A Quantitative Basis for a Scale of Na^+ Affinities of Organic and Small Biological Molecules in the Gas Phase

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Received November 30, 1998

Abstract: High-pressure mass spectrometric experiments and ab initio calculations have been carried out in order to establish a series of accurate gas-phase sodium ion affinities of organic molecules with a wide variety of functional groups. Ab initio calculations have also been performed on the sodium complexes of three amino acids: serine, cysteine, and proline. A systematic critical evaluation of experimental and computational literature results shows that a significant number require revision. Based on comparisons with accurate experimental measurements, the ab initio procedure used is shown to yield sodium ion affinities with an accuracy of ca. 1 kcal·mol^{-1}. This enables the construction of the first reliable table of gas-phase Na^+ affinities for organic and small biological molecules.

Introduction

Sodium and potassium and, to a lesser extent, lithium are known to have important effects in biological systems.[1] For example, they participate in enzyme regulation, stabilization of structural elements, transport through transmembrane channels, etc. While extensive data are available for gas-phase binding of lithium to a variety of molecules,[2] there is comparatively little for the more biologically important sodium and potassium.

With the advent of application of mass spectrometry to biologically interesting molecules, many ionization sources have been developed which give rise to sodium-cationized adducts.[3] One assumption that is frequently made is that, in CID experiments used to elucidate structure, bond cleavage is directed by the site of sodium binding.[4] For this reason, it is also of considerable interest to understand the energetic and structural characteristics of sodium binding to biomolecules such as peptides.

To gain a better understanding of the interaction of sodium ion with large biological molecules, a knowledge of the structure and energetics of the binding to smaller model systems is required. In the past decade, a variety of experimental and theoretical studies have been carried out to determine the binding energies of sodium to organic and inorganic molecules. One early study was performed by Dzidic and Kebarle for sodium−water clusters using high-pressure mass spectrometric (HPMS) equilibrium measurements.[5] Castleman and co-workers, carrying out similar measurements, obtained a group of sodium binding enthalpies and entropies for a series of small organic and inorganic molecules.[6−10] The only other method which has been used to obtain absolute sodium binding energies is the threshold collision-induced dissociation (CID) technique. Kebarle and co-workers obtained results for amides and amino acids,[11] while Armentrout et al. studied water,[12] CO,[13] dimethyl ether,[14] two polyethers,[14] and a series of azoles.[15] Relative binding energies have also been obtained by Cooks's kinetic method[16] for a series of organic molecules including alcohols, amines, esters, and amides,[17] amino acids,[18] the nucleobases,[19] small linear and cyclic dipeptides,[20] larger dipeptides[21,22] and derivatives.[22]

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10.1021/ja9841198 CCC: $18.00
Published on Web 09/10/1999

In recent years, quantum chemical methods have been shown to be capable of accurately reproducing experimental gas-phase ion energetics. Extensive studies for series of sodium affinities include those for simple hydrides[23,24] and methyl derivatives,[24] binary hydrides and halides,[23,25] and ethers and polyethers.[26−28] Detailed studies of single molecules interacting with sodium have been carried out for a number of other organic molecules.

The number of experimentally determined absolute sodium binding enthalpies and entropies is relatively limited. This is because the sodium binding energies for larger organic molecules are sufficiently high that they are beyond the temperature range of the HPMS technique. The threshold CID method requires theoretical vibrational frequencies in order to derive the true threshold from the experimentally obtained data. The Cooks kinetic method requires an absolute sodium binding energy for each functional group type examined in order for the relative sodium scales to yield accurate absolute values. For this reason, it would be extremely desirable to have good agreement between experimentally obtained and theoretically calculated values for a significant number of cases. A careful examination of the body of experimental and theoretical results summarized above shows that such agreement does not currently exist. For instance, the experimentally obtained and theoretically calculated data for ammonia,[6,24] methylamine,[9,24] methanol,[9,24] hydrogen chloride[7,23,25] and dimethoxyethane[7,28] show differences of up to ~5 kcal·mol^{-1}. In the latter case, there is even a large disagreement between threshold CID[14] and HPMS[7] measurements. For this reason, we have undertaken the current study to obtain a series of HPMS measurements of sodium binding energetics and, at the same time, to carry out high-level ab initio calculations for the same molecules. In addition, this series of ab initio calculations has been extended to organic molecules which bind sodium more strongly in order that accurate reference values are available for existing and future measurements by the kinetic method. Some other affinities have been calculated in order to resolve inconsistencies in the literature. Finally, the interaction of Na^+ with several amino acids has been investigated in order to gain insight into the structural features for sodium adducts of multidentate binding, biologically relevant molecules.

Experimental Section

The equilibrium measurements were made with a pulsed ionization high-pressure mass spectrometer (PHPMS) constructed at the University of Waterloo, configured around a VG 70-70 mass spectrometer whose geometry has been changed from that of an E-B to a B-E instrument. The apparatus and its capabilities have been described in detail previously.[29]

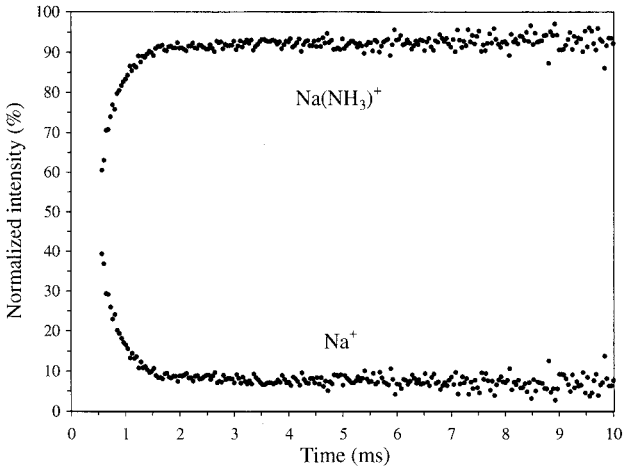

Figure 1. Normalized ion intensity profiles for the clustering of sodium ion onto NH_3 at 304 °C; $P(N_2)$ = 11.87 Torr, $P(NH_3)$ = 0.13 Torr.

