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**Probing the C-H $\cdots\pi$ Weak Hydrogen Bond in Anesthetic Binding:
The Cluster of Sevoflurane-Benzene****

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Supporting information for this article is available in the WWW under ...

Abstract

Cooperativity between weak hydrogen bonds can be revealed in molecular clusters isolated in the gas phase. Here we examine the structure, internal dynamics and origin of the weak intermolecular forces between sevoflurane and a benzene molecule, using multi-isotopic broadband rotational spectra. This heterodimer is held together by a primary C-H $\cdots\pi$ hydrogen bond, assisted by multiple weak C-H $\cdots$ F interactions. The multiple non-bonding forces hinder the internal rotation of benzene around the anesthetic, producing detectable quantum tunneling effects in the rotational spectrum.

Weak hydrogen bonds are characterized by very low interaction energies ($< 20 \text{ kJ mol}^{-1}$), making these forces especially sensitive to modulation and cooperativity. Model molecular clusters formed by haloalkanes and small organics reveal how $\text{C-H}\cdots\text{O}$,^[1] $\text{C-H}\cdots\text{S}$,^[2] $\text{C-H}\cdots\text{N}$ ^[3], or $\text{C-H}\cdots\text{F-C}$ ^[4] interactions tend to associate to maximize the number and strength of non-bonding forces, as illustrated by the nine simultaneous $\text{C-H}\cdots\text{F}$ contacts in the cage structure of the difluoromethane trimer.^[5] Much less structural information is available on the weaker (dispersion-dominated) $\text{C-H}\cdots\pi$ interaction, despite its influence in organic, organometallic and biological chemistry. Reviews by Nishio,^[6] Desiraju and Steiner^[7] based most of their conclusions on crystallographic or *ab initio* studies. Alternatively, rotational spectroscopy recently analyzed several clusters involving phenyl π acceptors,^[8,9,10,11] in absence of perturbing crystal or matrix effects. In particular, $\text{F}_3\text{CH}\cdots\text{benzene}$ ^[8] represents a prototypical $\text{C-H}\cdots\pi(\text{Ph})$ interaction, with the C-H bond pointing to the center of the aromatic ring. However, the short hydrogen bond distance $r_{(\text{H}\cdots\text{Benzene})} = 2.366(2) \text{ \AA}$ suggests a stronger interaction than with other π acceptors, prompting our interest for systems with a less acidic H, larger size and the possibility of competing interactions. The cluster of sevoflurane-benzene is interesting from a chemical and biological point of view. Sevoflurane is a common volatile anesthetic and the benzene cluster might model the local interaction with aromatic side-chains at the protein receptors.^[12] Chemically, sevoflurane combines different donor and acceptor groups, including oxygen lone-pairs, several C-F “organic fluorine” bonds (recognized as weak acceptors), and two kinds of activated isopropyl and fluoromethyl C-H bonds. Recently, van der Veken *et al.* studied the vibrational spectra, reporting the observation of two different species.^[13] However, the interpretation of the experimental data was largely based in quantum chemical calculations. In comparison, our rotational study has identified forty-six separate high-

resolution spectra from distinct isotopologues, accurately resolving the molecular structure and the internal dynamics of the benzene ring.

The results of the conformational screening of sevoflurane-benzene can be found in Figure 1 and Table 1 (five lowest-energy conformers). The most stable conformations contain a variety of weak hydrogen bonding effects, mostly based on a C-H $\cdots$ π interaction originated in the isopropyl or fluoromethyl groups, or in combinations of C-H $\cdots$ F and C-H $\cdots$ π weak contacts. The predicted global minimum (conformer 1) shows an intriguing topology for benzene not seen in other conformers, where eclipsing one hydrogen with the fluoromethyl group allows for the other 5 hydrogens to be optimally staggered between the sevoflurane substituents. This arrangement makes conceivable some contribution from the two bifurcated and one single C-H $\cdots$ F interactions, which could enhance the attractive character of the primary C-H $\cdots$ π link. The simplicity of this optimally staggered C-H $\cdots$ π interaction is energetically favored by ca. 10.3-13.5 kJ mol⁻¹. Conformers 1 and 2 correspond to the observations of van der Veken *et al.*, who found a population ratio of conf 1: conf 2 $\approx$ 15:1 in Xe cryosolution based on the intensities of the vibrational bands.^[13]

