.25	−0.66
	Me	0.34	−0.23	0.11	−0.54
0.53	H_o	2.69	−0.20	2.49	−0.92
	H_m	1.05	−0.44	0.61	−1.30
	Me	0.21	−0.22	−0.01	−0.66
−0.69	H_o	1.41	−0.41	1.00	−0.57
	H_m	2.30	−0.41	1.89	−0.02
	Me	0.52	−0.22	0.30	−0.35

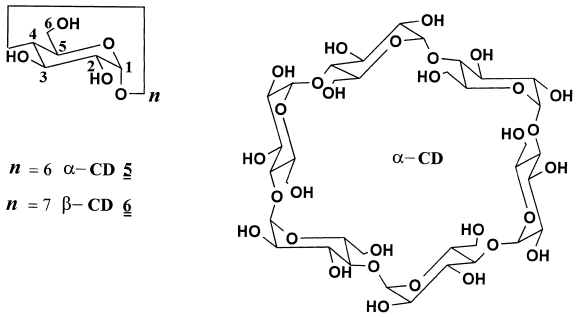
[a] Distance *d* in [Å] between center of CP44 cavity and guest phenyl moiety, see Scheme 1. Positive values indicate that the SO_3 group is closer to the CP44 center than the CH_3 group. Experimental shifts in D_2O (H_o: 1.57, H_m: 1.91, Me: 0.65); further details see Table 1.



Scheme 1. CIS values (in ppm) of the host **CP44** on the guest *p*-TsOH. For calculation of CIS values the center of the aromatic *p*-TsOH moiety is moved up and down, yielding differences *d* (see Table 2) to the CP44 cavity center which is described by line D.



Scheme 2. CIS (experimental values, in ppm) of an aromatic guest (naphthalene-2-sulfonate) on the azoniacyclophane host **CP66** (in D_2O).



Scheme 3. Cyclodextrin structure and numbering.

Table 3. cis values (in ppm) on the cyclophane host CP66 exerted by the guest naphthalene-2-sulfonate.[a]

Inclusion Mode	Proton	$\Delta\chi_{arom}$	LEF	$\Delta\chi_{arom}$ + LEF	CIS_{exptl}
axial	1	0.10	– 0.07	0.03	0.10
	2	0.14	– 0.03	0.11	0.45
	3	0.02	0.00	0.02	0.00
	4	– 0.14	– 0.02	– 0.16	– 0.15
	5	– 0.53	0.03	– 0.50	– 0.60
	6	– 0.40	0.00	– 0.40	– 0.90
	7	– 0.95	0.02	– 0.93	– 1.25
pseudoequatorial	1	0.01	– 0.10	– 0.09	
	2	– 0.03	– 0.05	– 0.02	
	3	0.09	– 0.04	0.05	
	4	0.01	– 0.01	0.0	
	5	0.12	0.03	0.09	
	6	– 0.01	– 0.04	– 0.05	
	7	– 0.42	0.00	– 0.42	

[a] Footnotes see Table 1.

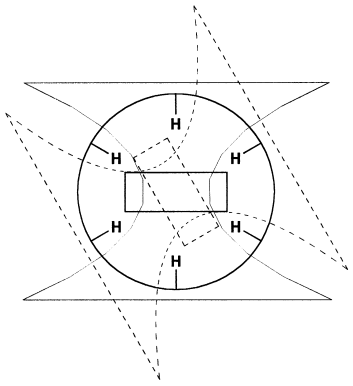


Figure 2. Orientation of phenyl rings and ring current anisotropy cones within the α-CD cavity; solid lines: model with minima avoiding repulsions between host and guest protons; dashed lines: model including conformers with such repulsions.

CP66 cavity, with possible small contributions of other conformations.

Cyclodextrin complexes[21]: Very similar geometries for α-CD complexes (Scheme 3, Figure 2) were obtained by gas-phase molecular (quenched) dynamics (MD) simulations and MD calculations in a water box of 30 Å radius (1370 water molecules); these showed that the two water molecules in the α-CD cavity are completely expelled by complexation with aryl derivatives such as *p*-nitrophenol **PN** or benzoic acid **BA**. The complex conformations closely agree with those described in the literature on the basis of intermolecular NOEs between the inner 3- and 5-protons of the CD cavity and the *o*- and *m*-protons of the guests.[21] In all cases force field calculations as well as NOEs showed the benzene moiety deep inside the cavity, with the hydrophilic substituent of the guest oriented towards the wider side of the CD torus. The CD cavity can accommodate the benzene ring with several rotamers along the vertical axis within the torus, as indicated in Figure 2 together with the corresponding aromatic shielding conus. In contrast to the early analyses of Komiyama et al.,[1] where rotational conformers as indicated by the the dashed lines in Figure 2 were used, we found that only the conformer indicated by the solid line structure represents an energy minimum; this structure was used with SHIFT in the summation of the $\Delta\chi$ and LEF contributions on all the inner cavity protons H-3 and H-5.