Gas mixtures were prepared in a temperature-controlled 5-L stainless steel reservoir using nitrogen as the high-pressure bath gas, which served as the inert third body stabilization species. Other components of the mixture were present in amounts between 0.1 and 1%. Trace amounts of carbon tetrachloride were added to the mixture to act as an electron scavenger, to effect ambipolar ion diffusion, which lengthens the duration of the ion intensity profiles. The gas mixture was bled into the ion source through a heated stainless steel inlet line to a pressure of 8−12 Torr. Ionization was accomplished by using a 500-μs pulse of 2-keV electrons, focused into the ion source through a 200-μm aperture. Several methods were used to attempt to generate a Na^+ signal. Solid sodium was placed in a reservoir attached to the source and heated. This resulted in an excellent Na^+ intensity; however, virtually every compound attempted reacted with sodium such that equilibrium could not be observed. It was found that, by heating various sodium salts, including nitrate, citrate, and valerate, a reasonable Na^+ signal could be obtained. For all of the experiments carried out in this work, Na^+ was produced from ionization of sodium vapor, generated from pyrolysis of sodium valerate. Prior to the experiment, the inside walls of the ion source block were coated with a layer of sodium valerate. The sodium signal started to appear around a temperature of 560 K. The ions diffuse out of the ion source through a 200-μm aperture into the source chamber, where the pressure is 50 μTorr. The ions are then accelerated toward the first cone through a 50−150-V potential drop, where they enter the ion optics region and are accelerated to 2.9 keV. The signal was monitored by a PC-based multichannel scaler data acquisition system configured at 10−100 μs dwell time per channel. A total of 250 channels were acquired using a duty cycle of ~10 ms greater than the duration of the most persistent ion. This prevents pulse-to-pulse carryover in ion abundances. The results of 3000−20 000 electron gun pulses were accumulated, dependent upon the signal intensity. Representative normalized data are shown in Figure 1 for the association reaction of Na^+ onto NH_3. These equilibrium measurements were generally well behaved, and typical uncertainties of ±0.2 kcal·mol^{-1} and ±2 cal·mol^{-1}·K^{-1} can be assigned for the ΔH and ΔS values, respectively. These uncertainties are somewhat greater than those obtained statistically from the van't Hoff plots due to small additional uncertainties in pressure and temperature.

Computational Details

Sodium affinities were determined with a procedure already detailed in previous papers.[30−32] Geometries of neutral and sodium-bound molecules were first optimized at the MP2(full)/6-31G* level. Vibra-

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Table 1. Experimental[a] and Calculated[b] Results for Enthalpies and Entropies of Complexation to the Sodium Cation, in kcal·mol^{-1} (1 kcal·mol^{-1} = 4.184 kJ·mol^{-1})

	experimental		theoretical	
molecule	ΔH_{298}	ΔS	ΔH_{298}	ΔS
NH_3	25.6 ± 0.2	21.8 ± 2.0	25.4	23.1
CH_3NH_2	26.3 ± 0.2	22.6 ± 2.0	26.5	23.4
CH_3OH	24.0 ± 0.2	20.5 ± 2.0	24.3	21.8
H_2O			22.1	21.8
H_2S			13.8	19.9
CH_3SH			17.5	21.8
SO_2			14.7	22.5
H_2CNH			27.0	23.1
H_2CO			22.9	21.2
CH_3COCH_3	30.8 ± 0.5	21 ± 5	30.0	21.3
HCOOH			23.7	22.0
$HCONH_2$			33.1	24.3
$HCON(CH_3)_2$			37.1	22.8
CH_3CONH_2			35.6	24.5
CH_3COOCH_3			28.9	21.1
CH_3CN			30.3	22.4
CH_3OCH_3			24.5	21.7
$C_2H_5OC_2H_5$			28.0	22.6
imidazole			34.9	23.3
CO_2			11.2	18.9
CH_4			6.1	18.5
C_2H_2			12.3	18.9
C_2H_4			12.7	20.0
C_6H_6			21.8	24.5
C_6H_5OH			22.2, 22.3	25.9, 23.0
serine			44.9	29.8
cysteine			40.1	27.1
proline			44.2	26.4

[a] PHPMS. [b] Ab initio calculations at the MP2/6-311+G(2d,2p)//MP2/6-31G* level, corrected for BSSE, see text.

tional frequencies were also obtained at this level. Test calculations on formamide and dimethyl ether at the MP2/6-31+G* level showed negligible structural differences. Final energetics were obtained at the MP2(full)/6-311+G(2d,2p)//MP2/6-31G* level in order to minimize basis set superposition errors (BSSE). Even so, BSSE remains non-negligible and was subtracted from the computed interaction energies in the full counterpoise approximation. This is known to lead to slightly overestimated BSSE corrections, but the use of the 6-311+G(2d,2p) basis set ensures that the magnitude of this overestimation will be small, since the computed total BSSE is small (less than 2 kcal·mol^{-1} in all cases). Calibration calculations for small sodium complexes have shown that this procedure leads to well-converged energetics.[31] This method also has the advantage of remaining tractable for molecules with up to ~10 non-hydrogen atoms. Zero-point vibrational energies and thermal corrections at 298 K were obtained from the unscaled MP2/6-31G* vibrational frequencies. Finally, these complexation energies were converted to enthalpies by the addition of a factor of *RT* (0.6 kcal·mol^{-1} at 298 K). The excellent agreement (see Table 1) found between experimental and calculated complexation enthalpies would indicate that, for molecules of reasonable size, calculated enthalpies should be accurate to within ±1 kcal·mol^{-1}.

