10116 *J. Phys. Chem. A* **2002,** *106,* 10116−10123

Torsion Energy Profiles and Force Fields Derived from Ab Initio Calculations for Simulations of Hydrocarbon−Fluorocarbon Diblocks and Perfluoroalkylbromides

Agílio A. H. Pádua*

Laboratoire de Thermodynamique des Solutions et des Polymères, CNRS UMR 6003,
Université Blaise Pascal Clermont-Ferrand, 63177 Aubière, France

Received: March 6, 2002

Force fields with explicit atoms are proposed for the molecular simulation of two families of substituted perfluorocarbons: hydrocarbon−perfluorocarbon diblocks, or partially fluorinated alkanes, and 1-bromoperfluoroalkanes, or perfluoroalkylbromides. Both types of molecules are of interest for formulations of synthetic in vivo gas carriers, or blood substitutes, and for drug-delivery systems. Some semifluorinated alkanes have amphiphile character between hydrogenated and fluorinated liquid phases. The present molecular models are based on the OPLS all-atom force field, published in 2001 for perfluoroalkanes, completed with potential energy functions for the torsion around chemical bonds near the junction between the hydrocarbon and fluorocarbon blocks and close to the bromine atom, respectively. The dihedral terms have been derived from ab initio calculations on series of molecules of both families containing between two and five carbon atoms. Whenever possible, comparisons were made with experimental barriers to internal rotation. An analysis of the atomic charges was also performed, but no modification was introduced in the specification of the original force fields for hydrocarbons and fluorocarbons. Force-field parameters for the bromine atom were developed from quantum chemical and molecular dynamics studies on bromotrifluoromethane. As a test of the proposed models, a molecular dynamics simulation was used to calculate the properties of perfluorooctylbromide (PFOB) and perfluorooctylethane (PFOE) and to predict the solubility of oxygen and carbon dioxide in these liquids. The results of the predictions agree well with experiment.

Introduction

The interactions between small gaseous molecules and fluorocarbons have been attracting considerable attention from two fields of application a priori not closely related. One is the formulation of synthetic gas-carrier fluids, also called blood substitutes, for medical use in vivo. A comprehensive review of this field, from a chemist's point of view, appeared recently.[1] The second is the use of fluorinated compounds as a means to improve the solubility of chemicals in supercritical[2] reaction or extraction media, which is connected to technological operations of purification, polymerization, and catalysis.[3] Besides the presence of (per)fluorinated molecules, other common aspects shared by these two classes of applications are the creation of emulsions (such as water-in-fluorocarbon reverse micelles[3−6]) and the importance of the interactions between small molecules and relatively long fluorinated species.

From the perspective of gas carriers, the fluorinated molecules constitute the solvent in which the respiratory gases, principally oxygen and carbon dioxide, dissolve. Some of the more promising synthetic formulations contain perfluorooctylbromide (PFOB), a molecule that shows improved lipophilicity over perfluoroalkanes and therefore has a shorter retention time in the organism.[1,7] Besides the potential role as gas carriers, some hydrocarbon−fluorocarbon diblocks, or partially fluorinated alkanes, are under investigation from the aspect of emulsions between fluorinated and organic (lipidic)[1] or aqueous[6] domains, the ultimate interest here being on drug delivery via the pulmonary route. This amphiphilic character between hydrogenated and fluorinated phases of molecules from the family of hydrocarbon−fluorocarbon diblocks is of fundamental interest to the study of interfaces.[8,9]

The search for appropriate chemicals to use in formulations such as blood substitutes or drug delivery agents often requires extensive heuristic trials on large numbers of different molecules.[1,7] The variety of criteria[1] for an acceptable candidate is extremely difficult to meet, and molecular modeling tools could serve as guides and also give insight into the fundamental reasons at the molecular level underlying some interesting properties (gas solubility, lipophilicity, etc.) The absence of detailed molecular models for the compounds in question was the main motivation for the present work.

In the field of supercritical fluids, the roles are reversed, and the fluorinated molecules become solutes or amphiphiles in supercritical carbon dioxide. In the structure of such amphiphiles, the most common occurrences of fluorinated functional groups, responsible for the improved solubilities, are as perfluoroether[3−5] and perfluorocarbon[10] tails. Mixed-tail, dichain surfactants such as $(C_7F_{15})(C_7H_{15})CHSO_4^-Na^+$ have also been tested as amphiphiles in carbon dioxide.[11] A molecular model of this surfactant has recently been the subject of a simulation study[12] in which stable reverse micelles of water in carbon dioxide formed. The occurrence of microdispersions in mixtures of semifluorinated alkanes with dense carbon dioxide is also documented.[13]

Still, in the context of supercritical fluids, contradictory results concerning the nature of the interactions between fluorinated compounds and carbon dioxide have been reported. On the experimental side, one high-pressure NMR study[14] suggested

---

* E-mail: agilio.padua@univ-bpclermont.fr.

10.1021/jp025732n CCC: $22.00

the existence of specific interactions, in contrast to a previous infrared study,[15] where it appeared that carbon dioxide had a less repulsive interaction with ethane and butanol than with their fluorinated counterparts, and also in contradiction with other more recent high-pressure NMR studies[16,17] where no evidence of specific interactions was found. On the theoretical side, ab initio calculations at the Hartree−Fock/6-31G(d) level attributed a larger binding energy to the pair perfluoroethane−carbon dioxide than to ethane−carbon dioxide, and the authors postulated a stronger electrostatic interaction with the fluorinated molecule.[18] The opposite result was obtained at the Möller−Plesset level of theory using a larger basis set (cc-pVTZ) and correcting for basis set superposition errors, with no evidence for enhanced interactions between carbon dioxide and perfluoroethane.[19] These quantum calculations were performed on small perfluorocarbons in clusters containing few molecules.

Solubilities in liquid mixtures are governed by solute−solute, solvent−solvent, and solute−solvent interactions and by entropic as well as enthalpic criteria, so theoretical studies uniquely of solute−solvent energetics in the ideal gas phase give but partial information. Molecular simulation of fluids is an appropriate tool to use in investigating the dependency of a property such as the solubility on the different molecular interactions and on thermodynamic state variables as well. The present work is focused on the solubility of gaseous molecules in long substituted perfluorocarbons, but the similarity of the interaction pairs that are the subject of the present study establishes a connection to the field of supercritical solvents. Detailed molecular models such as the ones proposed here may contribute to the elucidation of questions such as the one presented above.

