

Enflurane: Structure and Conformational Properties

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Received February 27, 1998

Abstract: The geometric structure and the conformational properties of enflurane (2-chloro-1-(difluoromethoxy)-1,1,2-trifluoroethane, $\text{CHFCl}-\text{CF}_2-\text{O}-\text{CHF}_2$) have been studied by gas electron diffraction (GED) and by quantum chemical methods. The GED intensities are reproduced best with a mixture of three conformers, which possess a trans configuration of the C–C–O–C skeleton and gauche orientation of the CHF_2 group (H gauche with respect to the central C–O bond). The three conformers differ by the rotational orientation of the CHFCl group, with either C–Cl (58(8)%), C–H (32(10)%), or C–F (10(10)%) trans to the central C–O bond. Nineteen different stable conformations are predicted by the HF/3-21G* approximation. The same number of structures are obtained with the B3PW91/6-311G(2d) hybrid method, but the kinds of conformations and their relative energies, derived with these two methods, differ appreciably. The B3PW91 results agree with the MP2/6-311G(2d) calculations and the conformational properties derived from the GED experiment, but not with those obtained with the HF approximation. All experimental bond lengths are within the expected range for such bonds and all bond angles are close to tetrahedral except for the C–O–C angle (117.3(21)°).

Introduction

Ethyl ethers have been known for many years to possess anesthetic properties. More than 150 years ago diethyl ether was used as inhalation anesthetic by Long¹ and Morton.² The need for inhalation anesthetics with better properties, such as noncombustibility, high potency, high volatility, low toxicity, and chemical stability, led to the synthesis of halothane ($\text{CHClBr}-\text{CF}_3$),³ enflurane ($\text{CHFCl}-\text{CF}_2-\text{O}-\text{CHF}_2$),⁴ and isoflurane ($\text{CF}_3-\text{CHCl}-\text{O}-\text{CHF}_2$).⁴ Today, these three compounds have become the most frequently administered clinical inhalation anesthetics. Recently, desflurane, $\text{CF}_3-\text{CHF}-\text{O}-\text{CHF}_2$, has been released as a new, highly volatile narcotic gas.

Halothane and the three halogenated ethyl methyl ethers enflurane, isoflurane, and desflurane possess one asymmetric carbon atom and are synthesized and used for clinical purposes as racemic mixtures of the *R* and *S* enantiomers. Although the physiological effects of these compounds have been studied in great detail, the mechanism of their anesthetic action is not fully understood. For a long time the drugs were supposed to depress the nervous system by nonspecific perturbation of nerve membranes.⁵ Recent studies, however, indicate that the action of anesthetics is much more specific and direct binding on proteins is likely.⁶ This view is strongly supported by the observation that inhalation anesthetics act stereoselectively. The *S*(+) enantiomer of isoflurane is about 50% more potent than the *R*(-) form.⁷ These experiments were performed with

enantiomerically pure samples which were obtained by gas chromatography.⁸

If, indeed, the action of inhalation anesthetics depends on specific binding on proteins, a detailed understanding of such interactions at the molecular level requires the knowledge of structural and conformational properties of these compounds. In the present study we report the results of a gas electron diffraction (GED) investigation of these properties of enflurane, 2-chloro-1-(difluoromethoxy)-1,1,2-trifluoroethane. The experimental analysis is supported by ab initio (HF/3-21G*, MP2/6-311G(2d)) and density functional calculations (B3PW91/6-311G(2d)). Results of similar studies for isoflurane and desflurane will be reported elsewhere.⁹

The absolute configurations of the enantiomers of enflurane are known from the synthesis.¹⁰ *R*(-) and *S*(+)-enflurane cannot be distinguished in a GED experiment, which measures interatomic distances and not atomic positions. The interatomic distances of the two enantiomers are identical. For a gas-phase structural study enflurane is the most complicated compound among the widely used inhalation anesthetics, because of the large number of possible conformations. Compounds with three skeletal single bonds, each of which is characterized by a 3-fold potential, possess in principle $3^3 = 27$ conformations. All of them are different in the case of enflurane. Each conformation can be described by the torsional orientations around the three bonds. A certain conformation is defined qualitatively by specifying the torsional orientation of the three dihedral angles $\phi_1(\text{Cl}-\text{C}1-\text{C}2-\text{O}3)$, $\phi_2(\text{C}1-\text{C}2-\text{O}3-\text{C}4)$, and $\phi_3(\text{C}2-\text{O}3-\text{C}4-\text{H}4)$ with one of the symbols t, g⁺, or g⁻, where the letter in the symbol for $\phi_2(\text{C}1-\text{C}2-\text{O}3-\text{C}4)$ is capitalized. For a