For the sodium complexes of amino acids, several isomers were considered in each case. Geometry optimizations and vibrational frequency calculations were carried out at the HF/6-31G* level in order to identify the most stable isomer.[32] This structure was then refined at the MP2/6-31G* level. Vibrational frequencies, thermal corrections, and entropies were obtained at this level only for the lowest energy isomer. In cases where the energy difference between the lowest two structures was small (typically 2 kcal·mol^{-1} or less), both were reoptimized at the MP2/6-31G* level. The rest of the computational procedure was as described above.

Complexation entropies were also computed from the MP2/6-31G* frequencies and geometries. Comparisons with known entropies of stable neutral molecules show that this level of theory accurately reproduces absolute entropies. It must be noted that, in the sodium adducts, the three new vibrational modes will have very low frequencies which make significant contributions to the entropy. Inspection of the individual contributions of such modes suggests that typical accuracies for the complexation entropies should be ±2 cal·mol^{-1}·K^{-1}.

All calculations were run using the Gaussian94 package.[33]

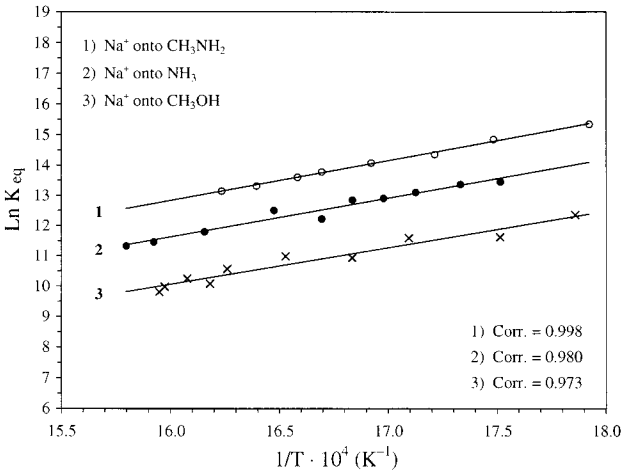

Figure 2. van't Hoff plots for the clustering reactions of sodium ion onto methylamine, ammonia, and methanol.

Results

For the general association reaction (eq 1), the free energy

$$Na^+ + M \rightarrow NaM^+ \quad (1)$$

change may be obtained from the experimentally observed steady-state intensity ratios of the two ions (Figure 1) and the known pressure of the molecule M in the ion source using the general equilibrium expression (eq 2).

$$\Delta G = -RT \ln(K) \quad (2)$$

$$\ln(K) = -\Delta H/RT + \Delta S/R \quad (3)$$

If the equilibrium is examined at several temperatures, the enthalpy and entropy changes for the association reaction can also be obtained from a van't Hoff plot of ln(*K*) vs 1/*T*. From eq 3, it can be seen that the slope of such a plot will yield the enthalpy change for the reaction, and the intercept will give the entropy change. Representative van't Hoff plots for the systems studied here are shown in Figure 2, and the thermochemical data obtained are summarized in Table 1. The method used to generate sodium ions was such that a fresh coating of sodium valerate was required very frequently. This necessitated breaking vacuum and reestablishing a good base pressure in the apparatus afterward. As a result, these measurements were extremely time-consuming. In addition, there were apparently some reactions occurring between sodium valerate and some of the compounds that were attempted. Accordingly, only the four equilibria in Table 1 were of a quality considered sufficient to derive accurate thermochemical data.

Also included in Table 1 are the ab initio values of enthalpies and entropies of association computed following the procedure outlined above.

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Table 2. Compilation of Existing Sodium Ion Affinities (kcal·mol^{-1}; Experimental Values Are in Italics; Values from the Present Work Are in Boldface)

