Theoretical Calculation of Gas-Phase Sodium Binding Energies of Common MALDI Matrices

Juan Zhang,† Tae-Kyu Ha,‡ Richard Knochenmuss,† and Renato Zenobi*,†

Laboratory of Organic Chemistry, Swiss Federal Institute of Technology (ETH), ETH-Hönggerberg, CH-8093 Zürich, Switzerland, and Laboratory of Physical Chemistry, Swiss Federal Institute of Technology (ETH), ETH-Hönggerberg, CH-8093 Zürich, Switzerland

Received: February 6, 2002; In Final Form: April 23, 2002

The gas-phase sodium binding energies for four small aromatic molecules, which are used as matrices in matrix-assisted laser desorption/ionization (MALDI) mass spectrometry, were calculated using the B3LYP hybrid density functional theory at the 6-31+G* level. The gas-phase sodium binding free energies were compared with recently reported experimental results obtained by the ligand-exchange equilibrium method. The compounds investigated in this work are 2,5-dihydroxybenzoic acid, para-nitroaniline, 2,4,6-trihydroxyacetophenone, and 3-hydroxypicolinic acid. In general, good agreement was found between the experimental gas-phase sodium binding free energies and the theoretical results. Detailed geometrical information and vibrational frequencies for both neutral molecules and sodium complexes are shown. The theoretical results give insight into the gas-phase sodium ion transfer reaction mechanism.

Introduction

Sodium ions are known to play an important role in matrix-assisted laser desorption/ionization mass spectrometry (MALDI MS).[1−3] Since the last decade MALDI MS has become an important analytical technique for large biomolecules and polymers. Using MALDI as ionization technique most molecules are detected as protonated and deprotonated ions. However, some molecules, such as polar polymers and carbohydartes are primarily ionized by attachment of alkali metal ions, mainly sodium.[4,5] Cationization by alkali metal ions can also be unfavorable and troublesome for the analysis of some biomolecules, e.g. oligosaccharides.[5−7] Alkali metal adducts appear in a MALDI spectrum as extra peaks, in addition to protonated signals or other cationized signals (for example NH_4^+), although the alkali metal salts are present in MALDI samples only at the trace level. Thus, the ion current is distributed over many more peaks, decreasing the sensitivity. Furthermore, simultaneous observation of protonated analyte ($[M+H]^+$) and metal ion adducts, e.g. ($[M+Na]^+$) makes rapid identification of ionized species more difficult.

Studies of MALDI ionization mechanisms show that cationization along with protonation are important secondary ionization processes which are largely under thermodynamic control.[8] Thus, the thermochemical properties of metal ion complexes are required to clarify the ionization mechanisms. Gas-phase sodium basicities of some relevant MALDI matrices were recently measured.[9] However, the determination of the metal ion binding energies of nonvolatile organic molecules, such as most MALDI matrices, is difficult and time-consuming. In addition, structural information on metal ion complexes, which is also useful for understanding of the gas-phase reaction mechanisms, cannot be easily obtained experimentally. For these reasons, it is required to examine theoretical models and investigate the agreement between theoretically calculated and experimentally determined values.

Some recent theoretical studies were carried out with the aim to interpret experimental measurements of gas-phase binding energies for various ion-ligand systems.[10−25] Reaction enthalpies for the $M^+L = M^+ + L$ reaction, where $M^+ = Na^+$ and K^+ and L = acetamide, glycine, and glycine−glycine (GG) have been studied by Klassen and co-workers.[10] The enthalpy changes for the reactions were determined from collision-induced dissociation (CID) threshold measurements of gas-phase ions produced by electrospray ionization (ESI). For the sodium complexes, the enthalpy values ranged between 142 and 176 kcal mol^{-1}, which were compared with the theoretical ones obtained by HF/6-31G* or MP2/6-31G(2d) ab initio calculations. Good agreement between the experimental and the theoretical values was obtained. For the sodium-glycine complex, there are three equilibrium structures possible which have almost the same stability, as revealed by the ab initio calculations. An extensive list of the calculated harmonic vibrational frequencies for all the complexes and ligands included in this study was presented. Gas-phase lithium cation basicities for some sulfur compounds have been reported by Borrajo et al.[11] It was shown that density functional methods provide better correlation with the experimental results than the ab initio method at the HF and MP2 levels. Experimental data were in accord with the conclusion from calculations that the chelation of lithium provides little stabilization over linear complexation.

An extensive study for the gas-phase sodium basicities of some model cyclic and linear dipeptides and their derivatives has been performed by Cerda et al., using tandem mass spectrometry (MS/MS).[15] Experimental results were also compared with the values obtained by ab initio calculations at the HF and MP2 levels of theory. For the $[GG]Na^+$ complex, nine stable isomers were located whose energy differences range up to about 100 kJ mol^{-1}. Also, for the neutral GG species, four possible equilibrium structures were determined, with energy differences among them ranging up to about 20 kJ mol^{-1}. By

---

† Laboratory of Organic Chemistry, Swiss Federal Institute of Technology (ETH).

‡ Laboratory of Physical Chemistry, Swiss Federal Institute of Technology (ETH).

10.1021/jp0203548 CCC: $22.00

using the two most stable isomers of [GG]Na^+ and the most stable isomer of GG, the Na^+ affinity of the GG species was calculated as 189.5 and 190.0 kJ mol^{-1}, respectively, for those most stable isomers. This compares well with the experimental values of 177 or 179 kJ mol^{-1}. The calculated Gibbs free energies, after correcting for basis set superposition error (BSSE) amount to about 150 kJ mol^{-1}.

Calculations for clusters consisting of an Li^+, Na^+, or Mg^{2+} and up to six acetonitrile (CH_3CN) molecules were carried out using HF, DFT/B3LYP and MP2 methods with the 6-31+G* basis set.[22] It was found to give acceptable results at reasonable computational cost. The three methods led to the same minima, which correspond to highly symmetric structures, in which the dipole moment of acetonitrile points at the cation. The calculated enthalpy and the Gibbs free energy changes are found to agree well among these methods.