The analysis of the rotational spectrum was possible thanks to recent advances in broadband (chirped-pulse) Fourier-transform microwave (CP-FTMW) spectroscopy.^[14,15] An overview of the 2-8 GHz MW spectrum is shown in Figures 2 and S1 (Supporting Information). The strongest transitions arise from the sevoflurane monomer (signal-to-noise ratio SNR $\approx$ 20000:1). The sevoflurane-benzene parent species was ca. 50 times weaker, more than sufficient to detect all independent spectra from each heavy-atom monosubstituted isotopologues (¹³C, ¹⁸O) in natural abundance ($\sim$ 0.2-1%). Hyperfine splittings were immediately noticeable in the transitions of the

complex, and eventually attributed to the internal rotation of the benzene monomer about the sevoflurane frame. The symmetry point group of the internal rotor is C_6 , which contains four irreducible representations (A , B , E_1 and E_2). Therefore, each rotational transition is split into four separate symmetry components. We collect in Table 2 the experimental rotational constants derived for the parent species, for which the six-fold internal rotation barrier was determined as $V_6 = 32.8687(27) \text{ cm}^{-1}$. The details of the barrier calculation will be reported separately. Isotopic substitutions in sevoflurane are similarly complicated by the internal rotation. However, substitutions on benzene break its C_6 symmetry, resulting in simpler asymmetric-top spectra. For this reason, our strategy was based on the use of a sample of monodeuterated benzene, allowing a manageable assignment of all the sevoflurane isotopologues in the cluster. The sensitivity of the experiment was so high as to detect the doubly-substituted $D/^{13}C$ isotopologues in natural abundance with good intensity (e.g. $\text{SNR} \geq 3:1$). Finally, and despite the extremely high spectral density, 33 of the 60 possible $D/^{13}C$ isotopologues were assigned and every carbon had at least one associated isotopologue assignment. The spectral assignment was aided by automatic routines developed in Virginia.^[16] The rotational parameters and experimental transitions for all 46 measured species are presented in Tables 2 and S1-S47. No other conformations of sevoflurane-benzene were detected. Two sevoflurane homodimers will be reported separately.

The analysis of the multi-isotopic rotational spectra led to an accurate experimental structure for the cluster, including all heavy atoms and the six benzene hydrogens. Application of the Kraitchman’s equations^[17] confirmed that the sevoflurane monomer^[18] is not distorted upon complexation, as usually assumed for weak and moderately strong hydrogen bonds. Later, a least squares fitting resulted in the ground-state effective (r_0) structure.^[19,20] The dimer has $3N-6 = 75$ independent degrees of

freedom for a total of 138 experimental observations (three moments of inertia per species). Therefore, sevoflurane-benzene offers the possibility to determine a nearly full effective structure for a molecular complex, which is very rare. On assumption of *ab initio* constraints (M06-2X) only for the positions of the three sevoflurane hydrogens and F-C-F bond angles, the molecular structure of Table S49 was obtained. A comparison with the theoretical geometries can be found in Figures 3 and S3, and Table S50. Interactive 3D-PDFs can be found in Figures S4-S6.

Consequently, we have addressed the structure, internal dynamics and origin of the weak unions between sevoflurane and a benzene molecule through multi-isotopic rotational spectra. A single conformation was observed in the cold ($T_{rot} \approx 2$ K) supersonic jet, corresponding to the predicted global minimum primarily bound through the isopropyl C-H bond of sevoflurane. There is no indication of the second species with fluoromethyl bonding suggested from a weak band in the low-resolution IR spectra,^[13] either because of thermal depopulation, or because of conformational relaxation in the jet. The C-H $\cdots\pi$ (Ph) weak hydrogen bond $r_{(H\cdots Benzene)} = 2.401(16)$ Å is slightly longer than in the complex with trifluoromethane ($r_{(H\cdots Benzene)} = 2.366(2)$ Å), but still reflects the important activation role of the electronegative F and O atoms. The electrostatic contribution due to the interaction of the acidic hydrogen and the Lewis basic π benzene cloud likely enhances the C-H $\cdots\pi$ interaction with respect to aliphatic systems.^[21] The geometry of the complex suggests that the main C-H $\cdots\pi$ interaction is modulated by secondary C-H $\cdots$ F weak contacts between three aromatic hydrogens and the fluorine atoms in sevoflurane. The calculated distances for the secondary interactions range from 3.095(14) Å in OCH₂F $\cdots$ H₁ to 3.293(12)-3.531(15) Å in CF₃ $\cdots$ H interactions. These values are 0.5-1 Å longer than the conventional fluorine hydrogen bonding distances, but not unreasonable for bifurcated or secondary weak