molecule	binding energy	molecule	binding energy	molecule	binding energy	molecule	binding energy
H_2O	*24.0*,[a] *23.4*,[b] *24.1*,[z] *21.0*,[cc] 22.5,[c] 24.0,[d]	CH_3NH_2	*32.1*,[j] 27.0,[c] ***26.3***,[i] **26.5**[i]	imidazole	*33.7*,[y] **34.9**[i]	cytosine	*40.9*[ll]
	23.5,[e] 24.2,[f] 24.1,[g]	CH_3CN	*32.5*,[r] 30.6,[r] **30.3**[i]	1*H*-1,2,4-triazole	*29.8*[y]	adenine	*39.7*,[ll] *31.3*[pp]
	23.6,[h] **22.1**[i]	CH_3OCH_3	*22.2*,[s] 25.9,[t] **24.5**[i]	2*H*-1,2,3-triazole	*23.1*[y]	thymine	*33.0*,[ll] *33.2*[pp]
H_2S	14.7,[c] 11.9,[d] **13.8**[i]	$C_2H_5OC_2H_5$	*31.0*,[j] **28.0**[i]	2*H*-tetrazole	*27.6*[y]	uracil	*32.3*,[ll] *31.3*[pp]
NH_3	*29.1*,[j] *28.4*,[cc] 27.0,[d]	$(CH_3OCH_2)_2$	*47.2*,[j] *38.5*,[s] 41.7[ij]	C_2H_4	**12.7**[i]	*c*-GlyGly	*34.2*[mm]
	25.7,[c] ***25.6***,[i] **25.4**[i]	12-crown-4	*60.7*,[s] 61.7[ij]	C_2H_2	**12.3**[i]	*c*-AlaGly	*35.6*[mm]
CH_4	*7.2*,[j] 3.8,[k] **6.1**[i]	H_2CO	23.5,[u] **22.9**[i]	C_6H_6	*28.0*,[oo] **21.8**[i]	*c*-AlaAla	*36.1*[mm]
H_2	3.1,[l] 2.8,[n] 3.1[bb]	CH_3CHO	27.5[u]	C_6H_5OH	**22.2**,[i] **22.3**[i]	GlyGly	*42.9*,[x] *42.3*,[mm] *40.8*,[hh] 46.0[mm]
N_2	*8.0*,[j] 7.2,[l] 7.4,[n] 6.9[bb]	CH_3COCH_3	*33.4*,[j] *33.1*,[r] 31.1,[r] ***30.8***,[i] **30.0**[i]	$HC(NH)NH_2$	32.6[kk]		
				$H_3CC(NH)NH_2$	39.7[aa]	GlyAla	*42.8*[mm]
				$H_2NC(NH)NH_2$	40.1[aa]	AlaGly	*42.5*[mm]
CO	*12.5*,[j] *7.4*,[m] 9.6,[n] 8.4[o]	HCOOH	28.7,[v] **23.7**[i]	glycine	*36.6*,[x] 37.6,[dd] 36.9[ee]	AlaAla	*43.0*[mm]
		CH_3COOCH_3	*31.8*,[r] 29.9,[r] **28.9**[i]	alanine	*38.1*,[ff] 39.6[dd]	GlyGly-OEt	*43.3*[mm]
CO_2	*15.9*,[j] *13.7*,[p] **11.2**[i]	$HCONH_2$	33.1,[w] 39.7,[v] **33.1**[i]	valine	*39.7*[ff]	GlyGly-NH_2	*43.7*[mm]
HCl	*12.2*,[j] 10.6[q]	$HCON(CH_3)_2$	*36.2*,[r] 38.4,[r] **37.1**[i]	cysteine	**40.1**[i]	arabinose	*39.2*,[nn] 37.0[nn]
HF	17.2[q]	CH_3CONH_2	*34.7*,[x] *34.6*,[r] 37.0,[r]	proline	**44.2**[i]	xylose	*39.5*,[nn] 41.5[nn]
LiCl	48.2[q]		**35.6**[i]	serine	**44.9**[i]	glucose	*40.2*,[nn] 40.8[nn]
LiF	51.4[q]	$CH_3CONHCH_3$	*35.7*,[x] *35.9*,[r] 38.6[r]	CH_3Gly	*39.9*,[ff] 44.8[dd]	ribose	*40.7*,[nn] 42.9[nn]
NaCl	57.1[q]	$CH_3CON(CH_3)_2$	*37.5*,[x] 39.5[r]	α-AB[ii]	*39.0*[ff]	galactose	*40.9*,[nn] 43.9[nn]
NaF	61.5[q]	C_2H_5OH	28.0[r]	$GlyCH_3$	40.5[dd]	mannose	*41.4*,[nn] 48.4[nn]
SO_2	*18.9*,[j] **14.7**[i]	*i*-C_3H_7OH	*29.7*,[r] 28.8[r]	$GlyNH_2$	*41.4*[x]	melibiose	*45.9*[nn]
CH_3SH	17.1,[c] **17.5**[i]	*i*-$C_3H_7NH_2$	*31.4*,[r] 30.8[r]	$(H_2NCOCH_2)_2$	*44.5*[x]	gentiobiose	*46.6*[nn]
CH_3OH	*26.6*,[j] 24.5,[c] 26.8,[r] ***24.0***,[i] **24.3**[i]	*c*-C_5H_5N	*31.7*,[r] 31.0[r]	*N*-acetyl-Gly	*39.7*,[gg] *38.0*[hh]	lactose	*47.4*[nn]
		H_2CNH	**27.0**[i]	guanine	*42.1*,[ll] *42.8*[pp]		

[a] ΔH_{298}, ref 5. [b] ΔH_{298}, ref 12. [c] ΔH_{298}, ref 24. [d] Corrected to ΔH_{298}, ref 35. [e] ΔH_{298}, ref 26. [f] ΔH_{298}, ref 37. [g] Corrected to ΔH_{298}, ref 38. [h] ΔH_{298}, ref 39. [i] ΔH_{298}, this work. [j] ΔH_0, ref 9. [k] D_e, ref 41. [l] D_e, ref 42. [m] ΔH_0, ref 13. [n] ΔH_{300}, ref 44. [o] ΔH_0, ref 45. [p] ΔH_{380}, ref 46. [q] D_0, ref 25. [r] ΔH_{298}, ref 17. [s] ΔH_{298}, ref 14. [t] ΔH_{298}, ref 27. [u] ΔH_{298}, ref 47. [v] D_e, ref 48. [w] D_0, ref 49. [x] ΔH_{298}, ref 11. [y] ΔH_{298}, ref 15. [z] ΔH_{298}, ref 34. [aa] ΔH_{298}, ref 57. [b b]D_e, ref 43. [cc] E_{th}, ref 40. [dd] Corrected to ΔH_{298}, ref 59. [ee] ΔH_{298}, ref 32. [ff] ΔH, ref 18. [gg] ΔH, ref 20. [hh] ΔH, ref 22. [ii] α-Aminobutyric acid. [jj] ΔH_{298}, ref 28. [kk] ΔH_{298}, ref 56. [ll] ΔH, ref 19. [mm] ΔH, ref 20. [nn] ΔH, ref 66. [oo] ΔH, ref 10. [pp] ΔH_{298}, ref 64.