Some studies have involved ionic systems complexed by a variable number of water molecules. In a recent study, Driesner et al. have reported an extensive theoretical study on the complexation of the cations of Li, Na, K, and Mg and variable number of water ligand in relation to a model study for the oxygen and hydrogen isotope fractionation process. Good agreement with measured results was obtained for both oxygen and hydrogen isotope effect caused by these cations. The normal modes of vibrations were calculated for minimum energy structures obtained by the DFT method with the B3LYP functional in combination with the 6-311G* basis set.

Ohanessian and co-workers have given a comprehensive summary of the experimental and computational results for Na^+ affinities of small organic and biological molecules.[18] They also obtained computational results for the gas-phase sodium affinities of different compounds including small organic and inorganic molecules, as well as some amino acids. The calculations were performed at the MP2/6-31+G(2d, 2p)//MP2/6-31G* level. A comparison between experimental and theoretical results of NH_3, CH_3NH_2, CH_3OH, and CH_3COCH_3 shows good agreement, they differ by ca. 4 kJ mol^{-1} at most. They have also studied sodiated phenol and found that there are two energy minima on the potential surface, one with complexation of sodium by the oxygen, and the other with binding of sodium above the ring. Dougherty and Ma have written a review about the cation-π interaction, in which many theoretical studies on metal ion-π interaction were summarized.[14] For this the basis set 6-31G** and 6-31G* were used. Hill et al. have done many theoretical studies on cation/ether complexes. They used Hartree−Fock and second-order perturbation theory methods to determine structures and binding enthalpies of complexes formed from a single alkali metal cation (Li^+ through Cs^+) and ethers.[12,16] The 6-31+G*/6-31G* hybrid basis and metal ECP basis were found to give a good agreement with CID experimental results in general. Finally, Feller reported a complete basis set estimation of the binding enthalpy of the Na^+ (ethylene) and Na^+ (benzene) complexes.[20] This theoretical study was undertaken to resolve the disagreement between the values of the Na^+(L) binding enthalpies obtained from CID using guided ion beam mass spectroscopy (GIBMS) techniques and those obtained from equilibrium high-pressure mass spectrometry studies. It was found that the calculated enthalpy for the ethylene complex could be compared well to the CID GIBMS value, whereas that for the benzene complex was approximately midway between the two existing experimental values, which differ by 27 kJ mol^{-1}.

Our quantum mechanical study is done on some important MALDI matrices, i.e., 2,5-dihydroxybezoic acid (DHB), para-nitroaniline (PNA), 2,4,6- trihydroxy-acetophenone (THAP), and 3-hydroxypicolinic acid (3HPA). The variety of substituents on the aromatic ring determine the various features of these matrices, i.e., the proton and metal ion affinity/basicity. Knowledge of such thermodynamic data is the basis for supporting or discounting proposed MALDI mechanisms,[8] but unfortunately, they have largely been lacking so far. Experimental values of the gas-phase sodium basicities (the negative gas-phase sodium binding free energies) of these matrices have recently been determined experimentally using Fourier transform ion cyclotron resonance mass spectrometry (FT ICR MS).[9] In this work, the free energy change in the gas-phase sodium ion transfer from sodiated matrix to a reference species with known gas-phase sodium basicity was determined by studying ligand-exchange equilibria. The gas-phase sodium binding free energies of MALDI matrices obtained by this method are thus relative values, tied to the gas-phase basicity of the reference species.

TABLE 1: Theoretical Sodium Binding Enthalpies, Free Energies, and Experimental Binding Free Energies of MALDI Matrices in kJ mol^{-1} ($T = 298.15$ K)

matrices	$-\Delta H_{298}$	$-T\Delta S_{298}$	$-\Delta G_{298}$	$GNaB_{exp}$[9]
PNA	191.3	32.7	158.6	157 ± 2
DHB	194.4	34.3	160.1	158 ± 3
THAP	203.6	35.7	167.9	154 ± 2
3HPA	200.8	34.4	166.4	163 ± 3

Computational Methods

The equilibrium geometries and the harmonic vibrational wavenumbers of all the species considered in the present study were calculated with density functional theory (DFT), using combined Becke's three-parameter exchange functional and the gradient-corrected functional of Lee, Yang, and Parr (B3LYP functional).[26−28] The 6-31+G* atomic basis set was employed throughout. The IR frequencies and intensities were computed using the analytical derivative procedure implemented in the Gaussian 94 and Gaussian 98 packages.[29,30]

Binding energies were corrected for BSSE using the counterpoise procedure.[31] The harmonic vibrational frequencies calculated by quantum chemical methods (ab initio and DFT) are typically larger than those observed experimentally. The overestimation of the calculated harmonic frequencies is, however, found to be relatively uniform, and as a result generic frequency scaling factors are applied in order to compare them with the experimental values.[32] The sodium binding energies were obtained by calculating the reaction energy of reaction **1**

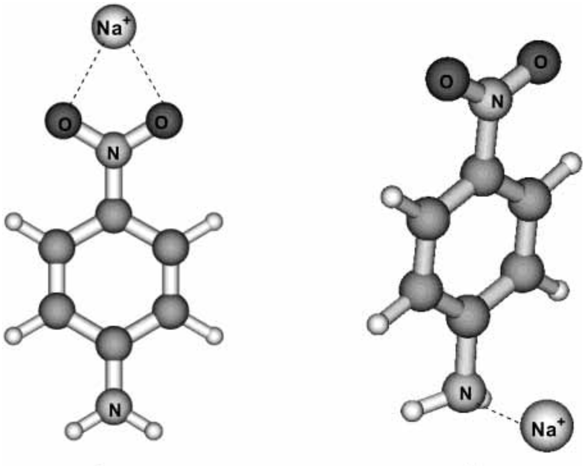
$$MNa^+ \rightarrow M + Na^+ \tag{1}$$

Calculations were done for the reactants and products in the reaction **1** at 1.0 atm and 298.15 K.