Vapor−liquid equilibrium in perfluorohexane−carbon dioxide and hexane−carbon dioxide mixtures has been simulated using united-atom descriptions of hexane and perfluorohexane.[20] The results of a pure prediction (assuming Lorentz−Berthelot combining rules for the unlike interactions) were in good agreement with experiment: mole fractions of carbon dioxide in phases rich in hexane and perfluorohexane were overestimated by about 10 and 13%, respectively. The authors of this study concluded that the addition of electrostatic interactions or explicit fluorine atoms to the molecular models for perfluorocarbons might improve their results.

Some molecular dynamics studies of partially fluorinated chains have been published, but all are based on united-atom models. Most simulations of partially fluorinated chains were directed to the study of Langmuir monolayers of amphiphiles such as $C_7F_{15}C_4H_8COOH$.[21,22] One simulation study of the vapor−liquid interface of perfluorocarbon−hydrocarbon diblocks has also been reported.[23] But in all these works the force-field terms for the junction between the fluorocarbon and hydrocarbon domains were assumed ad hoc to be some average of pure hydrocarbon with pure fluorocarbon terms. No detailed study of the structural and conformational properties of the hydrocarbon−fluorocarbon junction is known to us. Concerning the other family of molecules treated in the present work, few molecular simulation efforts have treated brominated compounds.[24]

Only recently, all-atom force fields were proposed for perfluoroalkanes of long chains (three or more carbons).[25] This OPLS-AA model provides a more detailed molecular description than previous attempts based on the united-atom approach.[21,26] The new OPLS-AA model incorporates an adequate treatment of the conformational energetics of the molecules, as was already the case for the united-atom models, but adds explicit sites and partial charges to individual carbon and fluorine atoms (the united-atom model contains no electrostatic interactions). In the explicit-atom model, all bond distances and angles are flexible.

To attain the objective of the present work, it is necessary to complete this explicit-atom force field with the missing terms necessary to model by computer simulation the two families of molecules that are hydrocarbon−fluorocarbon diblocks, or perfluoroalkylalkanes, and 1-bromoperfluoroalkanes, or perfluoroalkylbromides. The relevant terms to develop in the force-field specifications are torsional potential energy profiles that govern the configuration energetics of the molecules and nonbonded van der Waals interactions (Lennard-Jones parameters and electrostatic charges), in particular for the bromine atom, that are predominant to determine the thermodynamic properties of the pure substances and mixtures.

A description of the conformational energetics of hydrocarbon−fluorocarbon diblocks requires a study of the torsion potentials for several chemical bonds in the region of the junction between the fluorinated and hydrogenated segments. The “pure” hydrocarbon and perfluorocarbon segments have already been parametrized within the OPLS-AA framework.[25,27] The collection of the required dihedral terms was derived from ab initio quantum mechanical calculations and was built up starting from the simplest hydrocarbon−fluorocarbon diblocks: first, semifluorinated ethane and partially fluorinated propanes followed by fluorinated butane and pentanes. To describe the vicinity of the bromine substituent in 1-bromoperfluoroalkanes, an analogous route was taken but was complemented here by computer simulations on bromotrifluoroethane that lead to new parameters for the bromine atom. Once the force field was defined, computer simulations were performed to obtain some properties of the models, in particular, those of the fluorinated solvents perfluorooctylethane (PFOE) and perfluorooctylbromide (PFOB) and their interactions with oxygen and carbon dioxide gases.

A survey of the literature showed that a closely related problem had been tackled very recently: that of parametrizing an explicit-atom force field for the modeling of poly(vinylidene fluoride) (PVDF).[28,29] Only here, the oligomers studied do not contain hydrocarbon and perfluorocarbon diblocks but an alternating sequence of hydrogenated and fluorinated carbon atoms instead. The series of small model molecules investigated in the context of this work on polymers (partially fluorinated butanes, pentanes and heptanes), which is necessary to build up the different terms in the force field, closely resembles the ones studied below for the hydrocarbon−fluorocarbon diblocks.

Quantum Mechanical Calculations

The new torsion potentials were developed following a strategy similar to the one adopted in the OPLS-AA force field for perfluorocarbons.[25] The present torsion profiles were obtained from relaxed potential energy scans at a series of values for the chosen dihedral angles that were held fixed while the remaining internal coordinates of the molecules were allowed to vary toward (relative) energy minima. Quantum calculations were performed using Gaussian 98.[30]

For hydrocarbon−fluorocarbon diblocks, the present calculations were performed at the MP2/cc-pVTZ(-f)//HF/6-31G(d) level of theory, thus using the same basis set as in the OPLS-AA model of perfluoroalkanes:[25] the flexible cc-pVTZ basis set[31] was used for single-point energy calculations in geometries optimized at the HF/6-31G(d) level, as is common practice in the development of force fields for molecular simulations.[27,32,33] We used frozen-core MP2 whereas the torsion potentials in OPLS-AA for perfluorocarbons were derived using local MP2.

TABLE 1: Barriers to Internal Rotation in Alkyl- and Bromine-Substituted Fluoroethanes and Fluoropropanes[a]

molecule	ΔE/kcal mol^{-1}	ΔZPVE/kcal mol^{-1}	$\Delta(E + \text{ZPVE})$/kcal mol^{-1}	expt/kcal mol^{-1}
CH_3-CF_3	3.26	−0.24	3.02	3.2 (IR)[48]
$CF_3-CH_2CH_3$	4.13	−0.05	4.08	
$CH_3-CH_2CF_3$	2.77	−0.16	2.61	2.635 ± 0.004 (MW)[51]
$CF_3-CF_2CH_3$	4.95	+0.08	5.03	
$CH_3-CF_2CF_3$	3.01	−0.20	2.81	
$CBrF_2-CF_3$	5.71	+0.01	5.72	5.01± 0.07 (IR)[49] 5.33± 0.10 (IR)[50] 4.7 ± 0.3 (DNMR)[52] 6.40 (IR 1959)[52]

[a] Comparison of the present calculations at the MP2/TZ2P,cc-pVTZ(-f)//HF/TZV,6-31G(d) level with spectroscopic values from the literature. $\Delta E = E_{\text{ecl}} - E_{\text{stg}}$.

In terms of the relative energies that are of interest to us, the difference between both methods is small, as will be discussed below.