Discussion

The results obtained in the present work will be discussed individually in turn and in comparison with previous experimental and theoretical data. A summary of selected data is shown in Table 2. There are three primary methods for experimental determination of Na^+ binding energies. The first of these, HPMS, in principle gives accurate macroscopic thermochemical data. The other two methods involved here are threshold CID and kinetic method experiments. The former gives 0 K bond dissociation energies, which can be corrected to 298 K enthalpies if vibrational frequencies are available from either experiment or ab initio calculations. The kinetic method yields only relative values of sodium binding energies at an imprecisely defined temperature and relies on the inclusion of a reference molecule of accurately known sodium binding energy in the competitive dissociation experiments. Further, it is important that all species in such experiments should be similar in functional group type. As can be seen from the data in Table 2, the HPMS experiments of Castleman and co-workers[6−10] are consistently higher than the sodium binding energies obtained from other experimental and theoretical data.

Quantum chemical methods also provide access to both enthalpies and entropies. There exists an abundant literature on sodium complexes; however, previous experience has shown that reliable results require the use of extended basis sets including diffuse functions. Therefore, only such calculations are included in Table 2 and the discussion that follows. Calculations on sodium complexes of exotic or unstable molecules have also been carried out, often at very high levels of theory; however, such species are not included in the present discussion since they are particularly difficult to generate experimentally.

H_2O. Water is the first molecule for which an experimental sodium binding energy was determined, and an abundant literature has followed. Kebarle's HPMS determination[5] of an enthalpy of binding at 298 K (ΔH_{298}) of 24.0 ± 1.0 kcal·mol^{-1} is in excellent agreement with the more recent threshold CID measurement of ΔH_0 of 22.6 ± 1.8 kcal·mol^{-1} by Armentrout et al.,[12] with the appropriate thermal correction of +0.8 kcal·mol^{-1}. A high-temperature equilibrium measurement of clustering in flames by Burdett and Hayhurst[34] also yields a recommended value of 24.1 ± 1.4 kcal·mol^{-1}. Earlier threshold CID experiments by Marinelli and Squires[40] led to a smaller value of 21.0 kcal·mol^{-1}. Several recent calculations[24,26,35−39] using high-level wave functions yield binding energies (either in the form of ΔH_{298} or ΔH_0) which lie well within the uncertainties assigned to the experimental data (see Table 2). Since so many values are available for $Na(H_2O)^+$, where this has not been done in the original reference, the data are corrected to ΔH_{298} values using the thermal corrections determined in the present work. Our own value of 22.1 kcal·mol^{-1} for ΔH_{298} is among the smallest of these.

H_2S. There are no experimental data available for Na^+ binding to H_2S. Recent calculations give ΔH_{298} values of 14.7[24] and 11.9 kcal·mol^{-1}.[35,36] Our value of 13.8 kcal·mol^{-1} is in good agreement with the G2 result of Remko and Sarissky.[24]

NH_3. The experimental value of Castleman et al.[6] of 29.1 kcal·mol^{-1} is not in good agreement with the values of 27.0 and 25.7 kcal·mol^{-1} calculated by Magnusson[35] and Remko and Sarissky,[24] respectively. A slightly lower experimental value of 28.4 kcal·mol^{-1} has been obtained by Marinelli and Squires[40] from threshold CID experiments. HPMS experiments were

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carried out for Na^+ clustering onto NH_3, which gave a value of 25.6 kcal·mol^{-1}. In addition, calculations in the present work yield 25.4 kcal·mol^{-1}. The excellent agreement between the present experimental value and the best calculated values gives confidence that the binding energy of ammonia to Na^+ is significantly lower than previously accepted.

CH_4. There exist both experimental[7,9] ($\Delta H_{298} = 7.2$ kcal·mol^{-1}) and calculated[41] ($D_e = 3.8$ kcal·mol^{-1}) binding energies of Na^+ to methane. The effect of correcting D_e to ΔH_{298} is expected to be almost negligible for small molecules. Thus, the existing values are not in good agreement. Our own calculations examined the possibilities of structures in which the sodium interacts with either one, two, or three hydrogen atoms. As in the previous calculations, the last structure was found to be the most stable, by 0.8 kcal·mol^{-1}. The corresponding ΔH_{298} of 6.1 kcal·mol^{-1} is in good agreement with the experimental value.

H_2. Three calculations predict a very small binding energy of Na^+ to dihydrogen: $D_e = 3.1$,[42] 3.1[43] and $\Delta H_{300} = 2.8$ kcal·mol^{-1},[44] with a T-shaped geometry.

N_2. Experimental[7,9] ($\Delta H_{298} = 8.0$ kcal·mol^{-1}) and calculated ($D_e = 7.2$,[42] 6.9[43] and $\Delta H_{300} = 7.4$[44] kcal·mol^{-1}) binding energies of Na^+ to dinitrogen are in good agreement. Calculations show that the complex is linear.

CO. The two experimental values for sodium binding to CO of 12.5[7,9] and 7.4 ± 1.9 kcal·mol^{-1} [13] are in obvious disagreement. Previous computations yield binding energies in good agreement with the latter: $\Delta H_0 = 8.4$[45] and $\Delta H_{300} = 9.6$ kcal·mol^{-1}.[44] The most favorable interaction of Na^+ is with the carbon end of the molecule.