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Table 1. Conformational Properties of Enfluran (Dihedral Angles^a in deg and Relative Energies in kcal mol⁻¹) from Theoretical Calculations^b

conformer	HF/3-21G*		B3PW91/6-311G(2d)		MP2/6-311G(2d)	
	(ϕ_1, ϕ_2, ϕ_3)	ΔE	(ϕ_1, ϕ_2, ϕ_3)	ΔE	(ϕ_1, ϕ_2, ϕ_3)	ΔE
I	t, T, g ⁺	(181, 205, 69)	(182, 179, 17)	0.00	(181, 177, 25)	0.04
II	g ⁻ , T, g ⁻	(-66, 170, -26)	(-63, 183, -17)	0.03	(-63, 185, -24)	0.00
III	g ⁺ , T, g ⁻	(62, 155, -72)	(62, 180, -18)	0.15	(62, 183, -25)	0.16
IV	g ⁺ , T, g ⁺	(62, 201, 75)	(61, 177, 11)	0.16	(61, 174, 24)	0.17
V	t, G ⁻ , g ⁺	(176, -84, 4)				
VI	t, G ⁻ , g ⁻		(184, -80, -7)	1.20		
VII	g ⁺ , T, t		(61, 162, 165)	1.30		
VIII	g ⁺ , G ⁺ , g ⁺	(64, 77, 4)	(57, 73, 14)	1.32		
IX	g ⁺ , T, t	(62, 200, 202)	(63, 196, 195)	1.34		
X	t, T, t	(181, 203, 199)	(183, 169, 195)	1.46		
XI	g ⁻ , T, t	(-66, 158, 160)	(-65, 162, 165)	1.51		
XII	g ⁻ , T, t	(-65, 201, 204)	(-61, 199, 196)	1.57		
XIII	g ⁻ , G ⁻ , g ⁻	(-64, -90, -61)	(-58, -82, -49)	1.84		
XIV	t, G ⁺ , g ⁻	(179, 91, 63)	(177, 84, 49)	1.88		
XV	g ⁻ , G ⁻ , t	(-51, -88, 168)	(-55, -85, 168)	2.06		
XVI	t, G ⁺ , t	(176, 89, 193)	(174, 88, 192)	2.13		
XVII	t, G ⁺ , g ⁻	(153, 34, -97)	(172, 38, -67)	3.75		
XVIII	g ⁺ , G ⁻ , g ⁺		(83, -53, 53)	3.94		
XIX	g ⁻ , G ⁻ , g ⁺		(-57, -41, 71)	4.33		
XX	t, G ⁻ , t	(188, -46, 189)	(196, -84, 186)	4.60		
XXI	g ⁻ , T, g ⁻	(-66, 157, -69)				
XXII	g ⁺ , G ⁺ , t	(59, 57, 162)				
XXIII	g ⁺ , G ⁺ , g ⁺	(62, 61, 69)				

^a ϕ_1 (Cl-C1-C2-O3), ϕ_2 (C1-C2-O3-C4), ϕ_3 (C2-O3-C4-H4). ^b The most stable conformer of each method is shown in bold letters.

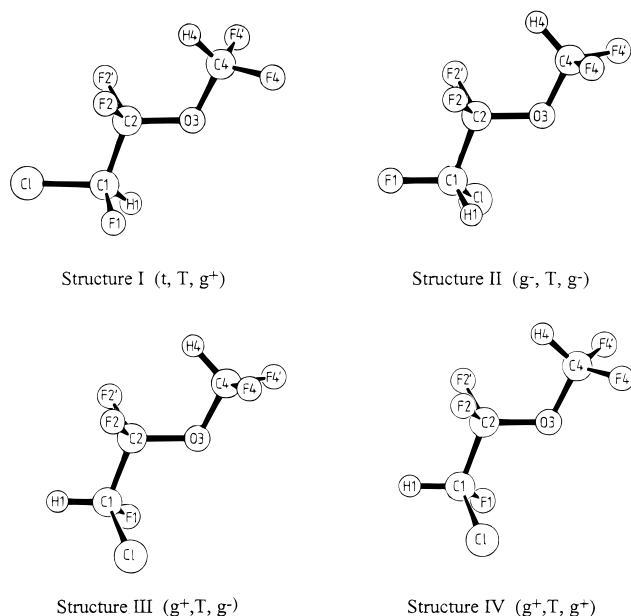


Figure 1. Molecular models of structure **I** (t, T, g⁺), structure **II** (g⁻, T, g⁻), structure **III** (g⁺, T, g⁻), and structure **IV** (g⁺, T, g⁺) of enflurane.

