Hydrogen Bond in Molecules with Large-Amplitude Motions: A Rotational Study of Trimethylene Sulfide···HCl[**]

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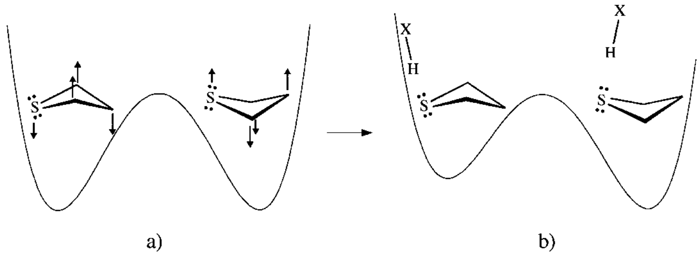
In four-membered ring compounds, the various intramolecular forces determine both the conformation and the dynamics of the large-amplitude ring-puckering motions.[1] The conformation is described by the potential function for the out-of-plane vibration (ring puckering) and depends on the balance between two large opposing forces. The first of these is the classical ring strain, which tends to make the molecule planar. The second is the torsional force associated with adjacent CH_2 groups, which tends to pucker the ring. If the ring strain dominates, the potential function contains a single minimum at the planar conformation, while if the torsional force is predominant, the potential function has a double minimum with a barrier at the planar conformation.

The trimethylene sulfide (thietane) ring undergoes a large-amplitude ring-puckering motion. The associated potential function has a double minimum with a barrier to the planar conformation of 274(2) cm^{-1} [2, 3] (Figure 1a). Tunneling motion through this barrier interconverts the isoenergetic, puckered trimethylene sulfide (TMS) conformers and makes equivalent the nonbonding electron pairs at the sulfur atom, which can act as proton acceptors. When complexed with a hydrogen halide HX (X = F, Cl) in the gas phase, a question arises: Is the ring puckering such a prominent large-amplitude motion in TMS that it prevails also in its hydrogen-bonded complexes? If the double minimum is retained after complexation, the interaction of HX with the lone pairs at S would result exceptionally in two different axial and equatorial complexes, since the two nonbonding electron pairs were not equivalent. These conformations would have different energies and could be observed as structurally different species in an asymmetric double-minimum potential function (Figure 1b).



a) b)

Figure 1. Ring-puckering potential functions for a) trimethylene sulfide and b) the trimethylene sulfide···HCl complex. The potential function of the complex is speculative.

In order to clarify this situation, we have undertaken a study of the complex formed between TMS and HCl. The experimental study has been carried out in the collisionless environment of a supersonic jet, where the complexes are easily formed and can be characterized by Fourier-transform microwave spectroscopy. The high sensitivity of this technique makes it possible to isolate and observe the axial and equatorial conformers which could be formed in the supersonic expansion.

Initial predictions of the rotational spectrum for both axial and equatorial conformers were obtained considering a C_s symmetry with the HCl molecule[4] located in the symmetry plane of TMS[5] at bond angles and distances taken from the related complex tetrahydrothiophene···HCl.[6] From this model, the two conformers of TMS···HCl were predicted to be nearly prolate asymmetric tops with their dipole moments oriented along the *a* and *b* principal inertial axes. A planar conformation of TMS giving rise to only one conformer for the complex was also considered. Using mixtures with argon as carrier gas, several groups of lines were detected and identified as corresponding to ^{a}R branch transitions of the axial conformer. No sign of the equatorial conformer was observed employing argon as carrier gas. When TMS and HCl were diluted in helium, less intense new bands appeared along with those attributed to the axial form in the regions previously scanned and they were readily assigned to the equatorial conformer. The assignment of both conformers was completed with the measurement of *b* type transitions. The spectra of several isotopic species were also detected and assigned for both forms.

Recently, axial and equatorial hydrogen bond complexes have been also reported for tetrahydropyran···HCl,[7] thiane···HCl,[8] and tetrahydropyran···HF.[9] In these cases, the existence of two nonequivalent pairs of lone electrons at the oxygen or sulfur atoms is a consequence of the structure of the acceptor molecule itself. In the present case, the equivalence of the nonbonding pairs at sulfur is broken by effect of complexation. The observation of the axial and equatorial conformers in the TMS···HCl complex constitutes the first experimental evidence of the implication of a large-amplitude motion in the conformational behaviour of a complex.