CO_2. There are two experimental values for the Na^+-CO_2 binding energy. The HPMS measurement[7,9] of 15.9 kcal·mol^{-1} and flowing afterglow measurement[46] of 13.7 kcal·mol^{-1} are significantly different, and, in fact, both seem to be larger than would be expected given the sodium binding energies for other small molecules. Since no computational values were available for comparison, ab initio calculations were undertaken. A careful exploration of the potential energy surface generated a single minimum, in which Na^+ binds CO_2 in a linear manner with a Na−O distance of 2.27 Å. The calculated binding enthalpy is 11.2 kcal·mol^{-1}, significantly smaller than the flowing afterglow value.

HCl and Other Inorganic Halides. The sodium affinities (D_0) of the fluoride and chloride of hydrogen, lithium, and sodium have been computed at the MP2(full)/6-31+G* level by Schleyer and co-workers.[25] The value obtained for HCl of 10.6 kcal·mol^{-1} is in reasonable agreement with the sole experimental measurement[7,9] of 12.2 kcal·mol^{-1}. It is interesting to note that calculations at the same level find that the sodium binding energy of HF (17.2 kcal·mol^{-1}) is greater than that of HCl, which is a natural consequence of the electrostatic binding in these adducts. In contrast, the proton affinity of HCl is some 20 kcal·mol^{-1} greater than that of HF. The electrostatic nature of the bonding is manifested even more strikingly in the sodium binding to alkali halides, where a maximum value of 61.5 kcal·mol^{-1} is found for $NaF-Na^+$. It is worth noting that Schleyer and co-workers showed that inclusion of the sodium core electrons in the correlation treatment is essential for obtaining a reliable affinity for HF, since frozen core computations lead to a large negative affinity. This effect has been described in detail by Petrie,[23] who obtained good agreement with the previous result at a higher level of theory.

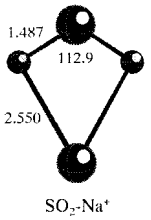

Figure 3. Optimized structure of SO_2-Na^+ at the MP2/6-31G* level.

SO_2. The available experimental value[7,9] of 18.9 kcal·mol^{-1} for SO_2 is significantly larger than the value of ΔH_{298} computed in the present work of 14.7 kcal·mol^{-1}. As discussed below, it seems likely that the latter value is more accurate. The calculated structure of the sodium complex of SO_2 (see Figure 3) illustrates nicely the primarily electrostatic nature of the bonding. The sodium is aligned with the SO_2 dipole and bisects the OSO angle, which is contracted to 113° compared to 120° in the isolated molecule. This contraction increases the dipole moment of the SO_2 moiety, resulting in a more favorable interaction. Significantly, the S−O bond distances remain essentially unchanged at 1.48 Å.

CH_3SH. The recent G2 computations by Remko and Sarissky[24] and the present ones yield ΔH_{298} values in excellent agreement (17.1 and 17.5 kcal·mol^{-1}, respectively). No experimental data are available.

CH_3OH. A value of 26.6 kcal·mol^{-1} for the binding enthalpy of Na^+ to methanol is available from the HPMS experiments of Castleman and co-workers.[9] A slightly lower computed G2 value of 24.5 kcal·mol^{-1} (ΔH_{298}) has recently been obtained by Remko and Sarissky.[24] Feng and Gronert[17] have also carried out calculations at the MP2/6-31+G* level and obtained a 298 K sodium affinity of 26.8 kcal·mol^{-1}. It is likely that the difference is due to the neglect of BSSE in the latter calculations. HPMS experiments have also been carried out in the present work, which yield a value of 24.0 kcal·mol^{-1}, in excellent agreement with our own computed value of 24.3 kcal·mol^{-1} as well as that of Remko and Sarissky.

CH_3NH_2. A value of 32.1 kcal·mol^{-1} for the binding enthalpy of Na^+ to methylamine is available from the HPMS experiments of Castleman and co-workers.[9] A significantly lower computed G2 value of 27.0 kcal·mol^{-1} (ΔH_{298}) has recently been obtained by Remko and Sarissky.[24] HPMS experiments have also been carried out in the present work, which yield a value of 26.3 kcal·mol^{-1}, in excellent agreement with our own computed value of 26.5 kcal·mol^{-1} as well as that of Remko and Sarissky.

CH_3CN. The only experimental value available for the binding enthalpy of Na^+ to acetonitrile is that of Feng and Gronert,[17] 32.5 kcal·mol^{-1}, based on kinetic method experiments. Their scale is anchored by the Na^+ affinity of $CH_3CON(CH_3)_2$ (see below), which has been determined by Kebarle and co-workers on the basis of threshold CID measurements.[11] In the same work,[17] they computed a value of 30.6 kcal·mol^{-1} at the MP2/6-31+G* level, which is in excellent agreement with the value of 30.3 kcal·mol^{-1} computed in this work.

Ethers. Armentrout and co-workers[14] have carried out threshold CID measurements for the Na^+ complex of dimethyl ether and obtained a ΔH_{298} of 22.2 kcal·mol^{-1}. Feller and co-

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workers[27] have carried out MP2/6-31+G* calculations, including BSSE and thermal corrections, to obtain a value of 25.9 kcal·mol^{-1}. The value obtained in this work of 23.6 kcal·mol^{-1} lies between these two. For diethyl ether, the only experimental sodium binding enthalpy value is that from the HPMS experiments of Castleman and co-workers[9] of 31.0 kcal·mol^{-1}. The present calculations give a value of 28.0 kcal·mol^{-1} for the same quantity. Polyethers have also been investigated both computationally and experimentally. The HPMS value for dimethoxyethane[7,9] of 47.2 kcal·mol^{-1} is much larger than the threshold CID result[14] of 38.5 kcal·mol^{-1} and the calculated value of Feller and co-workers[28] of 41.7 kcal·mol^{-1}. In addition, the sodium ion affinity of 12-crown-4 has been determined to be 60.7 and 61.7 kcal·mol^{-1} by threshold CID experiments[14] and ab initio computations,[28] respectively.