Results and Discussion

The sodium binding energies obtained by theoretical calculation in this work and the experimental results of sodium binding free energies are summarized in Table 1. The computational results will be discussed individually for each matrix and compared with experimental data obtained in previous work.[9] The calculated vibrational frequencies with their IR intensities of the matrix molecules as well as their sodium complexes in the most stable structure are summarized in Tables submitted as Supporting Information.

PNA. There are three sodium coordination possibilities for PNA, namely, the interaction of Na^+ with the two oxygens of the nitro group, with the amino nitrogen and with the aromatic



I II

Figure 1. Optimized structures of PNANa$^+$ complex at the B3LYP/6-31+G* level.

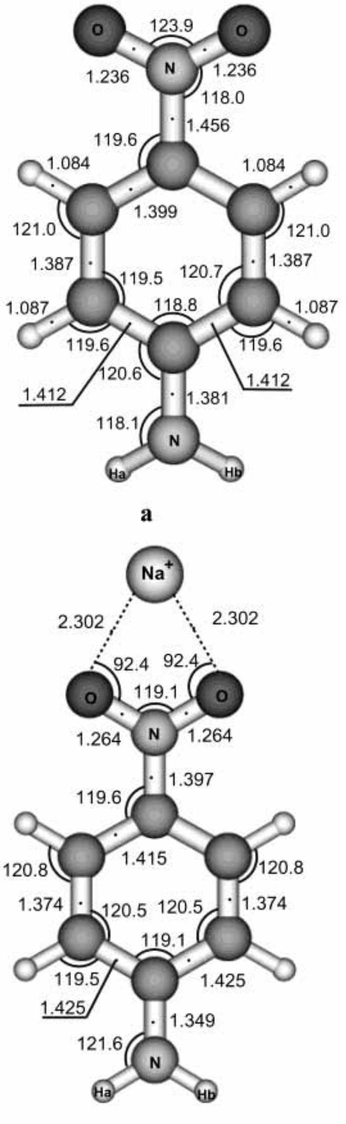
ring. The geometry optimization result shows, however, no local minimum for the interaction of Na$^+$ with the aromatic ring. Figure 1 shows two optimized structures for the two PNANa$^+$ isomers. The isomer **I** with Na$^+$ bound to the nitro group is more stable than isomer **II** with Na$^+$ bound to the amino nitrogen. The energy difference between theses two isomers is 117.6 kJ mol^{-1}.

In structure **I**, a bidentate Na$^+$ coordination by two nitro oxygens with a planar structure is found. Detailed geometrical information obtained by geometry optimization of neutral PNA and of the PNANa$^+$ complex is shown in Figure 2. In contrast to the geometry of the amino group in neutral PNA (Figure 2a), the PNANa$^+$ complex structure shows that the amino group is planar. The most notable geometrical change upon binding of the sodium ion is thus the change of dihedral angles Ha-N−C−C and Hb-N−C−C. In PNA, Ha-N−C−C = 196.8° and Hb-N−C−C = 340.8°, whereas the dihedral angles in the PNANa$^+$ complex are Ha-N−C−C = 180° and Hb-N−C−C = 360°, which gives a C_{2v} symmetry. The N−O bond lengths (1.264 Å) of the nitro group in the PNANa$^+$ complex are longer than that in neutral PNA (1.236 Å). The −ONO angle is greater in the complex than in the neutral molecule. All these structural changes lead to a global dipole moment in the complexed PNA (μ = 1.7197 D).

To obtain the sodium binding free energy of PNA, vibrational frequencies were calculated for both optimized neutral PNA and the more stable complex isomer (isomer **I** in Figure 1). The sodium binding free energy of PNA is 158.6 kJ mol^{-1}. This is in good agreement with the experimental value, 157 ± 2 kJ mol^{-1}.[9]

DHB. we considered the most plausible structures of the DHBNa$^+$ complex. Carboxyl and hydroxyl functional groups are the most likely candidates for binding the sodium. The interaction between a sodium ion and a single hydroxyl oxygen leads to relatively low sodium affinity (ΔH less than 100 kJ mol^{-1}).[18] For this reason, we focused on the complexation of the sodium ion by both carboxylic oxygens or by the hydroxyl oxygen and one of the carboxylic oxygens. As for the PNANa$^+$ complex, no local minimum for the complexation of sodium by the π-system was found.

The optimized structures of the DHBNa$^+$ complex are shown in Figure 3. The structures are divided into two groups: "**a**" and "**b**". The difference between these two groups is the torsion angle of the H atom of the 5-hydroxyl group. "**a**" denotes structures with a dihedral angle H5−O5−C5−C4 = 0° (refer to Figure 4), whereas "**b**" is for H5−O5−C5−C4 = 180°. All of these structures show that sodium ion sits in the molecular plane of DHB. **Va** and **Vb** are the most stable structures giving a coordination of sodium by both the 2-hydroxyl and the carboxylic oxygens. The energy difference between these two structures is 0.6 kJ mol^{-1}. Structures **IVa** and **IVb** are the second most stable conformations of the DHBNa$^+$ complex, in which the sodium is bound to the carboxylic oxygens, and a H-bond is formed between the carboxylic hydrogen and the 2-hydroxyl oxygen. The energy difference between structure **V** and **IV** is around 4 kJ mol^{-1}. From a geometrical point of view, the four-membered ring in structures **IVa** and **IVb** is less favorable than the six-membered ring in structures **Va** and **Vb**. Although the way of the sodium coordination in structures **IIa** and **IIb** is similar to that in structures **IVa** and **IVb**, structure **II** contains over 20 kJ mol^{-1} more energy. Although the sodium is bound by the two carboxyl oxygens, one of the carbonyl oxygens disperses the charge to both the sodium ion and the 2-hydroxyl hydrogen. In this case, the charge transfer from this carbonyl O-atom to sodium is less efficient than that in structures **V** and **IV**. Among these twelve DHBNa$^+$ complexes, structures **IIa**, **IIb** as well as **IIIa**, **IIIb** show a somewhat special behavior.



b

Figure 2. Detailed geometrical information of PNA and PNANa$^+$ complex at the B3LYP/6-31+G* level.