All observed rotational transitions showed a quadrupole hyperfine structure due to the presence of a chlorine nucleus. The frequencies (available as Supporting Information) were fitted[10] to a Hamiltonian including the semirigid-rotor terms of the Watson Hamiltonian in the A reduction and the I^r representation[11] and the quadrupole coupling terms.[12] The associated observable parameters are the rotational (A, B, C) and centrifugal distortion constants (Δ_J, Δ_{JK}, Δ_K, δ_J, δ_K), and the elements of the quadrupole coupling tensor (χ_{ij}; $i, j = a, b, c$), respectively. The spectroscopic constants obtained from this analysis are listed in Tables 1 and 2.

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Table 1. Spectroscopic constants for axial TMS ⋯ HCl.

	$C_3H_6{}^{32}S\cdots H^{35}Cl$	$C_3H_6{}^{32}S\cdots H^{37}Cl$	$C_3H_6{}^{32}S\cdots D^{35}Cl$	$C_3H_6{}^{34}S\cdots H^{35}Cl$	α-$^{13}C^{12}C_2H_6{}^{32}S\cdots H^{35}Cl$	β-$^{13}C^{12}C_2H_6{}^{32}S\cdots H^{35}Cl$
A [MHz]	4457.5910(27)[a]	4457.0074(41)	4446.6646(19)	4377.42(17)	4402.44(27)	4384.08(24)
B [MHz]	1437.25677(62)	1392.8089(11)	1431.2428(11)	1429.95245(39)	1424.91556(66)	1431.48978(80)
C [MHz]	1341.24209(61)	1302.4054(11)	1335.0355(10)	1327.52957(42)	1334.64141(68)	1329.49502(82)
Δ_J [kHz]	1.7653(32)	1.6762(43)	1.7429(47)	1.6975(88)	1.756(14)	1.757(18)
Δ_{JK} [kHz]	15.491(19)	14.770(39)	15.279(35)	[15.491][b]	[15.491]	[15.491]
Δ_K [kHz]	– 14.34(47)	– 13.25(69)	[– 14.34]	[– 14.34]	[– 14.34]	[– 14.34]
δ_J [kHz]	0.1570(28)	0.1439(42)	0.1543(40)	[0.1570]	[0.1570]	[0.1570]
δ_K [kHz]	– 4.87(22)	– 4.85(42)	– 4.81(48)	[– 4.87]	[-4.87]	[– 4.87]
χ_{aa} [MHz]	– 35.8240(79)	– 28.3140(72)	– 36.560(11)	– 36.347(43)	– 35.682(88)	– 35.41(10)
$(\chi_{bb}-\chi_{cc})$ [MHz]	– 16.376(12)	– 12.831(14)	– 16.701(14)	– 15.826(67)	– 16.44(19)	– 16.89(20)
$\lvert\chi_{ab}\rvert$ [MHz]	32.05(46)	25.21(63)	32.78(52)	[32.05]	[32.05]	[32.05]
N[c]	145	111	111	39	23	19
J_{max}	8	7	7	6	5	5
σ[d] [kHz]	1.8	1.6	2.5	1.3	2.3	1.8
P_c[e] [u Å^2]	44.10160(70)	44.10173(88)	44.10377(80)	44.0919(28)	45.4027(42)	44.0958(39)

[a] Standard error in parentheses in units of the last digit. [b] Parameters in square brackets were fixed to the $C_3H_6{}^{32}S\cdots H^{35}Cl$ value. [c] Number of fitted quadrupole components. [d] Root mean square deviation of the fit. [e] $P_c=(I_a+I_b-I_c)/2=\Sigma_i m_i c_i^2$. Conversion factor: 505379.1 MHz u Å^2.

Table 2. Spectroscopic constants for equatorial TMS ⋯ HCl.