quantitative specification the three dihedral angles ϕ_i are used. The first letter characterizes the orientation of the chlorine atom relative to the central C2-O3 bond (ϕ_1 (Cl-C1-C2-O3)), the second letter (capital letter) describes the structure of the CCOC skeleton (ϕ_2 (C1-C2-O3-C4)), and the third letter specifies the orientation of H4 relative to the central C2-O3 bond (ϕ_3 (C2-O3-C4-H4)). Atom numbering is shown in Figure 1. Since it is impossible to determine a reliable geometric structure of such an unsymmetrical molecule and its conformational properties from GED data alone, we combined this experimental investigation with theoretical calculations.

From the NMR coupling constants J_{FH} and J_{FF} of enflurane it was concluded that the methyl carbon atom C4 lies out of the C1-C2-O3 plane, i.e., the CCOC skeleton possesses a gauche configuration (G⁺ or G⁻). Furthermore, from these

coupling constants it was estimated that conformers with H1 trans to C2-O3 and such with H1 gauche to C2-O3 occur in a ratio of about 1:1.¹¹

Quantumchemical Calculations

The primary aim of these calculations was the determination of all stable structures which correspond to minima in the conformational space (ϕ_1, ϕ_2, ϕ_3). Structure optimizations were performed with the ab initio method HF/3-21G* and the B3PW91/6-311G(2d) hybrid density functional method, using the GAUSSIAN 94 program system.¹² The B3PW91 approximation was chosen, because this method resulted in good agreement with experimental as well as with MP2/6-311G(2d) results for isoflurane and enflurane.⁹ The hybrid method is computationally more economical than the MP2 method, and this is an important advantage in view of the large number of structure optimizations required in the present case. All 27 possible conformations were used as starting structures. For trans configurations around the central C2-O3 bond, starting values for ϕ_2 (C1-C2-O3-C4) slightly smaller and larger than 180° were used.

Both theoretical methods predict 19 different stable structures. In the case of the HF results the vibrational frequencies of all optimized structures were calculated to ensure that these structures correspond to minima on the energy hypersurface. Such calculations were not performed for all B3PW91 results, because of the large computational expense. Frequency calculations were performed only for the four lowest energy conformers. The optimized dihedral angles and the relative energies of the various conformers are listed in Table 1. The energies are given

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relative to the lowest energy form, which is the (g^- , T, t) conformer according to the HF method and the (t, T, g^+) form according to the B3PW91 approximation. The 19 conformers are listed in the sequence of their energies predicted by the B3PW91 method.

Although both methods result in the same number of stable conformers, the kinds of conformations and their relative energies, obtained with the two methods, differ appreciably. Four conformations which are predicted to be stable by the HF method are not stable structures according to the B3PW91 method and vice versa. The (t, G^- , g^+) and (t, G^- , g^-) forms (structures **V** and **VI**), the first of which is stable according to the HF, the second according to the B3PW91 method, differ only very little. The dihedral angle $\phi_3(C2-O3-C4-H4)$ of these two conformers is 4° and -7° , respectively. Both methods predict two different minima for the (g^- , T, t) type of conformation (structures **XI** and **XII**). These two structures differ by the dihedral angles ϕ_2 and ϕ_3 , which both are about 160° for structure **XI** and about 200° for structure **XII**. Their energies differ by less than $0.1 \text{ kcal mol}^{-1}$. A similar situation exists for the type (g^- , T, g^-) (structures **II** and **XXI**) and for (g^+ , T, t) (structures **VII** and **IX**) for which either the HF or B3PW91 method predicts two different minima.