For atoms C and F, the cc-pVTZ(-f) basis set is created by removing the *f* functions from the definition of the correlation-consistent, triple-ζ cc-pVTZ basis of Dunning,[31] resulting in a (10s5p2d)/[4s3p2d] {7711/311/11} contraction. Without the removal of the *f* functions, convergence problems were encountered when calculating the torsional potential in perfluorobutane. The same level of theory adopted here, using the cc-pVTZ(-f) basis set, was tested on a large collection of molecules and was demonstrated to yield accurate conformational energies.[34]

In the 6-31(d) basis set, atoms C and F share the same value of 0.800 in the exponent of the *d* polarization function. For the complete basis set method,[35] Petersson and co-workers replaced this constant value by *d* exponents taken from the 6-311G(d) basis set:[36] 0.626 for C and 1.750 for F. The resulting 6-31G† basis set might eventually prove more appropriate than 6-31G-(d) to describe molecules containing fluorine. Our tests on the torsion potential surface for the dihedral angle $C_H-C_H-C_F-C_F$ in 1,1,1,2,2-pentafluorobutane using both basis sets yielded relative energies that are close to within 0.01 kcal mol^{-1} at the MP2/cc-pVTZ(-f) level. Optimized geometries are also similar (distances within 0.003 Å, angles within 0.15°). The total electronic energies differ by 0.3 kcal mol^{-1}, and at the HF level, those obtained using 6-31G(d) are lower (the smaller *d* exponent gives more extended orbitals). In view of these results, it was decided to keep the 6-31G(d) basis set in the present geometry optimizations and frequency calculations.

For Br, the choice of basis sets is less obvious, and neither the cc-pVTZ nor the 6-31G functions are defined for this atom. Possible choices of basis sets for bromine are the 6-311G [8s6p2d] of McGrath and Radom,[37,38] the 6-311G [9s6p2d] of Binning and Curtiss[39,40] (both of these basis sets are contractions of the same (14s11p5d) primitives from Dunning[41]), the augmented Huzinaga triple-ζ [5s4p1d],[42] and also effective core potentials.[43] For the single-point energies, we opted for the double-polarized functions of triple-ζ quality used by T. J. Lee.[44−46] These TZ2P functions are based on the TZV basis set of Schäfer, Huber, and Ahlrichs,[47] which is a (17s13p6d)/[6s5p2d]{842111/64111/51} contraction augmented by two *d* polarization functions with exponents of 0.674 and 0.225. This basis set performed significantly better for energies, geometries, and harmonic frequencies than the 6-311G(d) [9s6p2d] basis set[39] for small molecules containing oxygen and bromine.[44,46] For the relaxed geometry optimizations in perfluoroalkylbromides, the TZV basis set[47] was used for Br together with the 6-31(d) basis set for C and F.

Substituted fluoroethanes (CH_3CF_3 and $CBrF_2CF_3$) and fluoropropanes ($CH_3CF_2CF_3$ and $CH_3CH_2CF_3$) were the starting points for the development of the present force-field terms associated with the torsional energy profiles. Internal rotation barriers in these molecules were calculated from the MP2/TZ2P,cc-pVTZ(-f) energies of staggered and eclipsed geometries optimized at the HF/TZV,6-31G(d) level. Zero-point energy corrections to internal rotation barriers were obtained from the frequencies calculated at the HF/TZV,6-31G(d) level, which were scaled by a factor of 0.90, using the previously optimized structures of both conformers. The imaginary normal mode of the eclipsed conformer was not included in the zero-point correction. In Table 1, the barriers to internal rotation thus calculated are compared to spectroscopic results from the literature (infrared/Raman,[48−50] microwave,[51] and differential nuclear magnetic resonance[52]). Agreement with experiment is within 0.2 kcal mol^{-1} for alkylfluorocarbons. The experimental results for 1-bromoperfluoroethane show large discrepancies, and judgments of accuracy are less obvious. For consistency reasons and given the good agreement between the calculations and experiment, we chose to use the quantum chemical barriers instead of the spectroscopic ones to derive the force-field parameters.

For 1,1,1,2,2-pentafluorobutane, 1,1,1,2,2-pentafluoropentane, and 1,1,1,2,2,3,3-heptafluoropentane, relaxed scans of the C−C−C−C dihedrals were performed at 10° intervals. The remaining C−C−C−C dihedral in the molecules having five carbon atoms was constrained to remain at 180°. The torsional energy profiles calculated ab initio are shown as the points in Figures 2 to 5.

Torsion Potentials

Procedure. The torsion potential energy profiles depending on dihedral angles, φ_i, associated with each chemical bond of interest were described by cosine series of the form

$$E_{\text{torsion}} = \sum_i \sum_{m=1}^{4} \frac{V_{m,i}}{2}[1 + (-1)^{m+1}\cos(m\varphi_i)] \qquad (1)$$

The values of the coefficients $V_{m,i}$ were found by a fitting procedure requiring structure optimizations with the force-field models. This is necessary to account for the effects of nonbonded interactions because, in the specification of the OPLS-AA force field, sites within the same molecule separated by three or more chemical bonds interact by Lennard-Jones and electrostatic potentials scaled by a factor of 0.5.[27] Sometimes these nonbonded interactions contribute to a large part of the torsional energy. First, the geometries of the eclipsed and staggered conformers were optimized using molecular simulation with the dihedral term under study set equal to zero. Then, the dihedral coefficients were adjusted to the differences between the ab initio barriers and those calculated using the incomplete force field.

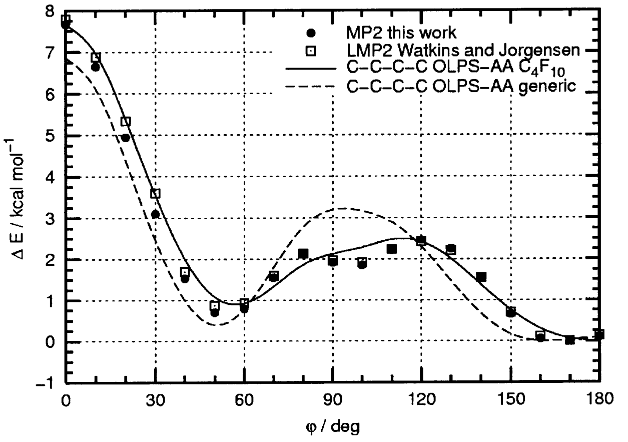

Figure 1. Torsion profile of C−C−C−C in C_4F_{10}. Comparison of the present calculations at the MP2 level with those of the OPLS-AA force field at the LMP2 level.[25] The lines represent the torsion energy obtained for the OPLS-AA force field using the present geometry optimization procedure based on molecular dynamics. Two dihedral functions were tested: one specific for perfluorobutane and another generic for perfluoroalkanes. This plot may be compared with Figure 1 in the paper by Watkins and Jorgensen.[25]

The simulation procedure employed to optimize the geometries consisted of a series of molecular dynamics (MD) quench runs on an isolated molecule: 10 000 time steps of 0.5 fs were simulated at each of the following temperatures: 10, 1, 0.1, and 0 K. Computer simulations were carried out using the molecular dynamics package DL_POLY.[53] The dihedrals being studied were constrained at the desired values by the addition of very steep harmonic terms where necessary.