	$C_3H_6{}^{32}S\cdots H^{35}Cl$	$C_3H_6{}^{32}S\cdots H^{37}Cl$	$C_3H_6{}^{32}S\cdots D^{35}Cl$	$C_3H_6{}^{34}S\cdots H^{35}Cl$
A [MHz]	4753.9408(19)[a]	4750.7390(30)	4738.3168(19)	4661.36(25)
B [MHz]	1354.88137(77)	1313.6645(18)	1349.71417(99)	1349.95623(42)
C [MHz]	1289.97569(73)	1252.3321(18)	1284.15074(97)	1278.57039(42)
Δ_J [kHz]	1.9645(29)	1.8595(42)	1.9447(30)	1.8908(72)
Δ_{JK} [kHz]	– 0.524(25)	– 0.526(39)	– 0.753(32)	[– 0.524]
Δ_K [kHz]	13.14(32)	[13.14][b]	[13.14]	[13.14]
δ_J [kHz]	0.2228(22)	0.2043(27)	0.2250(29)	[0.2228]
δ_K [kHz]	2.04(33)	2.42(84)	2.17(46)	[2.04]
χ_{aa} [MHz]	– 30.131(10)	– 23.932(12)	– 30.757(15)	– 30.614(46)
$(\chi_{bb}-\chi_{cc})$ [MHz]	– 22.700(12)	– 17.710(18)	– 23.156(18)	– 22.27(14)
$\lvert\chi_{ab}\rvert$ [MHz]	35.844(35)	28.19(17)	36.584(50)	[35.844]
N[c]	148	113	113	35
J_{max}	9	7	7	6
σ[d] [kHz]	1.6	1.8	1.9	2.3
P_c[e] [u Å^2]	43.76972(76)	43.7690(11)	43.77044(83)	43.7585(35)

[a]–[e] See footnotes to Table 1.

The first necessary step in the structural analysis is the experimental confirmation of the previously assumed C_s symmetry for the conformers. The near invariance of the planar moments P_c (see Tables 1 and 2) for the isotopic substitution of nuclei in the symmetry plane and the fact that these values are nearly equal to P_b of free TMS (P_b = 43.98299(16) u Å^2, calculated from data given in ref. [3]) are conclusive pieces of evidence that both conformers have C_s symmetry. The structures of both conformers given in Table 3 were determined from fits to the corresponding sets of rotational constants given in Tables 1 and 2. The angle α_{az} (Figure 2), which defines the position of the H atom of the HCl subunit, has been obtained from the values of the elements of the quadrupole coupling tensor.[6, 13] For the equatorial conformer, the parameters of the TMS ring were held fixed to those obtained for the axial conformer. It can be noted that the ring-puckering angle of TMS in the complex (γ = 24(2)°) is close to that of free TMS (γ = 28°).[2]

Table 3. Structural parameters concerning the hydrogen bond.[a]

	axial	equatorial
$r(S{-}C_\alpha)$ [Å]	1.82(2)[b]	[1.82][c]
$r(C_\alpha{-}C_\beta)$ [Å]	1.56(3)	[1.56]
$r(C_\alpha{-}C_\alpha)$ [Å]	2.287(5)	[2.287]
γ [°]	24.(2)	[24]
$r(S\cdots Cl)$ [Å]	3.539(8)	3.50(3)
ϕ [°]	87.0(7)	84.5(15)
∢CSC [°]	77.7(11)	–
$r(S\cdots H)$ [Å]	2.28(2)	2.26(6)
φ [°]	92.1(10)	91.1(17)
θ [°]	14.1(8)	18.4(5)

[a] See Figure 2 for symbol definitions. [b] Standard error in parentheses in units of the last digit. [c] Parameters in square brakets were kept fixed in the fit.

Several aspects on the axial and equatorial structures can be discussed. The hydrogen bond parameters $r(S\cdots H)$ and φ are practically identical for both conformers. If we consider the HCl molecule as a probe for the direction of the nonbonding electron pairs, these results strongly suggest that these lone pairs are located symmetrically with respect to the CSC plane of TMS at angles of about 90°. This can be rationalized considering the HOMO–LUMO model, which interprets the