Aldehydes and Ketones. There are no experimental data available for CH_2O. Accurate calculations by Remko[47] yield a ΔH_{298} of 23.5 kcal·mol^{-1}, while the present calculations give 22.9 kcal·mol^{-1}. In the same work, Remko reported a sodium affinity of CH_3CHO of 27.5 kcal·mol^{-1}. Castleman and co-workers[9] have carried out HPMS experiments for $(CH_3)_2CO$ and obtained a sodium binding enthalpy of 33.4 kcal·mol^{-1}. The kinetic method experiments of Feng and Gronert[17] lead to a value of 33.1 kcal·mol^{-1}, while their ab inito calculations give 31.1 kcal·mol^{-1}. Results from the calculations in the present work, 30.0 kcal·mol^{-1}, are in good agreement with the latter. In addition, our own HPMS measurements gave a value of 30.8 kcal·mol^{-1}, with slightly larger error limits than usual due to experimental difficulties with this system.

Acids and Esters. The only literature value, either experimental or computational, for the sodium affinity of formic acid is 28.7 kcal·mol^{-1}, which comes from MP2/6-31G*//HF/6-31G* calculations of Remko.[48] It is significantly larger than our own computed value of 23.7 kcal·mol^{-1}. It is likely that the use of a medium-sized basis set in the former work leads to an overestimation of the binding energy. The sodium ion affinity of methyl acetate has been determined by Feng and Gronert[17] to be 31.8 kcal·mol^{-1} by using the kinetic method and 29.9 kcal·mol^{-1} by ab initio calculations. The value of 27.7 kcal·mol^{-1} calculated in the present work is lower than that of Gronert, consistent with observations described above for other systems.

Amides. For formamide, only calculated values exist. A G2(MP2) D_0 value of 33.1 kcal·mol^{-1} has been obtained by Tortajada et al.,[49] in good agreement with our own calculation of ΔH_{298} of 33.1 kcal·mol^{-1} (the thermal correction leads to an increase of 0.6 kcal·mol^{-1} in the D_0 value). A somewhat overestimated value of 39.7 kcal·mol^{-1} has been obtained by Remko[48] at a lower level of theory. Feng and Gronert[17] have obtained a sodium binding enthalpy for *N*,*N*-dimethylformamide of 36.2 kcal·mol^{-1} from kinetic method experiments, as well as 38.4 kcal·mol^{-1} from ab inito calculations. Our own computations lead to an intermediate value of 37.1 kcal·mol^{-1}. For acetamide, threshold CID experiments by Kebarle and co-workers[11] lead to a sodium affinity of 34.7 kcal·mol^{-1}. This is in exact agreement with the value obtained by Feng and Gronert,[17] which is consistent with the fact that these authors anchored their relative scale with the absolute threshold CID value for *N*,*N*-dimethylacetamide.[11] It is in good agreement with our computed value of 35.6 kcal·mol^{-1} and in slightly less good agreement with their own calculated value of 37.0 kcal·mol^{-1}. Kebarle and co-workers[11] have determined CID thresholds for *N*-methyl- and *N*,*N*-dimethylacetamide and recommend values of 35.7 and 37.5 kcal·mol^{-1}, although, as noted by the authors, the choice of values is somewhat arbitrary, depending upon the choice of vibrational frequencies used to make the kinetic shift corrections to the experimental data. The affinity differences for the three acetamides considered by Feng and Gronert[17] are in nearly exact agreement with those recommended by Kebarle.[11] Their calculations give slightly larger values of 38.6 and 39.5 kcal·mol^{-1}, respectively, which seems to be a general trend for their calculations on amides.

Alcohols and Amines. Aside from the rather extensive studies of methanol and methylamine described above, there has been relatively little investigation of sodium ion affinities of alcohols and amines. Feng and Gronert[17] have included isopropyl alcohol, isopropylamine, and pyridine in their kinetic method scale and obtained values of 29.7, 31.4, and 31.7 kcal·mol^{-1}, respectively. It should be noted, however, that an important caveat for kinetic method measurements is that all molecules considered should be of the same functional group type, and this scale has been anchored to measurements for amides rather than alcohols and amines. The MP2 calculations carried out in conjunction with their experiments give values of 28.8, 30.8, and 31.0 kcal·mol^{-1} for isopropyl alcohol, isopropylamine, and pyridine, respectively. In addition, calculations for methanol and ethanol resulted in 26.8 and 28.0 kcal·mol^{-1}, respectively. Based on comparison with the experimental data and ab initio calculations of the present work, these calculated values seem to give overestimations of sodium affinities of 1−3 kcal·mol^{-1}.

Imines and Azoles. The sodium ion affinity of methanimine (CH_2NH) has been computed as a simple model for the binding of Na^+ to azoles in general. The value of 27.0 kcal·mol^{-1} is very close to that of methylamine, consistent with the relative values of formaldehyde and methanol. Calculations were also carried out on the sodium affinity of imidazole. The ΔH_{298} value of 34.9 kcal·mol^{-1} is in good agreement with a recent threshold CID measurement by Rodgers et al.[15] of 33.7 kcal·mol^{-1}. Sodium affinities for a series of triazoles and tetrazoles were also determined in that work (see Table 2). The highest affinity for the four azoles studied was that for imidazole. This is in agreement with an earlier extensive computational study of cationized azoles carried out at the HF/6-31G*//HF/3-21G$^{(*)}$ level.[50] This work showed that the most stable attachment of Na^+ and K^+ to an azole corresponds, whenever possible, to a bridged structure. This is at variance with H^+, Li^+, and Al^+ complexes, in which the cation is always bound to a single nitrogen atom. The limited level of wave function used leads to generally overestimated affinities, but some values are in good agreement with the recent threshold CID results.