For the substituted fluoroethanes and fluoropropanes, only eclipsed and staggered conformations were considered, and only the coefficients V_3 were adjusted to the barriers to internal rotation. When scanning the dihedral angles in the substituted fluorobutanes and fluoropentanes, we repeated the MD quench procedure for each value of the dihedral angle. These relaxed scans were performed at 10° intervals from 0 to 180°, and just as for the ab initio calculations, the second C−C−C−C dihedral in the substituted fluoropentanes was constrained at 180°.

To validate our geometry optimization procedure that is not based on the same techniques and software tools as those employed in the development of OPLS-AA, we repeated the calculation of the C_F−C_F−C_F−C_F dihedral in perfluorobutane for comparison with the original work.[25] Figure 1 shows the present ab initio calculations and those at the LMP2 level reported by Watkins and Jorgensen.[25] With the exception of the points at $\varphi = 20$ and 30°, the differences are smaller than 0.2 kcal mol^{-1}. The torsion profiles obtained for the OPLS-AA force field using the present geometry optimization procedure based on an MD quench are also shown. They match very closely those in Figure 1 of the paper of Watkins and Jorgensen,[25] who used Monte Carlo structure optimizations. In particular, the gauche minima characteristic of perfluorocarbons are correctly reproduced.

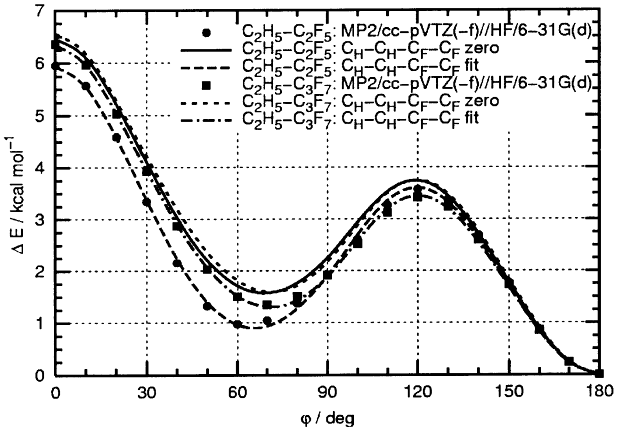

Figure 2. Torsion profiles of C_H−C_H−C_F−C_F in 1,1,1,2,2-pentafluorobutane and in 1,1,1,2,2,3,3-heptafluoropentane. The present ab initio calculations are shown together with results obtained using the force field, first by setting this specific dihedral function to zero and then with the final parameters.

Hydrocarbon−Fluorocarbon Diblocks. Once we were in possession of the set of dihedral functions for the two- and three-carbon members of the series listed in Table 2, obtained from the barriers to internal rotation, the parameters for the dihedral C_H−C_H−C_F−C_F were deduced from the torsion potential energy surface of 1,1,1,2,2-pentafluorobutane. This is the first dihedral in the series that does not exhibit simple 3-fold symmetry, and all four coefficients in eq 1 were adjusted. The torsion profile for this bond, calculated by ab initio and MD methods, is shown in Figure 2. It resembles more the dihedral profiles of alkanes rather than those characteristic of perfluoroalkanes. Some differences exist between the C_H−C_H−C_F−C_F torsion profile in 1,1,1,2,2-pentafluorobutane and in 1,1,1,2,2,3,3-heptafluoropentane; therefore, values for both are given in Table 2. For longer hydrocarbon−fluorocarbon diblocks, the coefficients obtained for 1,1,1,2,2,3,3-heptafluoropentane should be preferred.

Two additional functions complete the set: C_H−C_F−C_F−C_F from 1,1,1,2,2,3,3-heptafluoropentane and C_H−C_H−C_H−C_F from 1,1,1,2,2-pentafluoropentane, presented in Figures 3 and 4, respectively. When analyzing the results of the force field, one sees that for the torsions C_H−C_H−C_F−C_F and C_H−C_H−C_H−C_F the dihedral functions bring a relativelly small contribution to the configurational energy when compared to that of the nonbonded interactions. For C_H−C_F−C_F−C_F, the dihedral function is relatively more important, as is also apparent in the numerical coefficients in Table 2.

Perfluoroalkylbromides. By taking as a starting point the OPLS-AA force field for perfluoroalkanes, only two additional

TABLE 2: Coefficients of the Torsion Potential Energy Functions (kcal mol^{-1})

dihedral angle	obtained from	V_1	V_2	V_3	V_4
H−C_H−C_F−F	CH_3−CF_3	0.000	0.000	0.290	0.000
F−C_F−C_H−C_H	CF_3−CH_2CH_3	0.000	0.000	0.463	0.000
H−C_H−C_H−C_F	CH_3−CH_2CF_3	0.000	0.000	0.133	0.000
F−C_F−C_F−C_H	CF_3−CF_2CH_3	0.000	0.000	0.661	0.000
H−C_H−C_F−C_F	CH_3−CF_2CF_3	0.000	0.000	0.181	0.000
C_H−C_H−C_F−C_F	CH_3CH_2−CF_2CF_3	−0.760	−0.086	0.234	−0.156
C_H−C_H−C_F−C_F	CH_3CH_2−$CF_2CF_2CF_3$	−0.141	−0.183	−0.076	−0.076
C_H−C_F−C_F−C_F	CH_3CF_2−$CF_2CF_2CF_3$	3.507	−0.219	−0.693	−0.482
C_H−C_H−C_H−C_F	CH_3CH_2−$CH_2CF_2CF_3$	0.104	−0.312	0.048	−0.083
Br−C−C_F−F	$CBrF_2$−CF_3	0.000	0.000	0.906	0.000
Br−C−C_F−C_F	$CBrF_2$−$CF_2CF_2CF_3$	4.840	0.000	−0.883	0.000

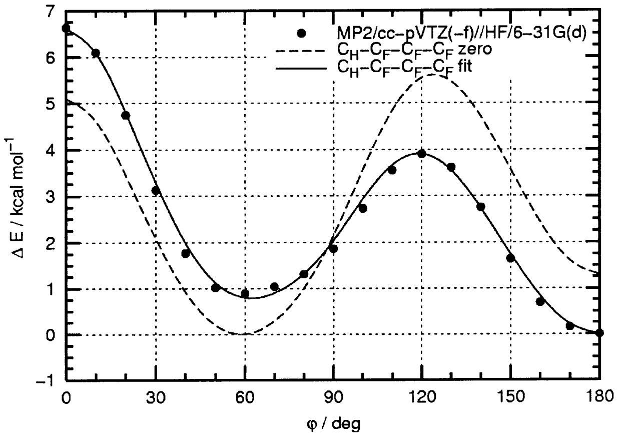

Figure 3. Torsion profile of $C_H-C_F-C_F-C_F$ in 1,1,1,2,2,3,3-heptafluoropentane.