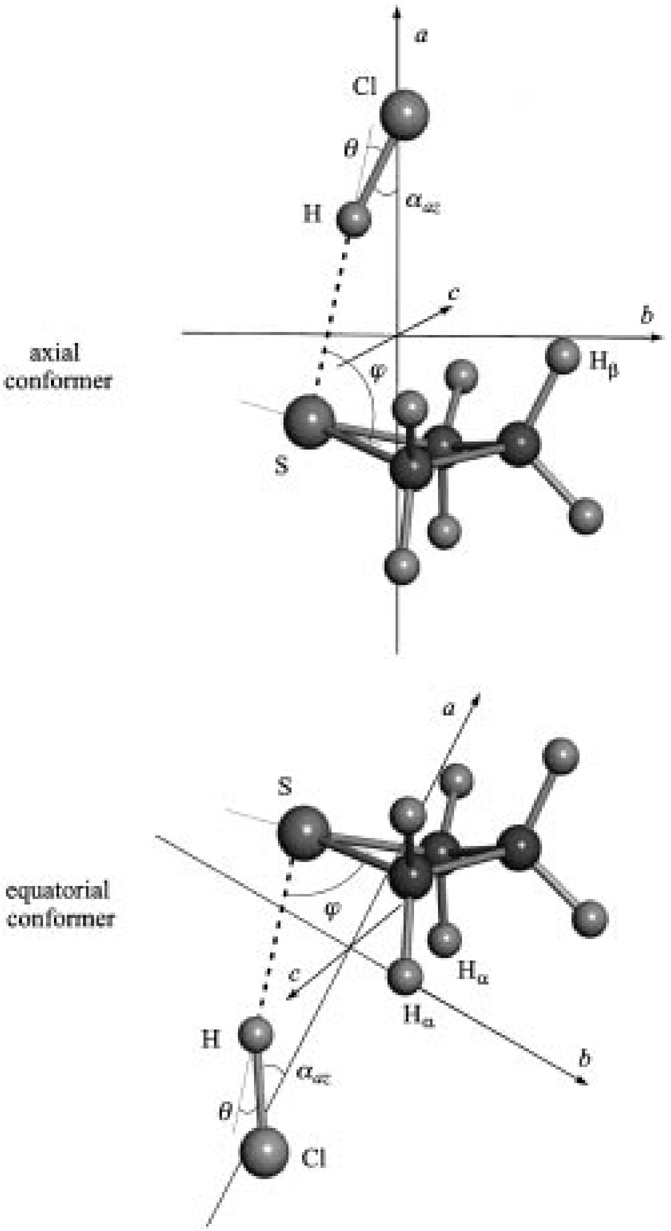

Figure 2. Structures of axial and equatorial conformers of TMS $\cdots$ HCl.

new bond as an interaction between the σ^* LUMO orbital of HCl and the n_π HOMO orbital of TMS, orthogonal to the S–C bonds. These results can also be understood in terms of the valence shell electron-pair repulsion (VSEPR) model,[14] from which an angle between the lone electron pairs larger than tetrahedral would be expected.

Another structural aspect to discuss is the remarkable deviation from the collinear arrangement of the S $\cdots$ H–Cl atoms shown by both conformers, reflected in the value of θ (see Figure 2). These deviations can be attributed to the existence of secondary hydrogen bonds between the chlorine atom and the nearest H atoms of the methylene groups.[6, 8, 13] The calculated distances $r(\mathrm{Cl}\cdots\mathrm{H}_\beta) = 3.20$ and $r(\mathrm{Cl}\cdots\mathrm{H}_\alpha) = 3.26$ Å for the axial and the equatorial conformers, respectively, lie in the range reported for related complexes.[6, 8, 13, 15]

An interesting fact is the relaxation from the equatorial to the axial conformer observed in the supersonic expansion. When argon is used as carrier gas, the intensity ratio of about 2.5:1 between axial and equatorial conformers observed with helium does not prevail and only the axial form is detected. This proves conclusively that this form is the most stable one. It is commonly accepted that a heavy inert gas produces a relaxation from the high-energy conformer to the most stable one when the interconversion barrier between them is lower than a certain value (about 400 cm^{-1}).[16] In our case, the interconversion between axial and equatorial conformers can only take place through the paths sketched in Figure 3. The HCl inversion motion can be excluded, since the angle between the lone pairs (ca. 180°) implies a high barrier to interconversion as in the thiane $\cdots$ HCl complex,[8] for which relaxation has not been observed. Consequently, the interconversion should occur via ring puckering, so the ring inversion barrier remains at a low value in the complex. Thus, we can conclude that the large-amplitude ring-puckering motion is not substantially altered by hydrogen bond formation.

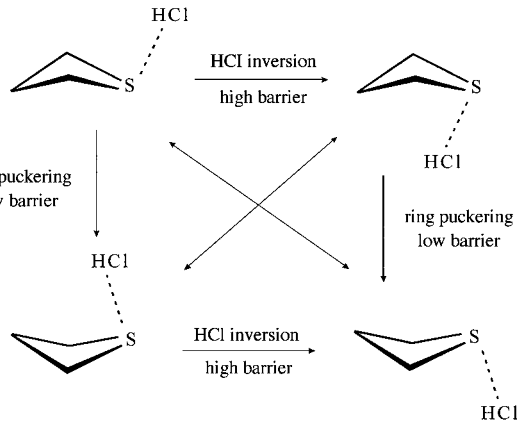

Figure 3. Possible interconversion paths between the axial and equatorial conformers of TMS $\cdots$ HCl.