hydrogen bonds, as bond distances up to 2.876-3.246 Å were identified in the difluoromethane trimer^[5] and related clusters.^[1,4] It is thus likely that the multiple weak fluorine hydrogen bonds are a contributor to the relative staggered orientation of the benzene ring and sevoflurane. An additional argument originates from the barrier hindering the internal rotation of the benzene moiety, which strikingly compares with the free-torsion between the two subunits of F₃CH...benzene. The theoretical data outline the difficulty to treat dispersion forces. The B3LYP method fails to reproduce the cluster geometry, as first observed by a poor agreement with the rotational constants. The B3LYP C-H... π hydrogen bond is ca. 0.5 Å longer than the experimental value and it predicts the ring slightly tilted with respect to the C-H bond (98°). Conversely, the MP2 and M06-2X values (92.3° and 91.9°, respectively) agree fairly well with the r_0 determination (92.65(43)°). Significantly, in B3LYP the benzene ring is actually rotated ca. 25° from the eclipsing orientation of the global minimum. Thus, this optimal staggering is actually dependent on the proper treatment of the dispersion contribution to the C-H... π weak hydrogen bond. These results suggest that both electrostatics and dispersion play important roles in determining the complexation geometry of sevoflurane-benzene. Similar discrepancies of B3LYP were observed for (phenol)₂.^[10] In comparison, the MP2 or M06-2X methods with a modest Pople triple- ζ basis set acceptably accounts for the spectral results. MP2 and M06-2X mostly differ by a slight rotation in the benzene orientation, which could be attributed to the low-lying benzene torsional mode (14 cm⁻¹).

In conclusion, the new developments in broadband rotational spectroscopy lead to unparalleled levels of sensitivity for molecules and molecular clusters of increasing size (>10-20 heavy atoms). A theoretical methodology with a balance between accuracy, computational cost and portability is crucial for further experiments. As a

result, rotational studies are essential in benchmarking the theoretical procedures for efficient description of weak non-bonding forces.

Keywords: Anesthetics, Noncovalent Interactions, Rotational Spectroscopy, Weak Hydrogen Bonding

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C-H... π Weak Hydrogen Bond

N. A. Seifert, D. P. Zaleski, C. Pérez, J. L. Neill, B. H. Pate, M. Vallejo-López, A. Lesarri, E. J. Cocinero, F. Castaño, I. Kleiner _____ **Page – Page**

Probing the C-H... π Weak Hydrogen Bond in Anesthetic Binding: The Cluster of Sevoflurane...Benzene

Cooperation is force: The cooperativity between a primary C-H... π hydrogen bond and multiple C-H...F weak interactions defines the dynamic non-bonding union between sevoflurane and benzene. The structure and internal rotation was determined with broadband rotational spectroscopy.

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Figure 1. The predicted lowest-energy conformers of sevoflurane-benzene (MP2/6-311++g(d,p)).

Figure 2. A section of the CP-FTMW spectrum of sevoflurane-benzene-D₁ (6.8 million acquisitions, positive traces). The six symbols correspond to a unique ²D-isotopologue (negative traces for predictions). The bottom panel shows a selection of ¹³C/²D double isotopologue transitions.

Figure 3. Views of the sevoflurane-benzene structure. The ball-and-stick frameworks correspond to the M06-2X/6-311++g(d,p) geometry. The small spheres represent the experimental r_0 structure.

Table 1: Predictions for rotational parameters and energetics of the lowest-energy conformers of sevoflurane-benzene in Figure 1.