The two computational methods result in different relative energies for the various conformers. However, it should be pointed out that these differences are small, in most cases in the order of $1-2 \text{ kcal mol}^{-1}$. The four conformers which are predicted to be lowest in energy by the HF approximation (structures **IX** to **XII**, $\Delta E = 0.00$ to $0.54 \text{ kcal mol}^{-1}$) are characterized by trans configuration around the central C2-O3 bond and trans orientation of H4 with respect to the C2-O3 bond. The two very similar (g^- , T, t) structures (**XI** and **XII**) which are lowest in energy have the F1 atom in the trans orientation, the other two either Cl (structure **X**) or H1 (structure **IX**). The four conformers which possess the lowest energies according to the B3PW91 calculations (structures **I** to **IV**, $\Delta E = 0.00$ to $0.16 \text{ kcal mol}^{-1}$) possess also a trans configuration of the C1-C2-O3-C4 skeleton; the CHF₂ group, however, adopts g^+ or g^- orientation. The calculated dihedral angles $\phi_3(C2-O3-C4-H4)$ for these forms are small ($< \pm 20^\circ$), which implies that the C4-H4 bond nearly eclipses the C2-O3 bond. Structures **I** to **IV** are shown in Figure 1. Structures **I** to **III** differ by the orientation of the CHFCl group, with Cl (structure **I**), F1 (structure **II**), or H1 (structure **III**) trans to the C2-O3 bond. Structures **III** and **IV** are very similar, they possess the same orientation of the CHFCl group and differ only by slightly different orientations of the CHF₂ group ($\phi_3 = -18^\circ$ and 11° , respectively). The barrier to internal rotation of the CHF₂ group from g^- to g^+ probably is very low. According to the HF method structures **I** to **IV** are about 1 to 2 kcal mol^{-1} above the global minimum (structure **XI**).

In addition to the HF and B3PW91 calculations structure optimizations were performed with the MP2/6-311G(2d) method for the four conformers which possess the lowest energies according to the B3PW91 approximation. This method predicts almost identical relative energies for structures **I** to **IV**, and the dihedral angles differ only by a few degrees. Vibrational frequencies were calculated with the B3PW91 method for the four low-energy structures **I** to **IV**. The Cartesian force constants were transformed to symmetry constants and vibrational amplitudes were derived with the program ASYM40.¹³

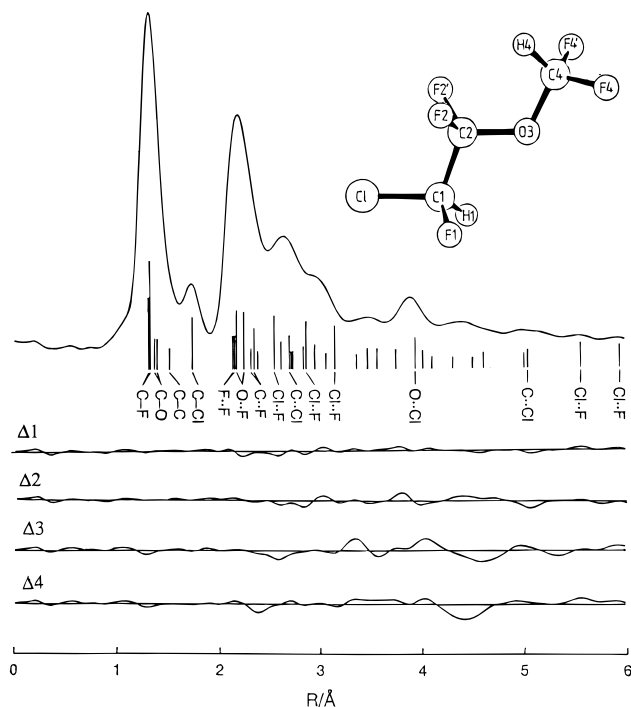


Figure 2. Experimental radial distribution function and difference curves $RDF(\text{exp}) - RDF(\text{calc})$: $\Delta 1$, mixture; $\Delta 2$, 100% (t, T, g^+); $\Delta 3$, 100% (g^- , T, g^-); $\Delta 4$, 100% (g^+ , T, g^-). Important interatomic distances for the predominant conformer (t, T, g^+), whose structure is shown, are given by vertical bars.