We believe that these experimental results constitute a keystone for future studies on the implication of large-amplitude motions in hydrogen bonding. We are carrying out further investigations in order to shed more light on this problem.

Experimental Section

The rotational spectra of the axial and equatorial conformers of TMS $\cdots$ HCl, generated in a supersonic jet, have been observed by Fourier-transform microwave spectroscopy (frequency range 5–18.5 GHz).[17] The complexes were formed by expanding gas mixtures of TMS (ca. 1%, Aldrich) and HCl (ca. 4%, Aldrich) or DCl (ca. 4%, Euriso-top) in either Ar or He (1–2 bar) through a pulsed nozzle into a vacuum chamber. Molecular pulses of 0.3–0.35 ms were macroscopically polarized by microwave pulses of about 0.2 μs within the Fabry–Pérot cavity. The rotational spectra were obtained as the Fourier transformation of the relaxation signal in the time domain.

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Revolutionizing Resin Handling for Combinatorial Synthesis

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The last decade has seen rapid growth both in combinatorial methodology and technology development.[1] Traditionally, resin beads have been handled as a free-flowing material, which although relatively simple for the synthesis of single compounds, does complicate the handling issues for large numbers of single compounds in multiple parallel synthesis. The major advances in this area; tea-bags,[2] crowns,[3] and Irori Kans[4] methodology permit the production and handling of discrete packets of resin materials for multiple parallel synthesis, although even here the filling, sealing, labeling of the units and the recovery of tagging devices complicates handling and have cost implications. More recent innovations include the monolithic polymer discs of Sherrington et al.,[5] which were then used by a number of other workers.[6]

We now report a fundamentally new approach to resin handling. The method is applicable to various resin types (polystyrene (PS), polystyrene–polyethyleneglycol graft polymer (PS-PEG)), either pre- or postloaded with virtually any linker or linker-scaffold combinations. The method is applicable to all routinely used resin bead sizes and substitutions. The approach can be used to generate individual resin-based supports in virtually any shape or form desired, and makes resin much more convenient to handle, yet maintains the original chemical properties of the resin.

The basis of this new method is resin sintering within an inert polymer matrix.[7] This was achieved by blending appropriate proportions, in this case 1:1, of ultra-high molecular weight polyethylene and the synthesis resin, to a homogeneous mix. This was then loaded into polytetrafluoroethylene(PTFE)-lined moulds and passed through a sintering oven under a nitrogen atmosphere. The temperature of the mixture was gradually increased as it passed through the oven, just to the point where the polyolefin matrix began to soften (determined experimentally). The moulds were then gradually cooled and the formed plugs ejected from the mould. The plugs were made in a cylindrical form, as this shape fitted nicely into the wells of a 96-well plate. This shape also combines ease of preparation of the mould with the physical strength of the plug. Plugs could however be made in a variety of different shapes or sizes, with an upper limit determined by the necessity for reasonably low-temperature gradients between the inside and outside of the plug during the sintering process. Various structural features such as handles, holes, or struts can be in-built for improving the ease of handling or increasing the strength of the shape by changing the mould. The cylindrical plugs made were 9 mm long, 7.5 mm diameter and had a mass of (170 ± 6) mg resulting in a very defined loading per plug. A typical plug contained 50% synthesis resin, which approximates to 85 mg of Merrifield resin (initially $0.96\,\text{mmol}\,\text{g}^{-1}$) thereby giving an initial loading of 81.6 μmol per plug. The plugs are porous, with solvent able to freely access through the pores of the matrix of the plug and into the synthesis resin held therein. This was demonstrated by soaking a plug in a solution of bromophenol blue in dichloromethane and then slicing the plug to ascertain the loading of the dye. Within one minute the dye had entered the polyethylene (PE) plug although presumably it would take longer to reach all the reactive sites. The plugs produced are solid devices in which the beads are intact and are physically attached to the polyethylene filler by a small amount of polymer flow onto the beads (Figure 1). Clearly, a proportion of resin bead is physically prevented from reacting freely, but this is small and only on the surface and thus insignificant. These plugs in effect function as minireactors.

A feature of these devices is the relative freedom from the well-known swelling properties of all manner of gel based resins. We attribute this to the void volume within the plug, and the flexibility of the internal structure allowing an

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