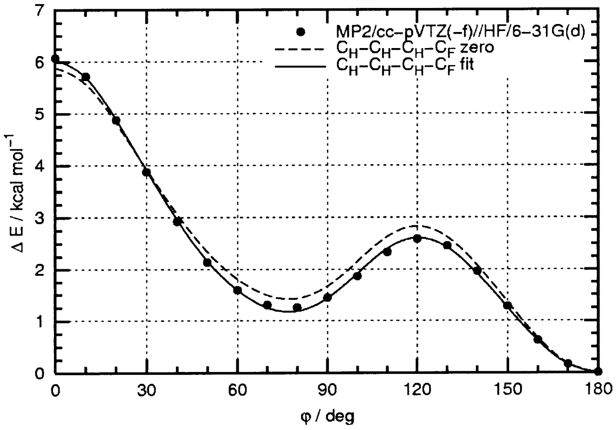

Figure 4. Torsion profile of $C_H-C_H-C_H-C_F$ in 1,1,1,2,2-pentafluoropentane.

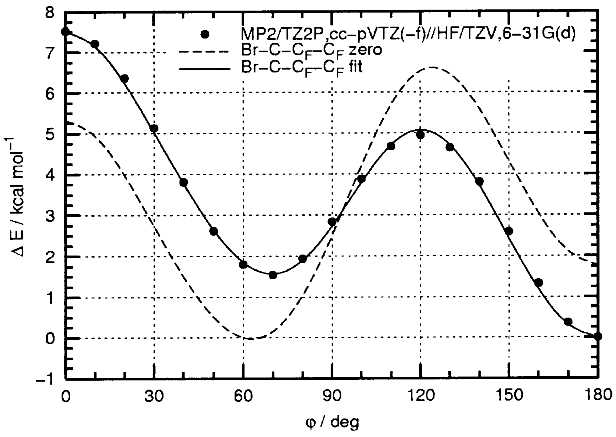

Figure 5. Torsion profile of $Br-C-C_F-C_F$ in 1-bromoperfluorobutane.

dihedral functions are required to describe the torsion potential surface in perfluoroalkylbromides: $Br-C_F-C_F-F$ and $Br-C_F-C_F-C_F$. These two terms were deduced from the internal rotation barrier in 1-bromoperfluoroethane (perfluoroethylbromide) and from the torsional potential energy profile of 1-bromoperfluorobutane (perfluorobutylbromide), respectively. The last function is represented in Figure 5, and the optimized coefficients are given in Table 2.

Atomic Charges

Having established the intramolecular part of the force field by means of the torsional energy profiles, the following step is to define the intermolecular and nonbonded intramolecular potentials. Quantum calculations may be used to provide information on the atomic charges, but in the OPLS-AA scheme, nonbonded interactions are derived by comparing computer simulation results to experimental thermodynamic properties such as liquid densities, enthalpies of vaporization, and hydration free energies.[27] This empirical strategy has been recognized as a good one for parametrizing force fields of nonreacting systems.[32] For the specific molecules of interest in the present work (PFOB and PFOE), the contribution of the bromine and alkyl functional groups to such thermodynamic properties will in principle be minored by the much larger perfluorinated chain, rendering an optimization of nonbonded parameters delicate by comparison with the experimental properties of these large molecules.

TABLE 3: Atomic Charges in Units of Elementary Charge Calculated by an ESP Fit to the MP2/cc-pVTZ(-f)//HF/6-31G(d) Electronic Densities of Some Conformers of 1,1,1,2,2-Pentafluorobutane, 1,1,2,2,3,3-Heptafluoropentane, Perfluorobutane, and Butane[a]

molecule	φ	C_{F_3}	C_{F_2}	F	C_{H_3}	C_{H_2}	H
$C_2H_5C_2F_5$	180°	+0.33	+0.15	−0.12	−0.23	+0.08	+0.06
	60°	+0.44	+0.25	−0.16	−0.24	−0.01	+0.07
$C_2H_5C_3F_7$	180°	+0.43	−0.01, + 0.31	−0.09, −0.16	−0.26	+0.07	+0.07
	70°	+0.34	+0.14, + 0.27	−0.13	−0.25	+0.07	+0.06
C_4F_{10}	180°	+0.48	+0.17	−0.13			
	170°	+0.41	+0.09	−0.10			
	50°	+0.43	+0.11	−0.12			
C_4H_{10}	180°				−0.35	+0.17	−0.03, + 0.08
	60°				−0.19	+0.10	+0.04
OPLS-AA		+0.36	+0.24	−0.12	−0.18	−0.12	+0.06

[a] Charges given for H and F atoms correspond to typical values, and whenever large differences were observed, the extrema are given.

For the hydrocarbon−fluorocarbon diblocks, because of the difference in electronegativity between H and F, a question arose concerning the charges in the atoms close to the hydrocarbon−fluorocarbon junction. It was decided that simple electrostatic potential (ESP) fit calculations should be performed not as a means to establish definitely the atomic charges of the sites but simply to check if these were significantly different from the ones in alkanes or perfluoroalkanes. The result of this inquiry would suggest the need to perform further calculations or else simply to adopt OPLS-AA charges. The atomic charges for several molecules, calculated by an ESP fit using the Merz−Singh−Kollman scheme[54] to electron densities obtained at the MP2/cc-pVTZ(-f) level, are listed in Table 3. Such calculations were performed for selected conformers corresponding to minima in the torsional profiles. In Table 3, the OPLS-AA atomic charges are also shown, and it is surprising how close the ESP charges are from those of the force field, with the exception of the carbon atoms in the methyl and methylene groups. The largest discrepancy occurs for the methylene carbon, negatively charged in the force field whereas the ESP fit places a positive charge on this atom. Because the carbon atoms are interior sites in the molecules and the discrepancies for hydrocarbon−fluorocarbon diblocks are of the same order as those for normal butane, it was decided not to modify the OPLS-AA atomic charges in the proposed model of hydrocarbon−perfluorocarbon diblocks.