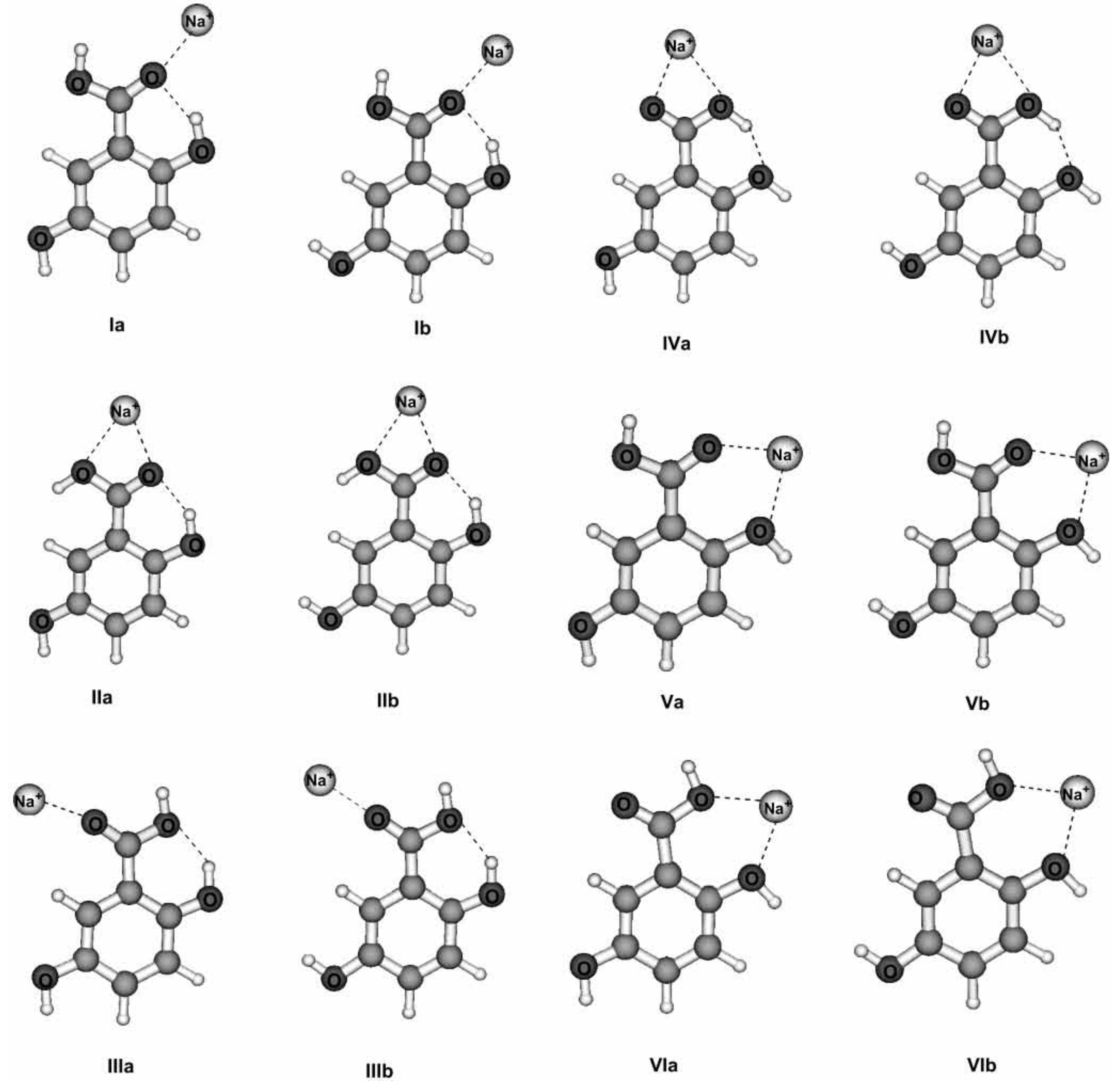


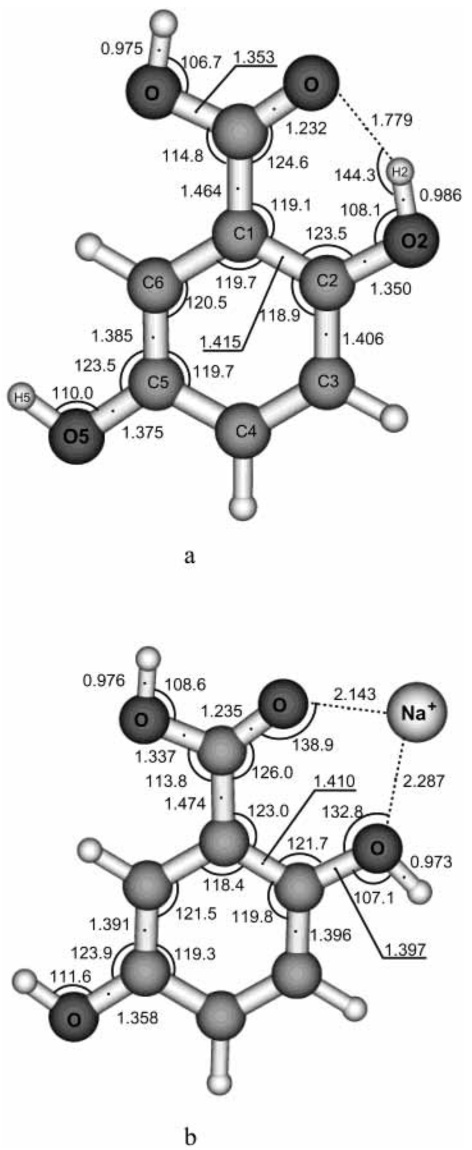
Figure 3. Optimized structures of DHBNa$^+$ complex at the B3LYP/6-31+G* level.