The results in Table 4 illustrate, that the neglect of electric field effects for complexes can also be misleading for cyclodextrin, and that better agreement compared with the earlier approaches[1] can be reached with force field generated geometries by explicit inclusion of the electrostatic effects. The critical point here is, as in related force field simulations, the choice of the point charges in guest molecules such as **PN** or **BA**; Scheme 4 shows the many options with **BA**. Best agreement between experimental and calculated shifts (Table 4) was obtained by the use of Gasteiger[22] point charges,

Table 4. Cyclodextrin – arene complexes; CIS values (in ppm) on host.[a]

Proton	$\Delta\chi_{arom}$	LEF			$\Delta\chi$ + LEF				
		Gasteiger	CT	CNDO	Gasteiger	CT	CNDO	CIS_{lit}[b]	CIS_{exptl}[c]
with *p*-nitrophenol:									
H3	– 0.36	– 0.06	– 0.41	– 0.16	**– 0.42**	– 0.77	– 0.52	**– 0.26**	**– 0.35**
H5	– 0.03	– 0.04	0.48	– 0.11	**– 0.07**	0.45	– 0.14	**0.08**	**– 0.05**
with benzoic acid:									
H3	– 0.40	– 0.07	– 0.10	– 0.02	**– 0.47**	– 0.50	– 0.42	**– 0.40**	**– 0.45**
H5	0.01	0.05	0.01	0.06	**0.06**	0.02	0.07	**0.09**	**0.17**

[a] With Johnson – Bovey model, LEF with local charges according to Gasteiger, charge template (CT, CHARMm) or CNDO. (see also Table 5). [b] Earlier calculations without LEF and with conformations fitted to the experimental shifts (Komiyama et al.). [c] Experimental data.

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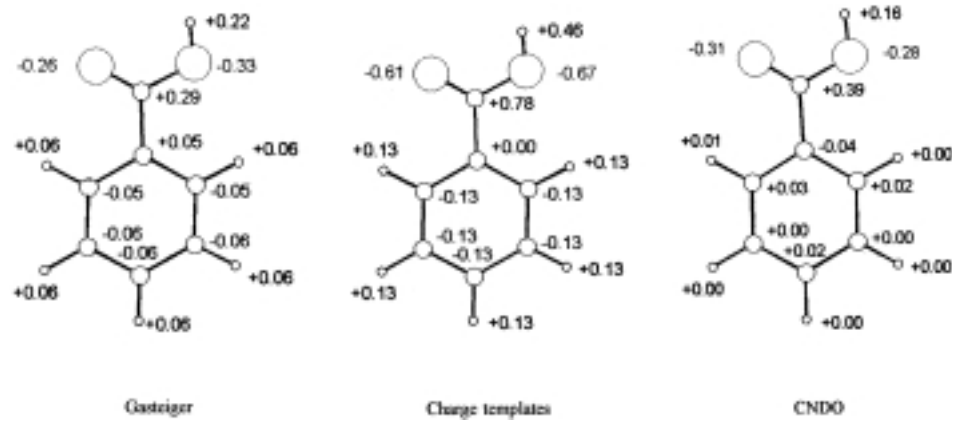

Scheme 4. Different charge distributions used in SHIFT calculations (for example benzoic acid).

and with underlying conformations which are averaged between the energy minima reflected in conformations depicted in Figure 2. For both **PN** or **BA** complexes with α-cyclodextrin the orientation and depth of immersion of the conformer agrees well with NOE data and with the SHIFT calculations.

In conclusion, the application of programs such as SHIFT leads to valuable structural evaluations of supramolecular complexes in solution. For these the shifts δ_0 in absence of the shielding effect, which is to be calculated, are available from measurements of the separate species before complex formation. The program also provides for the calculation of ^{13}C-NMR shifts and for higher order effects, such as square electric field effects; these, however, are more difficult to evaluate, and fortunately are not necessary for the analyses of associations between molecules. In contrast to for example molecular orbital calculations the use of classical equations allows the chemist to evaluate the shielding contribution of single groups within a molecule or within a supramolecular complex in a more direct and intuitive way. It should be stressed, that as with force field applications the reliability of the shift calculations depends strongly on the parametrization of the underlying equations. Before applying these to new effects, such as to amide functions, a sufficiently large number of conformationally well defined structures with such functions should be evaluated.

Acknowledgements

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