Concerning the brominated fluorocarbons, the partial charge on Br was established so as to reproduce the gas-phase dipole moment of CF_3Br (0.65 ± 0.05 D) while keeping the partial charges on the F atoms equal to the OPLS-AA values (−0.12*e*).

TABLE 4: Simulation Results for Bromotrifluoromethane, Perfluorooctylbromide, and Perfluorooctylethane

	CF_3Br		$C_8F_{17}Br$		$C_8F_{17}C_2H_5$	
property	simulation	expt[56,56]	simulation	expt[1]	simulation	expt[1]
T/K	215	215.59	300	298.15	3002	298.15
ρ_{liq}/g cm^{-3}	1.992 ± 0.006	1.991	1.95 ± 0.01	1.92	1.66 ± 0.01	1.65
$\Delta_{vap}H$/kJ mol^{-1}	18.67 ± 0.13	18.64	45.2 ± 0.8	44.8	45.2 ± 0.6	
O_2						
μ_r^∞/kJ mol^{-1}			2.28 ± 0.09		2.34 ± 0.08	
H/bar			243 ± 10		236 ± 7	
s/vol %			40 ± 2	50	39 ± 1	
CO_2						
μ_r^∞/kJ mol^{-1}			−1.89 ± 0.11		−1.78 ± 0.09	
H/bar			46 ± 2		45 ± 2	
s/vol %			213± 9	210	204 ± 8	

The charge obtained for bromine, using a geometry optimized at the HF/TZV,6-31G(d) level, is $-0.02e$. An ESP fit to the MP2/TZ2P,cc-pVTZ(-f) electron densities for CF_3Br also places a charge of $-0.02e$ on Br, although the charges obtained in this way for the fluorine atoms, $-0.05e$, are different from the OPLS-AA charges.

Molecular Simulations

The force field for hydrocarbon−fluorocarbon diblocks is completely specified by the dihedral functions developed in the present work when used in conjunction with OPLS-AA parameters for alkanes and perlfuoroalkanes. The parametrization of the different terms involving the bromine atom in perfluoroalkylbromides required additional calculations.

The C−Br bond was taken to be 1.93 Å long. This value correctly represents the C−Br distance in optimized geometries corresponding to conformational minima of perfluorobutylbromide, that is, at dihedral angles $Br-C_F-C_F-C_F$ of 70° (1.926 Å) and 180° (1.932 Å), and is also close to the equilibrium distance of 1.923 Å in CF_3Br optimized at the HF/TZV,6-31G(d) level. Normal vibrational-mode analysis of CF_3Br at this level of theory yielded a force constant of 1200 kJ mol^{-1} Å^{-2} for the C−Br bond. The C−C−Br angle was deduced from the optimized geometries of perfluorobutylbromide, and a representative equilibrium value is 112.7° (values in the range of 111.4 to 115.3° were obtained). The Br−C−F and $C-C_{Br}-F$ angles, where in the latter the central atom is the bromine-substituted carbon, are both correctly represented by an equilibrium value of 109.5°, which is identical to that for C−C−F in the OPLS-AA perfluoroalkane model. The valence-angle force constants for all angles ending in a bromine atom were assumed to be of 418.4 kJ mol^{-1} rad^{-2}.

Lennard-Jones parameters for bromine were obtained from computer simulations of liquid CF_3Br, chosen because it is the simplest perfluoroalkylbromide, thus the sensitivity of its properties to the Br atom is enhanced and also because sufficient thermodynamic data are available. A system of 200 CF_3Br molecules was simulated at 215 K (the normal boiling point) and atmospheric pressure in order to calculate the liquid density and enthalpy of vaporization (simulation details are identical to the ones described below for the larger molecules). Tests using several sets of intermolecular potential parameters for Br taken from the literature[24,55] ($\sigma = 3.538$ Å, $\epsilon = 2.138$ kJ mol^{-1}) or from the AMBER force field,[32] specifically from the parm99.dat input file[1] ($\sigma = 3.956$ Å, $\epsilon = 1.339$ kJ mol^{-1}), yielded poor results (not only for CF_3Br but also for PFOB). Therefore, Lennard-Jones parameters for Br were fit to experimental data from the literature for CF_3Br,[56,57] and the results are given in Table 4. The parameters describing Br are $\sigma = 3.84$ Å and $\epsilon = 1.48$ kJ mol^{-1}.

The force field for perfluoroalkylbromides is now completely specified, and it is possible to simulate the two compounds chosen as examples: PFOB and PFOE. Pure-fluid properties and properties resulting from the interactions with gases were both studied. The fluorocarbon molecules were assumed to be fully flexible except for the C−H bonds, which were replaced by rigid constraints. This allows the use of a time step of 1 fs while maintaining conservation of energy in the *NVE* ensemble (energy fluctuations within 1×10^{-4} and no drift). Long-range interactions were taken into accound using the Ewald summation method by considering up to nine reciprocal space vectors with a convergence parameter of 0.225. The relative difference between the absolute values of the Coulombic energy and virial was below 10^{-4}. Simulations were performed at constant pressure, temperature, and amount of substance (*NpT*) by means of the Nosé-Hoover thermostat and barostat with relaxation times of 1 and 2 ps, respectively. Systems consisting of 200 molecules of PFOB and PFOE were simulated for 100 ps at both liquid and vapor densities. From the liquid-phase simulations, 1000 configurations (snapshots) were stored. Liquid densites and enthalpies of vaporization were calculated from these runs at 300 K and 1 bar and are compared to literature values (freely available from http://www.ucsf.edu/AMBER) in Table 4. The densities of both substances are in very good agreement with experiment, and the same is true for the enthalpy of vaporization of PFOB. No data for PFOE were found in the literature.