The rotation of the 5-hydroxyl group makes a notable energy difference in structures **II** and **III** (for example, the energy difference between **IIIa** and **IIIb** is 9.7 kJ mol^{-1}), whereas in structure **I**, **IV**, **V**, and **VI**, this kind of rotation only results in small energy differences (the energy difference between **Ia** and **Ib** is 0.2 kJ mol^{-1}).

The corresponding neutral DHB structures were optimized individually. The different neutral structures are labeled with **N** and correspond to the sodium complex structures, e.g., the corresponding neutral of complex **Vb** is labeled by **VbN**. True minima were found for all six sets of neutral structures. We take three of them as examples, i.e., the corresponding neutrals of the sodium complex in structures **VbN**, **IVaN**, and **IbN**. The relative energies of these three neutrals with respect to the most stable one (**IbN**) are given in Table 2. The optimized geometry of the most stable structures of neutral (**IbN**) and the complex with their geometrical parameters are shown in Figure 4.

Comparing the most stable DHBNa$^+$ complex and the most stable neutral DHB conformation, a sodium binding free energy 119 kJ mol^{-1} is obtained, which does not agree well with the experimental results 158 ± 3 kJ mol^{-1}. For organic molecules that can coordinate sodium doubly or multiply, the sodium binding energies are mostly higher than 120 kJ mol^{-1}.[18] Considering that the DHB molecule contains both carboxyl and hydroxyl functional groups, 119.1 kJ mol^{-1} is clearly too low for the gas-phase sodium binding energy. However, by comparison of the most stable complex structure (**Vb**) with its corresponding neutral, GNaB = 160.1 kJ mol^{-1} is obtained. To understand this, we have to consider the way the experimental data were obtained.[9] The experiment was done using the ligand-exchange equilibria method by observing the sodium ion transfer from the sodiated matrix molecule to reference base (reaction **2**)

$$[\mathrm{M} + \mathrm{Na}]^+ + \mathrm{Re} \overset{\Delta G}{\rightleftharpoons} \mathrm{M} + [\mathrm{Re} + \mathrm{Na}]^+ \qquad (2)$$



a

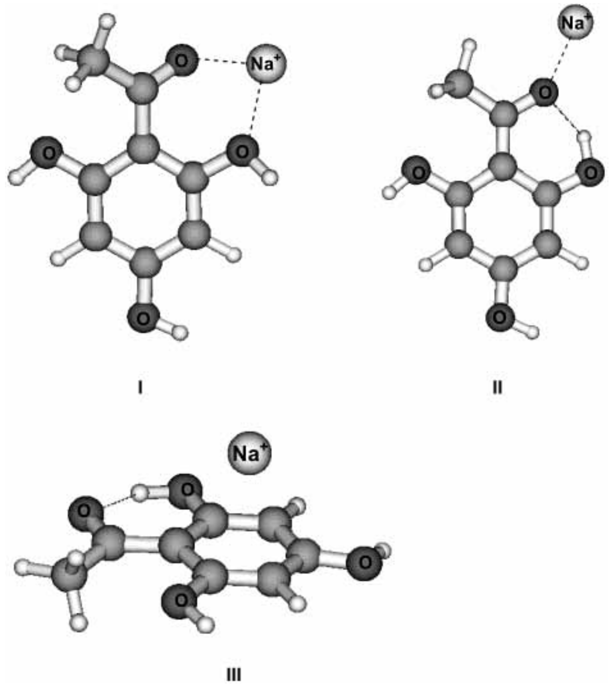
b

Figure 4. Detailed geometrical information of DHB and DHBNa$^+$ complex at the B3LYP/6-31+G* level.

The sodiated matrix [M+Na]$^+$, has the most stable conformation, **Vb** in Figure 3, whereas the neutral matrix molecule M may have or may not have the most stable conformation **IbN**. There are two different pathways for the conformational change of the neutral DHB. The first one is that DHB changes its conformation from **VbN** to **IbN**, whereas the sodium is transferred from DHB to a reference base; the second is that the relaxation of DHB from **VbN** into the most stable neutral conformation **IbN** takes place after losing sodium ion. In the latter case, the conformational change of neutral DHB cannot be observed. The conformation change from **VbN** (dihedral angle H2−O2−C2−C3 = 0°) into **IbN** (dihedral angle H2−O2−C2−C3 = 180°) involves the rotation of the 2-hydroxyl functional group with formation of an intramolecular hydrogen bond. A single-point-energy calculation of the transition state between neutral DHB conformations **IbN** and **VbN** with a dihedral angle H2−O2−C2−C3 = 90° (refer to Figure 4) shows that the energy barrier for **IbN** to the transition state is 20.1 kJ mol^{-1}. Neither the thermal energy at 298 K nor the reaction energy (less than 10 kJ mol^{-1}) is sufficient to overcome this energy barrier during the sodium transfer from DHB to reference base. The experimental results obtained from FT ICR MS are based on observing the sodium ion transfer reactions by measuring the intensities of the sodiated DHB and the sodiated reference base. Therefore, any energy consuming transformation after the sodium ion transfer are not expected to influence the mass spectra. Thus, comparing the energies of the most stable

TABLE 2: Calculated Relative Energies with Respect to the Most Stable Structures for PNA, DHB, THAP, 3HAPA as Well as Their Sodium Complexes in Different Conformers Obtained from Geometry Optimization at the 6-31+G* Level