Electron Diffraction Analysis

The experimental radial distribution function (RDF) was calculated by Fourier transformation of the molecular intensities and is presented in Figure 2. An artificial damping function $\exp(-\gamma s^2)$ with $\gamma = 0.0019 \text{ \AA}^2$ was applied to the intensities. Since the description of the geometric structure for a single conformer of enfluran requires 30 parameters, several constraints which are based on the B3PW91 results had to be made. (1) The difference between the two O-C bond lengths, $\Delta OC = (O3-C4) - (O3-C2)$, was fixed. (2) $C2-F2 = C2-F2' = C1-F1$ and $C4-F4 = C4-F4'$ was assumed and the difference between these two types of C-F bonds was fixed. (3) The C-H bond lengths and X-C-H bond angles (X = C, O or Cl) were not refined. (4) The C1-C2-F2 and O3-C2-F2 angles were assumed to be equal and the differences between this value and the C2-C1-F1 and O3-C4-F4 angles were set to the calculated results. (5) The F4-C4-F4' angle was not refined. (6) All vibrational amplitudes were fixed to the calculated values. The amplitudes for the most abundant (t, T, g^+) conformer are given in Table 2.

In the first step it was attempted to fit the experimental RDF with a single conformer. Structures which possess a gauche configuration around the central C2-O3 bond (G^+ or G^-) reproduce the experimental RDF badly in the range $R > 2.6 \text{ \AA}$. Conformers with trans orientation of the CHF₂ group result in a similarly bad agreement with the experimental RDF for $R > 2.5 \text{ \AA}$. Only structures with the trans structure of the C1-C2-O3-C4 skeleton and gauche orientation (g^+ or g^-) of the CHF₂ group (structures **I** to **IV**) fit the experimental RDF reasonably well.

Least-squares refinements were performed for these four conformers. The molecular intensities were multiplied with a diagonal weight matrix and known complex scattering ampli-

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Table 2. Calculated Vibrational Amplitudes in Å (B3PW91/6-311G(2d)) for the (t, T, g⁺) conformer

	C1	C2	O3	C4	Cl	F1	H1	F2	F2'	H4	F4
C2	0.050										
O3	0.066	0.047									
C4	0.069	0.064	0.048								
Cl	0.051	0.070	0.066	0.084							
F1	0.045	0.067	0.124	0.137	0.064						
H1	0.076	0.106	0.158	0.164	0.107	0.098					
F2	0.068	0.046	0.057	0.147	0.131	0.063	0.170				
F2'	0.067	0.046	0.057	0.127	0.147	0.157	0.098	0.057			
H4	0.141	0.155	0.098	0.076	0.190	0.209	0.209	0.362	0.226		
F4	0.196	0.242	0.063	0.045	0.312	0.150	0.279	0.483	0.258	0.097	
F4'	0.136	0.158	0.064	0.045	0.194	0.263	0.203	0.138	0.408	0.097	0.057

Table 3. Experimental and Theoretical Geometric Parameters for the Predominant (t, T, g⁺) Conformer and Conformational Composition of Enfluran

	GED ^a	B3PW91/6-311G(2d) ^b	MP2/6-311G(2d) ^b	HF/3-21G* ^b
O3-C2	1.383 (5)	<i>p</i> ₁	1.366	1.372
O3-C4	1.409 ^c		1.392	1.400
C1-C2	1.520 (9)	<i>p</i> ₂	1.533	1.509
C2-F2	1.343 (2)	<i>p</i> ₃	1.348	1.354
C1-F1	1.343 ^d		1.348	1.378
C4-F4	1.333 ^e		1.338	1.348
C1-Cl	1.752 (6)	<i>p</i> ₄	1.772	1.762
C-H	1.100 ^f		1.089	1.070
C1-C2-O3	110.7 (11)	<i>p</i> ₅	107.0	107.1
C2-O3-C4	117.3 (21)	<i>p</i> ₆	116.4	120.7
C1-C2-F2	110.0 (11)	<i>p</i> ₇	110.5	110.5
O3-C2-F2	110.0 ^g		111.0	110.5
C2-C1-F1	108.0 ^h		108.7	107.2
O3-C4-F4	107.3 ⁱ		108.0	107.6
C2-C1-Cl	111.0 (10)	<i>p</i> ₈	110.7	111.4
F1-C1-Cl	111.6 (11)	<i>p</i> ₉	110.3	109.5
F2-C2-F2'	106.1 (28)		106.8	107.6
F4-C4-F4'	108.0 ^f		108.0	109.1
C2-C1-H1	107.8 ^f		107.8	109.2
O3-C4-H4	112.7 ^f		112.7	111.6
Cl-C1-H1	107.8 ^f		107.8	109.1
φ ₁ (Cl-C1-C2-O3)	195 (4)	<i>p</i> ₁₀	181.9	181.2
φ ₂ (C1-C2-O3-C4)	180 (5)	<i>p</i> ₁₁	178.8	205.0
φ ₃ (C2-O3-C4-H4)	22 (4)	<i>p</i> ₁₂	16.6	68.6
% (t, T, g ⁺)	58 (8)		29	27
% [(g ⁺ , T, g ⁻)+(g ⁺ , T, g ⁺)]	32 (10)		44	44
% (g ⁻ , T, g ⁻)	10 (10)		27	29