The interaction potential models used for the solute gases are of the Lennard-Jones plus charges type: the rigid two-center model of Miyano[58] for the oxygen molecule and the EPM model of Harris and Yung[59] for carbon dioxide. The latter incorporates partial charges and may have a flexible bond angle, but in the present work, the carbon dioxide molecule was considered to be rigid. The interactions between the gaseous solutes and the fluorinated solvents were assumed to obey geometric combining rules for the Lennard-Jones parameters, and therefore no unlike interaction parameter was introduced. The chemical potential of the solute gases was calculated using the Widom test-particle insertion method:[60] in each of the solvent snapshots previously stored, insertion of the solute molecule at random positions and orientations was tried 90 000 times. For simulations at constant *NpT*, the residual chemical potential of the solute (index 2) at infinite dilution is given by[61]

$$\mu_2^{r,\infty} = -kT \ln \frac{\langle V \exp(u_{TP}/kT)\rangle_{NpT}}{\langle V\rangle_{NpT}} \tag{2}$$

in which u_{TP} is the interaction energy of the test particle with a configuration of solvent molecules occupying volume V and $\langle\cdots\rangle_{NpT}$ denotes an isothermal−isobaric ensemble average over the stored configurations. The residual chemical potential corresponds to the difference between the chemical potential of the species in solution and in the ideal gas state at the temperature and density of the solution. Knowing the residual chemical potential at infinite dilution and the density of the pure solvent (index 1), one may calculate the Henry's law coefficient as follows:

$$H_{2,1}(p, T) = \rho_1 kT \exp\left(\frac{\mu_2^{r,\infty}}{kT}\right) \qquad (3)$$

The Henry's law coefficients were translated into gas solubilities in volume percent, given in Table 4 together with experimental data for comparison.[1] Unfortunately, literature data were found for PFOB only. The simulated solubilities of both gases in this solvent agree well with the experimental values, keeping in mind that this is the result of a pure prediction because no unlike interaction parameters were introduced. Not only are the relative solubilities of carbon dioxide and oxygen in PFOB correctly predicted, but also the absolute solubilities obtained by simulation are close to the experimental values.

Conclusions

Torsional potential energy profiles for two classes of substituted perfluoroalkanes—hydrocarbon−fluorocarbon diblocks and 1-bromoperfluorolakanes—were calculated ab initio by incorporating correlation effects and using flexible basis sets. Dihedral angle functions for use in molecular simulations were derived from the quantum mechanical profiles. These dihedral functions, when used together with existing terms taken from the OPLS-AA force field for alkanes and perfluoroalkanes and with parameters for the bromine atom developed within the present work, provide complete molecular models of the two families of compounds.

In semifluorinated alkanes, calculations of electrostatic surface potentials suggest that atomic charges from the OPLS-AA specification can be used without modification for the atoms in the vicinity of the hydrocarbon−perfluorocarbon junction. For brominated perfluorocarbons, the atomic charge and Lennard-Jones parameters of bromine were derived, respectively, from the dipole moment and from thermodynamic properties of bromotrifluoromethane. Intramolecular force-field parameters concerning the bromine atom were obtained from the present quantum calculations on several 1-bromoperfluoroalkanes.

Molecular dynamics simulations of liquid perfluorooctylbromide and perfluorooctylethane were performed, and the densities of both as well as the enthalpy of vaporization of perfluorooctylbromide agree well with experimental data from the literature. The test-particle insertion method was then employed to determine the residual chemical potential of oxygen and carbon dioxide in liquid PFOB and PFOE, leading to predictions of the solubility of those gases in the fluorinated solvents. Comparison with experimental values for perfluorooctylbromide shows that the simulated solubilities are very good predictions both of the relative magnitudes and absolute values of the solubilities of the two gases. This result consolidates the view that the remarqued affinity between carbon dioxide and fluorinated molecules can be explained correctly in terms of classic, nonpolarizable intermolecular potential models, and no particular interactions seem to be present.

The molecular models proposed in this work constitute a new tool for the study by molecular simulation of perfluorinated molecules used as gas carriers (blood substitutes) and as amphiphiles and may eventually be extended to treat cosolvents in supercritical media. The models can be used to represent not only pure liquids but also interactions with other molecular species as well. An illustration of this possibility was provided through the correct prediction of the solubility of respiratory gases—oxygen and carbon dioxide—in perfluorooctylbromide.

Acknowledgment. This work benefitted from an allocation of computer resources and access to the Gaussian package at the Insitut du Développement et des Resources en Informatique Scientifique (IDRIS) du Centre National de la Recherche Scientifique, France.

References and Notes

(1) Riess, J. G. *Chem. Rev.* **2001**, *101*, 2797.

(2) Eckert, C. A.; Knutson, B. L.; Debenedetti, P. G. *Nature (London)* **1996**, *383*, 313.

(3) Johnston, K. P.; Harrison, K. L.; Clarke, M. J.; Howdle, S. M.; Heitz, M. P.; Bright, F. V.; Carlier, C.; Randolph, T. W. *Science (Washington, D.C.)* **1996**, *271*, 624.

(4) Singley, E. J.; Liu, W.; Beckman, E. J. *Fluid Phase Equilib.* **1997**, *128*, 199.

(5) Lee, C. T.; Bhargava, P.; Johnston, K. P. *J. Phys. Chem. B* **2000**, *104*, 4448.

(6) Sadtler, V. M.; Krafft, M. P.; Riess, J. G. *Colloids Surf., A* **1999**, *147*, 309.

(7) Le, T. D.; Arlauskas, R. A.; Weers, J. G. *J. Fluorine Chem.* **1996**, *78*, 155.

(8) Turberg, M. P.; Brady, J. E. *J. Am. Chem. Soc.* **1988**, *110*, 7797.

(9) Lo Nostro, P.; Chen, S.-H. *J. Phys. Chem.* **1993**, *97*, 9535.

(10) McClain, J. B.; Betts, D. E.; Canelas, D. A.; Samulki, E. T.; DeSimone, J. M.; Londono, J. D.; Cochran, H. D.; Wignall, G. D.; Chillura-Martino, D.; Triolo, R. *Science (Washington, D.C.)* **1996**, *274*, 2049.

(11) Eastoe, J.; Bayazit, Z.; Martel, S.; Steytler, D. C.; Heenan, R. K. *Langmuir* **1996**, *12*, 1423.

(12) Salaniwal, S.; Cui, S.; Cochran, H. D.; Cummings, P. T. *Ind. Eng. Chem. Res.* **2000**, *39*, 4543.

(13) Iezzi, A.; Bendale, P.; Enick, R. M.; Turberg, M.; Brady, J. *Fluid Phase Equilib.* **1989**, *52*, 307.

(14) Dardin, A.; DeSimone, J.; Samulki, E. T. *J. Phys. Chem. B* **1998**, *102*, 1775.

(15) Yee, G. G.; Fulton, J. L.; Smith, R. D. *J. Phys. Chem.* **1992**, *96*, 6172.

(16) Yonker, C. R. *J. Phys. Chem. A* **2000**, *104*, 685.