		E (a.u.)	ΔE (kJ mol$^{-1)}$
PNA		−492.132 360 6	
PNANa$^+$	I	−654.287 632 4	0
	II	−654.242 855 6	117.6
DHB	IbN	−571.292 426 1	0
	IVaN	−571.275 748 9	43.8
	VbN	−571.274 604 4	46.8
DHBNa$^+$	Vb	−733.431 330 8	0
	Va	−733.431 110 9	0.6
	IVa	−733.429 828	4.0
	IVb	−733.429 782 6	4.1
	IIa	−733.421 396 8	26.1
	IIIa	−733.419 371	31.4
	IIb	−733.418 913 3	32.6
	IIIb	−733.415 648 4	41.2
	Ia	−733.414 749 3	43.5
	Ib	−733.414 696 3	43.7
	VIb	−733.412 258 3	50.1
	VIa	−733.411 340 5	52.5
THAP		−610.590 723 8	
THAPNa$^+$	I	−772.729 028	0
	II	−772.728 109 5	2.4
	III	−772.7047	63.9
3HPA		−512.112 622 5	
3HPANa$^+$	I	−674.257 369 4	0
	II	−674.251 936 2	14.3
	III	−674.250 341	18.5
	IV	−674.246 929 4	27.4
	V	−674.237 048 3	53.4
	VI	−674.217 187 1	105.5



I

II

III

Figure 5. Optimized structures of THAPNa$^+$ complex at the B3LYP/6-31+G* level.

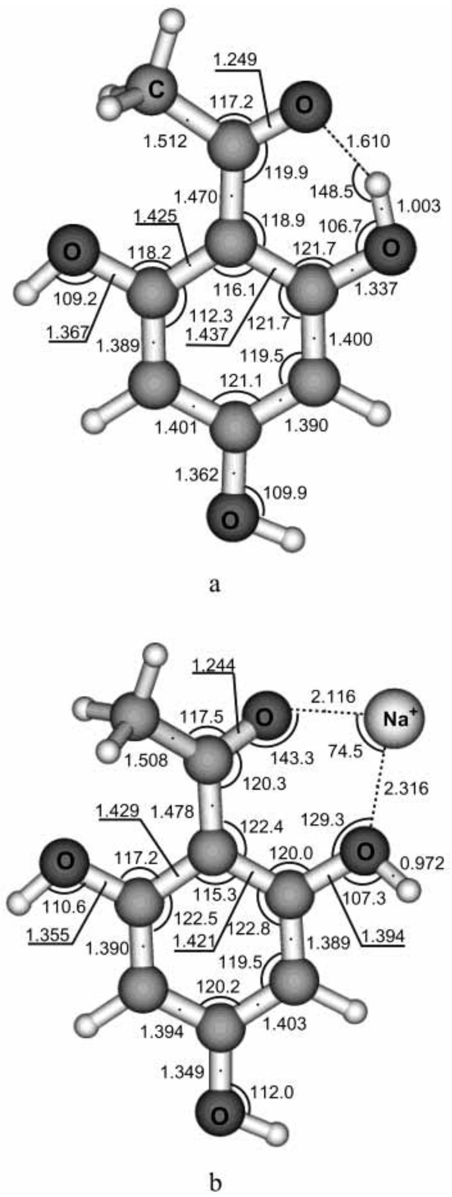


Figure 6. Detailed geometrical information of THAP and THAPNa$^+$ complex at the B3LYP/6-31+G* level.

complex conformation and the corresponding neutral structure is more reasonable.

In addition to the conformational change of the sodiated DHB, one should also consider conformational changes of the neutral reference base (dimethoxyethane, DXE) and its sodium ion complex. It is known that the sodium ion complex of dimethoxyethane possesses a syn-conformation,[16] whereas the conformation of neutral itself is anti. We therefore carried out a geometry optimization and the vibrational frequency calculation for neutral dimethoxyethane in syn-conformation, and found that there is no true minimum on the potential surface. There is no energy barrier between syn-, and anti-conformation. Therefore, the sodium binding energy of the reference base can be obtained by comparing the most stable complex and most stable neutral (anti-) conformation.[16]

THAP. The possibilities for Na$^+$ coordination are provided by the oxygen atoms of the carbonyl and hydroxyl functional groups (Figure 5). An energy minimum is also found when Na$^+$ coordinates to the aromatic ring. The most stable isomer is **I**, with a bidentate Na$^+$ coordination by the carbonyl oxygen and the 2-hydroxyl oxygen. The carbonyl group rotates out of the benzene ring plane in the THAPNa$^+$ complex. In structure **II**, sodium is bound to the carbonyl oxygen that also forms an intramolecular hydrogen bond to the 2-hydroxyl hydrogen. The optimized geometrical information of the most stable neutral and complex are shown in Figure 6.