	Theory (MP2 / M06-2X / B3LYP – 6-311++G(d,p))				
	Conf. 1	Conf. 2	Conf. 3	Conf. 4	Conf. 5
A / MHz ^[a]	508 / 515 / 500	650 / 670 / 636	663 / 698 / 636	543 / 557 / 538	685 / 697 / 667
B / MHz	376 / 379 / 319	264 / 263 / 209	256 / 253 / 211	358 / 355 / 305	273 / 279 / 228
C / MHz	353 / 358 / 302	235 / 235 / 191	234 / 233 / 193	325 / 318 / 281	229 / 234 / 196
$ \mu_a $ / D	2.2 / 2.3 / 2.1	1.9 / 2.3 / 2.1	1.1 / 1.3 / 2.1	1.1 / 1.0 / 1.1	1.6 / 1.8 / 1.6
$ \mu_b $ / D	0.5 / 0.3 / 0.2	0.6 / 0.4 / 0.8	1.3 / 1.7 / 0.8	0.8 / 0.8 / 0.9	1.1 / 1.0 / 1.1
$ \mu_c $ / D	1.6 / 1.6 / 1.7	1.3 / 1.3 / 1.2	1.3 / 1.0 / 1.2	1.3 / 1.3 / 1.3	0.5 / 0.6 / 0.6
$ \mu_{TOT} $ / D	2.7 / 2.8 / 2.7	2.4 / 2.6 / 2.6	2.2 / 2.3 / 2.6	1.8 / 1.8 / 1.9	2.0 / 2.1 / 2.1
D_J / kHz	0.02 / 0.02 / 0.07	0.02 / 0.01 / 0.1	0.02 / 0.01 / 0.07	0.02 / 0.02 / 0.04	0.008 / 0.007 / 0.05
D_{JK} / kHz	0.004 / 0.01 / 0.2	0.2 / 0.2 / -0.3	0.1 / 0.2 / -0.03	0.08 / 0.1 / 0.3	0.1 / 0.1 / 0.04
D_K / kHz	0.04 / 0.04 / 0.3	0.1 / 0.1 / 0.4	0.8 / 0.2 / 0.1	-0.07 / -0.1 / -0.2	0.2 / 0.1 / -0.02
d_1 / Hz	-2.8 / -2.8 / -14.4	1.4 / -1.6 / -5.6	1.0 / 0.7 / -3.4	-2.6 / -3.3 / -7.0	-0.8 / -0.5 / -7.0
d_2 / Hz	0.2 / 0.2 / -0.7	0.6 / -0.1 / -0.2	0.3 / 0.2 / -0.2	-0.3 / -0.2 / -0.3	0.0 / 0.1 / -0.5
ΔG / kJ mol ⁻¹	0.0 / 0.0 / 0.0	8.6 / 4.5 / -1.5	7.9 / 10.2 / 0.1	19.0 / 13.8 / 17.0	31.0 / 22.7 / 17.8
$\Delta (E+ZPE)$ / kJ mol ⁻¹	0.0 / 0.0 / 0.0	13.5 / 10.3 / 2.2	14.9 / 13.5 / 2.2	19.4 / 17.0 / 15.5	31.9 / 24.6 / 18.5
E_d / kJ mol ⁻¹	-17.8 / -31.1 / -20.5	-12.8 / -20.9 / -5.0	-11.9 / -19.1 / -5.3	-17.4 / -26.1 / -5.6	-12.4 / -20.6 / -4.4

^[a]Rotational constants (A , B , C), electric dipole moment components (μ_α , $\alpha = a, b, c$), Watson's S-reduced centrifugal distortion constants (D_J , D_{JK} , D_K , d_1 , d_2), Gibbs free energies at 298 K and 1 atm (ΔG), Electronic energies with zero-point corrections ($\Delta(E+ZPE)$) and dissociation energies (E_d).

Table 2: Experimental rotational constants for the parent species and the benzene ^{13}C and ^2D isotopologues of sevoflurane-benzene (full listing in Supporting Information).

Species	A /MHz ^[a]	B /MHz	C /MHz	Δ_J /kHz ^[b]	Δ_{JK} /kHz	Δ_K /kHz	N ^[c]	RMS /kHz
Parent (A)	508.42070(40) ^[d]	358.82931(13)	338.32685(13)	[0.03490]	[0.0550]	[-0.0630]	77	6.04
Parent (B)	507.74250(60)	358.82020(12)	338.30995(12)	"	"	"	107	6.41
Parent (avg)	508.08160(50)	358.82476(13)	338.31840(13)	"	"	"	--	--
5- ^2D	505.704895(85)	356.433250(86)	335.438320(92)	0.03490(44)	0.0550(14)	0.0630(16)	225	6.91
1- ^2D	505.425300(95)	355.461685(38)	335.793300(41)	"	"	"	175	6.24
2- ^2D	504.157430(60)	357.392938(38)	335.338172(35)	"	"	"	254	7.13
3- ^2D	503.901760(58)	356.776863(34)	336.551764(34)	"	"	"	247	6.37
4- ^2D	504.480480(54)	355.830667(33)	337.133881(31)	"	"	"	272	6.57
6- ^2D	506.345460(81)	355.463814(29)	335.477671(28)	"	"	"	188	4.81
5- ^{13}C	506.7452(77)	356.63733(29)	336.95711(22)	[0.03490]	[0.0550]	[-0.0630]	49	6.15
1- ^{13}C	507.7542(70)	356.32317(20)	336.13907(22)	"	"	"	57	5.23
2- ^{13}C	507.2520(41)	356.44752(14)	336.24013(15)	"	"	"	52	3.53
3- ^{13}C	506.5724(49)	357.20783(16)	336.21528(17)	"	"	"	52	3.74
4- ^{13}C	506.3589(71)	357.04374(21)	336.76461(21)	"	"	"	59	5.96
6- ^{13}C	507.3754(94)	356.67671(27)	336.29174(30)	"	"	"	56	6.09

^[a]Rotational parameters as defined in Table 1. ^[b]Centrifugal distortion fixed to the values for the 5- ^2D isotopologue. ^[c]Number of measured transitions (N) and RMS deviation of the fit (frequency accuracy 10 kHz) ^[d]Standard error in parentheses in units of the last digit.