^a *r*_a values in Å and angles in deg. Error limits are 3σ values. For atom numbering see Figure 2. ^b Mean values are given for parameters which are not unique. ^c (O3-C4) - (O3-C2) = 0.026 Å. ^d C1-F1 = C2-F2. ^e (C2-F2) - (C4-F4) = 0.010 Å. ^f Not refined. ^g (O3-C2-F2) = (C1-C2-F2). ^h (C1-C2-F2) - (C2-C1-F1) = 2.0°. ⁱ (C1-C2-F2) - (O3-C4-F4) = 2.7°.

tudes were used.¹⁴ Twelve geometric parameters *p_i* (see Table 3) were refined for each conformer. The quality of the fit of the experimental intensities was measured by *R*₅₀, which is the agreement factor for the long nozzle-to-plate data. Since the various conformers differ primarily by their long interatomic distances, the molecular intensities at small *s* values are more sensitive toward the conformational properties. These agreement factors were 4.97, 8.29, 7.69, and 7.70% for structures **I** to **IV**. From these refinements we conclude that the (t, T, g⁺) conformer (structure **I**) is the predominant form. Furthermore, these refinements demonstrate that the GED experiment cannot distinguish between (g⁺, T, g⁻) and (g⁺, T, g⁺) conformations which result in almost equal agreement factors. As pointed out above, these two conformers differ only by slightly different orientations of the CHF₂ group (φ₃(C2-O3-C4-H4) = -18° or 11° according to the B3PW91 method). The RDF's of these two structures are indistinguishable. The difference curves (RDF(exp) - RDF(calc)) for these refinements with single conformers are shown in Figure 2.

In the second step least-squares analyses were performed for mixtures of three conformers, (t, T, g⁺), (g⁻, T, g⁻), and (g⁺, T, g⁻), and a large number of different compositions. (g⁺, T, g⁻) stands for the sum of the two very similar forms (g⁺, T, g⁺) and (g⁺, T, g⁻) which cannot be distinguished in the GED experiment. The twelve geometric parameters *p_i* of the predominant (t, T, g⁺) conformer were refined and bond lengths and bond angles of the two other forms constrained, using the theoretical differences. The dihedral angles of the two minor conformers were set to the B3PW91 values. Variations of these dihedral angles by ±10° had no effect on the agreement factor. The vibrational amplitudes of all conformers were set to the theoretical values (see Table 2 for (t, T, g⁺) form). Attempts to refine some important vibrational amplitudes lead to a slight improvement of the fit and the refined amplitudes agreed with the theoretical values within their error limits (3σ values). The following correlation coefficients had values larger than |0.5|: *p*₁/*p*₃ = -0.55, *p*₂/*p*₆ = -0.56, *p*₅/*p*₇ = -0.51, *p*₆/*p*₁₁ = 0.53, and *p*₁₁/*p*₁₂ = 0.73. Numbering of the parameters *p_i* is given in Table 3. The best fit with *R*₅₀ = 4.41% (difference curve Δ1 in Figure 2) was obtained for a mixture of 58(8)% (t, T,

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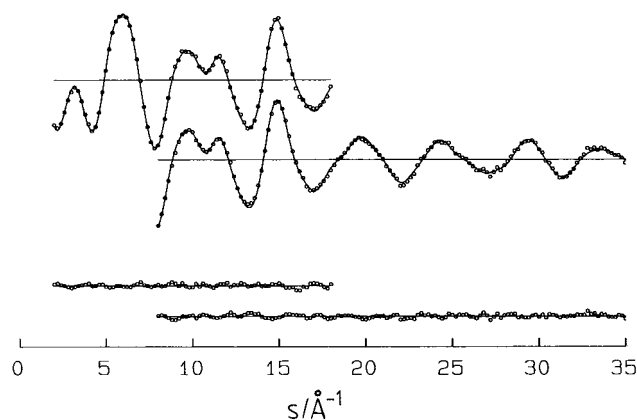


Figure 3. Experimental (dots) and calculated (full line) molecular intensities and differences for long (upper curves) and short (lower curves) nozzle-to-plate distances.

g^+), 32(10)% (g^+ , T, g^-) + (g^+ , T, g^+), and 10(10)% (g^- , T, g^-). The error limits were estimated from the variations of the agreement factor. Contributions from other conformers are estimated to be less than 5%.