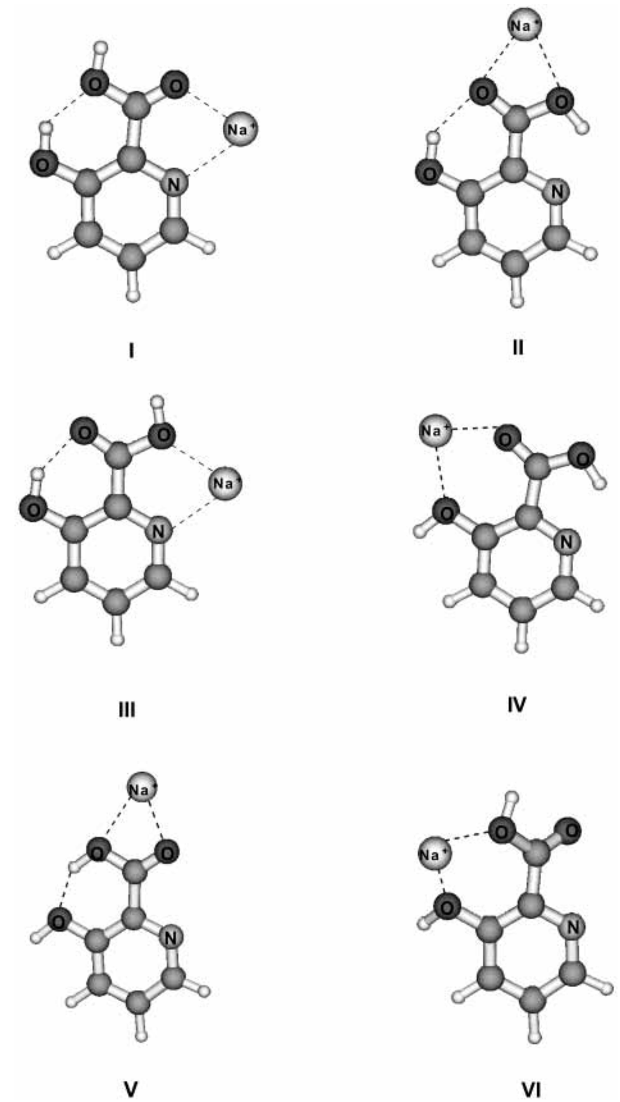


Figure 7. Optimized structures of 3HPANa$^+$ complex at the B3LYP/6-31+G* level.

Frequency calculations were carried out for all of the conformers **I**, **II**, and **III**, as well as their corresponding neutrals. The sodium binding free energy for the complex with the sodium ion bound to the carbonyl oxygen (structure **II**) is 114 kJ mol^{-1}. A sodium binding free energy of 117.5 kJ mol^{-1} is obtained if the most stable complex structure **I** is compared with the most stable neutral conformation **(**Figure 6). These values are quite different from the experimental value: 154 ± 2 kJ mol^{-1}. Again, if the conformer **I** of THAPNa$^+$ complex and its corresponding neutral are compared, a sodium binding free energy of 167.9 kJ mol^{-1} is obtained. This value is in better agreement, but still 14 kJ mol^{-1} (9%) higher than the experimental value.

3HPA. In Figure 7, the plausible conformations of the sodium complex are presented. The relative energies of the conformers with respect to the structure **I** are shown in Table 2. The most stable structure of the 3HPANa$^+$ complex is structure **I**, in which the sodium ion is complexed by the carbonyl oxygen and the aromatic nitrogen. The complexation of the sodium ion by both carboxylic oxygens gives the second stable structure (**II**), with

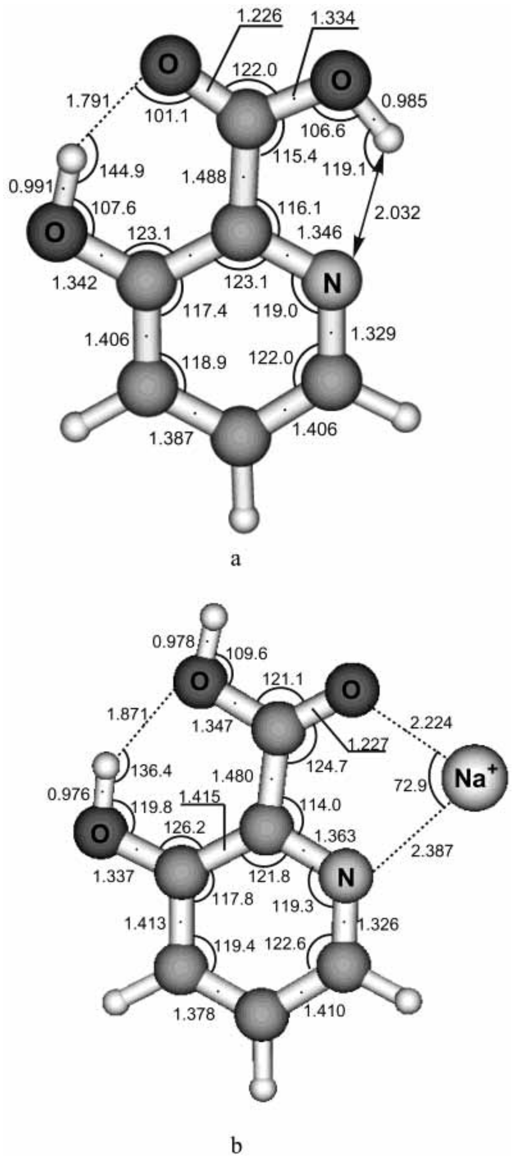


Figure 8. Detailed geometrical information of 3HPA and 3HPANa$^+$ complex at the B3LYP/6-31+G* level.

14.3 kJ mol^{-1} more energy than structure **I**. In structure **III**, the sodium ion is bound to the hydroxyl oxygen and the nitrogen. This structure is more stable than structure **IV**, in which sodium is complexed with the hydroxyl and the carbonyl oxygen. The intramolecular H-bond in structure **III** seems to be responsible for the stabilization of the whole complex. Although the way of sodium complexation in structure **V** is the same as that in structure **II**, structure **V** is much less stable than structure **II**. There is an intramolecular H-bond in structure **V** between the carboxylic H-atom and the hydroxyl oxygen, which is in fact energetically and geometrically less favorable than that in structure **III** (between hydroxyl H-atom and the carbonyl oxygen). On the other hand, the repulsive interaction between the carbonyl oxygen and the aromatic nitrogen renders the complex less stable. This effect becomes more obvious in structure **VI**: the carboxyl functional group rotates out of plane. Although the charge-dipole interactions are the decisive factor for the complex stability, the intramolecular interactions can sometimes not be neglected.

The optimized geometries of the most stable 3HPA and 3HPANa complex with detailed geometrical information are shown in Figure 8. The situation we had for DHB and THAP is repeated here, i.e., if we compare the most stable complex with the most stable neutral, the calculated sodium basicity is GNaB = 133 kJ mol^{-1}, whereas GNaB = 166.4 kJ mol^{-1} is obtained by comparison between the most stable complex and its corresponding neutral. The experimental value is 163 ± 3 kJ mol^{-1}. To reach the most stable conformation, the neutral 3HPA has to make a 180°-rotaion of the carboxyl group and break the H-bond. The energy barrier for this motion is certainly even higher than that for the rotation of the hydroxyl group in the case of DHB. This causes the 3HPA molecule to relax to its most stable conformation after losing the sodium ion.