(17) Yonker, C. R.; Palmer, B. J. *J. Phys. Chem. A* **2001**, *105*, 308.

(18) Cece, A.; Jureller, S. H.; Kerscher, J. L.; Moschner, K. F. *J. Phys. Chem.* **1996**, *100*, 7435.

(19) Diep, P.; Jordan, K. D.; Johnson, J. K.; Beckman, E. J. *J. Phys. Chem. A* **1998**, *102*, 2231.

(20) Cui, S. T.; Cochran, H. D.; Cummings, P. T. *J. Phys. Chem. B* **1999**, *103*, 4485.

(21) Shin, S.; Collazo, N.; Rice, S. A. *J. Chem. Phys.* **1992**, *96*, 1352.

(22) Shin, S.; Collazo, N.; Rice, S. A. *J. Chem. Phys.* **1993**, *98*, 3469.

(23) Hariharan, A.; Harris, J. G. *J. Chem. Phys.* **1994**, *101*, 4156.

(24) Någård, M. B.; Marković, N.; Pettersson, J. B. C. *J. Chem. Phys.* **1998**, *109*, 10350.

(25) Watkins, E. K.; Jorgensen, W. L. *J. Phys. Chem. A* **2001**, *105*, 4118.

(26) Cui, S. T.; Siepmann, J. I.; Cochran, H. D.; Cummings, P. T. *Fluid Phase Equilib.* **1998**, *146*, 51.

(27) Jorgensen, W. L.; Maxwell, D. S.; Tirado-Rives, J. *J. Am. Chem. Soc.* **1996**, *118*, 11225.

(28) Byutner, O. G.; Smith, G. D. *Macromolecules* **1999**, *32*, 8376.

(29) Byutner, O. G.; Smith, G. D. *Macromolecules* **2000**, *33*, 4264.

(30) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.9; Gaussian, Inc.: Pittsburgh, PA, 1998.

(31) Dunning, T. H., Jr. *J. Chem. Phys.* **1989**, *90*, 1007.

(32) Cornell, W. D.; Cieplak, P.; Bayly, C. I.; Gould, I. R.; Merz, K. M.; Fergusin, D. M.; Spellmeyer, D. C.; Fox, T.; Caldwell, J. W.; Kollman, P. A. *J. Am. Chem. Soc.* **1995**, *117*, 5179.

(33) Fox, T.; Kollman, P. A. *J. Phys. Chem. B* **1998**, *102*, 8070.

(34) Friesner, R. A.; Murphy, R. B.; Beachy, M. D.; Ringnalda, M. N.; Pollard, W. T.; Dunietz, B. D.; Cao, Y. *J. Phys. Chem. A* **1999**, *103*, 1913.

(35) Petersson, G. A.; Tensfeldt, T. G.; Montgomery, J. A., Jr. *J. Chem. Phys.* **1991**, *94*, 6091.

(36) Krishnan, R.; Brinkley, J. S.; Seeger, R.; Pople, J. A. *J. Chem. Phys.* **1980**, *72*, 650.

(37) McGrath, M. P.; Radom, L. *J. Chem. Phys.* **1991**, *94*, 511.

(38) Klatt, G.; Willetts, A.; Handy, N. C.; Esposti, C. D. *Chem. Phys. Lett.* **1995**, *237*, 273.

(39) Binning, R. C., Fr.; Curtiss, L. A. *J. Comput. Chem.* **1990**, *11*, 1206.

(40) Harwell, C. R.; Mrse, A. A.; Shelby, A. I.; Butler, L. G.; Hall, R. W. *J. Phys. Chem. A* **1999**, *103*, 8088.

(41) Dunning, T. H., Jr. *J. Chem. Phys.* **1997**, *66*, 1382.

(42) Rahaman, A.; Raff, L. M. *J. Phys. Chem. A* **2001**, *105*, 2156.

(43) Pacios, L. F.; Gómez, P. C. *J. Phys. Chem. A* **1997**, *101*, 1767.

(44) Lee, T. J.; Francisco, J. S. *Chem. Phys. Lett.* **1996**, *251*, 400.

(45) Lee, T. J. *Chem. Phys. Lett.* **1996**, *262*, 559.

(46) Parthiban, S.; Lee, T. J. *J. Chem. Phys.* **1998**, *109*, 525.

(47) Schäfer, A.; Huber, C.; Ahlrichs, R. *J. Chem. Phys.* **1994**, *100*, 5829.

(48) Bürger, H.; Niepel, H.; Pawelke, G. *Spectrochim. Acta, Part A* **1980**, *36*, 7.

(49) Durig, J. R.; Guirgis, G. A.; Fanning, A. R.; Larsen, R. A. *J. Mol. Struct.* **1988**, *174*, 183.

(50) Eltayeb, S.; Guirgis, G. A.; Fanning, A. R.; Durig, J. R. *J. Raman Spectrosc.* **1996**, *27*, 111.

(51) Antolinez, S.; López, J. C.; Alonso, J. L. *J. Chem. Soc., Faraday Trans.* **1997**, *93*, 1291.

(52) Brunelle, J. A.; Letendre, L. J.; Weltin, E. E.; Brown, J. H.; Bushweller, C. H. *J. Phys. Chem.* **1992**, *96*, 9225.

(53) Smith, W.; Forester, T. R. *The DL_POLY Package of Molecular Simulation Routines*, version 2.12; The Council for the Central Laboratory of Research Councils, Daresbury Laboratory: Warrington, U.K., 1999.

(54) Besler, B. H.; Merz, K. M.; Kollman, P. A. *J. Comput. Chem.* **1990**, *11*, 431.

(55) Singer, K.; Taylor, A.; Singer, J. V. L. *Mol. Phys.* **1977**, *33*, 1757.

(56) Kudchadker, A. P.; Kudchadker, S. A.; Patnaik, P. R.; Mishra, P. P. *J. Phys. Chem. Ref. Data* **1978**, *7*, 425.

(57) Kudchadker, A. P.; Kudchadker, S. A.; Shukla, R. P.; Patnaik, P. R. *J. Phys. Chem. Ref. Data* **1979**, *8*, 499.

(58) Miyano, Y. *Fluid Phase Equilib.* **1999**, *158*−*160*, 29.

(59) Harris, J. G.; Yung, K. H. *J. Phys. Chem.* **1995**, *99*, 12021.

(60) Widom, B. *J. Chem. Phys.* **1963**, *39*, 2908.

(61) Allen, M. P.; Tildesley, D. J. *Computer Simulation of Liquids*; Oxford University Press: Oxford, U.K., 1987.