Discussion

The experimental and calculated geometric parameters for the predominant conformer (t, T, g^+) and the conformational composition are summarized in Table 3. The theoretical compositions predicted by the B3PW91 and MP2 methods were derived from the relative energies, assuming $\Delta E = \Delta G^\circ$. Furthermore, it was assumed that only the four low-energy conformers are present. The contributions according to the HF calculations are not given, these would be less than 1%. From the experimental composition free enthalpy differences of ΔG° [$((g^+, T, g^-) + (g^+, T, g^+)) = 0.8$ (4) kcal mol $^{-1}$ and $\Delta G^\circ(g^-, T, g^-) = 1.1$ (6) kcal mol $^{-1}$ were derived. It should be pointed out that the conformational problem of enflurane is really underdetermined experimentally and this shows up in the large uncertainties (3σ values) for the enthalpy differences. The GED results indicate a somewhat stronger preference of the (t, T, g^+) conformer than predicted by the B3PW91 and MP2 calculations.

The bond lengths and bond angles which were refined in the GED analysis are reproduced very well by all three theoretical methods, with the exception of the C1–C2–O3 angle. The calculated values are 3–4° smaller than the experimental angle. The experimental dihedral angles ϕ_1 and ϕ_2 are very close to those obtained with the B3PW91 and MP2 methods. The larger difference between the experimental and calculated values for ϕ_1 is most likely due to a large amplitude torsional vibration around the C1–C2 bond. The B3PW91 method predicts torsional frequencies of 26, 52, and 69 cm $^{-1}$ for the (t, T, g^+) conformer.

All experimentally observed conformers of enflurane possess a trans configuration of the C–C–O–C skeleton. This is in contrast to the interpretation of NMR coupling constants which suggests a gauche (G^+ or G^-) configuration¹¹ (see Introduction). Trans structures were found to be predominant or to be the only detectable conformers also for the parent ethyl methyl ether¹⁵ and for several halogenated derivatives which have been studied by GED, microwave, or vibrational spectroscopy, such as CF₃–CH₃OCH₃,¹⁶ CH₃CH₂OCH₂F,¹⁷ CH₃CH₂OCH₂Cl,¹⁸ and CHCl₂–CF₂OCH₃.¹⁹ Furthermore, all conformations derived from the GED experiment possess gauche (g^+ or g^-) orientations of the CHF₂ group, i.e., the hydrogen atom H4 is gauche (actually close to cis) with respect to the C2–O3 bond. It might be expected that the anomeric effect between the oxygen lone pairs and the $\sigma^*(C-F)$ orbitals stabilizes the trans orientation for which both fluorine atoms F4 and F4' are gauche to the C2–O3 bond.²⁰ In enflurane, however, steric repulsions between the F2 and F4 fluorine atoms apparently override the anomeric effect.

Experimental Section

A commercial sample of enflurane was purified by gas chromatography (>99.9%). The electron diffraction intensities were recorded with a Gaskdiffraktograph KD-G2²¹ at 25 and 50 cm nozzle-to-plate distances and with an accelerating voltage of about 60 kV. The electron wavelength was determined from ZnO powder diffraction patterns. The sample reservoir was kept at –30 °C and the inlet system and gas nozzle were at room temperature. The photographic plates (Kodak Electron Image Plates 13 × 18 cm) were analyzed with standard procedures²² and averaged molecular intensities in the s ranges 2–18 and 8–35 Å $^{-1}$, in steps of $\Delta s = 0.2$ Å $^{-1}$, are presented in Figure 3.

Acknowledgment. We gratefully acknowledge financial support by the Deutsche Forschungsgemeinschaft and access to substantial computer time by the Research Centre Jülich (Germany). We thank Prof. Dr. V. Schurig, Institut für Organische Chemie, Universität Tübingen, for a highly pure sample of enflurane.

JA980661K

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