Conclusion

Theoretical studies on both structures and binding energies of sodium complex formed with MALDI matrices have been done using the B3LYP DFT method at the cost-effective 6-31+G* level. It gives, in general, a good agreement with experimental results on gas-phase sodium binding free energies. However, in most cases, the corresponding neutral structure of the most stable complex had to be employed to obtain agreement with experiment. The binding enthalpy and entropy values, which could not be obtained by ligand-exchange equilibria method, are available from ab initio calculations (see Table 1). Structural information about sodium-matrix complexes, which can only be obtained by ab initio method, were used to interpret the mechanism of the gas-phase sodium transfer from sodiated matrices to the reference base in the experimental measurements of the sodium basicities using the ligand-exchange equilibria method. The experimental results support the hypothesis that the conformational change of the neutral ligands takes place after losing the sodium ion. This work shows that ab initio calculations can provide an alternative way for determination of the required thermochemical data for the investigation of the MALDI mechanism.

Acknowledgment. This work has been funded by the Swiss Federal Institute of Technology. The generous allocation of computer time by the Competence Center for Computational Chemistry (C4 cluster, ETH Zürich) is gratefully acknowledged.

Supporting Information Available: Tables showing the calculated vibrational frequencies with their IR intensities of the matrix molecules as well as their sodium complexes in the most stable structure. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Karas, M.; Bachmann, D.; Bahr, U.; Hillenkamp, F. *Int. J. Mass Spectrom. Ion Proc.* **1987**, *78*, 53.

(2) Karas, M.; Hillenkamp, F. *Anal. Chem.* **1988**, *60*, 2299.

(3) Hillenkamp, F.; Karas, M.; Beavis, R. C.; Chait, B. T. *Anal. Chem.* **1991**, *63*, 1193A.

(4) Nielen, M. W. F. *Mass Spectrom. Rev.* **1999**, *18*, 309.

(5) North, S.; Okafo, G.; Birrell, H.; Haskins, N.; Camilleri, P. *Rapid Commun. Mass Spectrom.* **1997**, *11*, 1635.

(6) Whittal, R. A.; Palcic, M. M.; Hindsgaul, O.; Li, L. *Anal. Chem.* **1995**, *67*, 3509.

(7) Yoshino, K.; Takao, T.; Murata, H.; Shimonishi, Y. *Anal. Chem.* **1995**, *67*, 4208.

(8) Knochenmuss, R.; Stortelder, A.; Breuker, K.; Zenobi, R. *J. Mass Spectrom.* **2000**, *35*, 1237.

(9) Zhang, J.; Knochenmuss, R.; Stevenson, E.; Zenobi, R. *Int. J. Mass Spectrom.* **2002**, *213*, 237.

(10) Klassen, J. S.; Anderson, S. G.; Blades, A. T.; Kebarle, P. *J. Phys. Chem.* **1996**, *100*, 14 218.

(11) Borrajo, A. M. P.; Gal, J.-F.; Maria, P.-C.; Decouzon, M.; Ripley, D. C.; Buncel, E.; Thatcher, G. R. J. *J. Org. Chem.* **1997**, *62*, 9203.

(12) Hill, S. E.; Glendening, E. D.; Feller, D. *J. Phys. Chem. A* **1997**, *101*, 6125.

(13) More, M. B.; Ray, D.; Armentrout, P. B. *J. Phys. Chem. A* **1997**, *101*, 831.

(14) Ma, J. C.; Dougherty, D. A. *Chem. Rev.* **1997**, *97*, 1303.

(15) Cerda, B. A.; Hoyau, S.; Ohanessian, G.; Wesdemiotis, C. *J. Am. Chem. Soc.* **1998**, *120*, 2437.

(16) Hill, S. E.; Feller, D.; Glendening, E. D. *J. Phys. Chem. A* **1998**, *102*, 3813.

(17) Hoyau, S.; Ohanessian, G. *Chem. Eur. J.* **1998**, *4*, 1561.

(18) Hoyau, S.; Norrman, K.; McMahon, T. B.; Ohanessian, G. *J. Am. Chem. Soc.* **1999**, *121*, 8864.

(19) Driesner, T.; Ha, T.-K.; Seward, T. M. *Geochim. Cosmochim. Acta* **2000**, *64*, 3007.

(20) Feller, D. *Chem. Phys. Lett.* **2000**, *322*, 543.

(21) Ryzhov, V.; Dunbar, R. C.; Cerda, B. A.; Wesdemiotis, C. *J. Am. Chem. Soc.* **2000**, *11*, 1037.

(22) Cabaleiro-Lago, E. M.; Ríos, M. A. *Chem. Phys.* **2000**, *254*, 11.

(23) Amunugama, R.; Rodgers, M. T. *Int. J. Mass Spectrom. Ion Proc.* **2000**, *195/196*, 439.

(24) Petrie, S. *J. Phys. Chem.* **2001**, *105*, 9931.

(25) Vedernikova, I.; Claeys, M.; Salahub, D. R.; Casida, M. E. *Int. J. Mass Spectrom.* **2001**, *210/211*, 21.

(26) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 1372.

(27) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.

(28) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B.* **1988**, *37*, 785.

(29) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. *Gaussian 94*, revision C.5; Gaussian, Inc.: Pittsburgh, PA, 1995.

(30) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; J. A. Montgomery, J.; 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.; C. Pomelli, C. A.; 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.; Baboul, A. G.; 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.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision *A.9*, Gaussian, Inc., Pittsburgh, PA, 1998.

(31) Boys, S. F.; Bernadi, F. *Mol. Phys.* **1993**, *19*, 553.

(32) Scott, A. P.; Radom, L. *J. Chem. Phys.* **1996**, *100*, 16 502.