C_2H_4 and C_2H_2. Ethylene and acetylene were chosen as model compounds to investigate the interaction of Na^+ with a π bond. There appear to be no previous calculations for either complex; the present work shows that the sodium ion sits at the middle of the C−C bond, 2.66 and 2.63 Å above the plane of the molecule, respectively. The ΔH_{298} bond energies are nearly identical at 12.7 and 12.3 kcal·mol^{-1}, respectively.

C_6H_6 and Other Aromatics. An experimental binding enthalpy of 28.0 kcal·mol^{-1} has been determined by Castleman and co-workers[10] using HPMS measurements. Ab initio calculations by Mecozzi et al.[51] at the HF/6-31G** level and by Miklis

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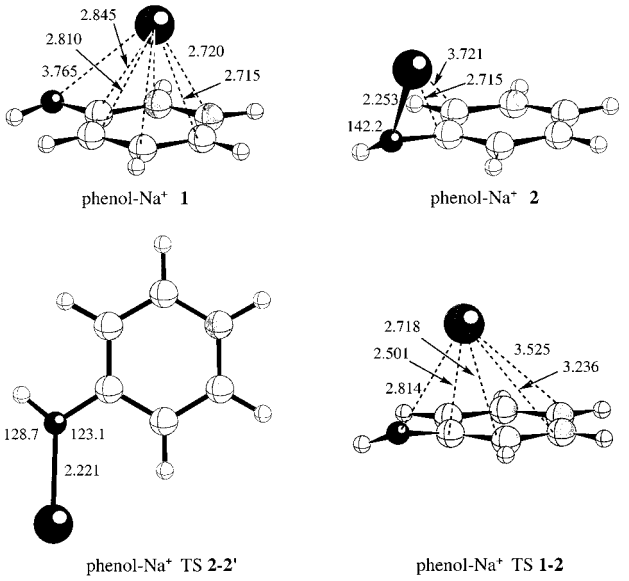

Figure 4. Optimized structures of stationary points on the phenol-Na^+ potential energy surface at the MP2/6-31G* level.

et al.[52] at the B3LYP/6-31G* level give 27.1 and 28.4 kcal·mol^{-1}, respectively, in excellent agreement with the experimental result. However, comparison with the experimental binding enthalpies of Li^+ and K^+ with benzene (37[2] and 18 kcal·mol^{-1},[53] respectively) suggests that the above values for Na^+ might be too large, since its binding enthalpies to a number of other organic molecules fall significantly closer to those for K^+ than for Li^+. Therefore, computations were carried out for the Na^+/benzene complex at the level defined in this work, which, as described above, has consistently proven to accurately reproduce the most reliable experimental results. These calculations yield a significantly lower value of ΔH_{298} of 21.8 kcal·mol^{-1}. An analysis of the details of the calculation shows that the D_0 value at the MP2/6-31G* level of 29.3 kcal mol^{-1} is considerably reduced to 21.4 kcal·mol^{-1} when an extended basis set is used and the BSSE is corrected for. The trend of overestimating binding enthalpies when using medium-sized basis sets is general; however, it is with the benzene complex that the effect is most dramatic.

Dougherty and co-workers[51] have extended their calculations to a large number of aromatic systems. Both π complexes and isomers in which the sodium ion is bound to a heteroatom were considered. With the exception of halogen-substituted benzenes, the species with Na^+ bound to the heteroatom was found to be more stable than the π complex; however, both types of structure represented true minima on the potential energy surface. In contrast, for pyridine and imidazole, no stable π complex was found to exist. Although the binding energies determined are probably consistently overestimated for the reasons described above, these authors clearly established the importance of the charge−quadrupole interaction in Na^+ π complexes of aromatic molecules.

To obtain detailed information about the structural isomers of such aromatic complexes, calculations were carried out on sodiated phenol. There exist two energy minima on the potential surface. The first (structure **1**, see Figure 4) involves binding of Na^+ above the ring, slightly displaced from the approximate C_6 axis away from the oxygen. Isomer **2** has the sodium cation attached to the oxygen, with the OH group rotated out of the aromatic plane. Attachment of Na^+ to the oxygen in a planar structure is a transition state for the interconversion of **2** and its mirror image **2′** with respect to the ring plane (**TS 2-2′**). The two minima **1** and **2** are connected by a transition state (**TS 1-2**, see Figure 4), which closely resembles a simple translation of the sodium ion between the vicinity of the oxygen atom and the ring centroid. Thus, there is a competition between the charge−quadrupole interaction of Na^+ with the aromatic ring (as in **1**) and the charge−dipole interaction with the polar alcohol group (as in **2**). At the MP2/6-311+G(2d,2p)//MP2/6-31G* level (without BSSE corrections), the relative energies of **1**, **2**, and **3** are 0.0, 0.6, and 2.2 kcal·mol^{-1}, respectively. The computed ΔH_{298} of complexation for structures **1** and **2** are 22.2 and 22.3 kcal·mol^{-1}, respectively. Since these two structures lie so close in complexation enthalpy, it is necessary to evaluate their respective complexation entropies in order to determine which lies lower in free energy and will, therefore, dominate experimentally. It turns out that structure **1** is significant less favorable entropically (ΔS(**1**) of 25.9 vs ΔS(**2**) of 23.0 cal·mol^{-1}·K^{-1}). This leads to ΔG_{298} values of 14.5 and 15.4 kcal·mol^{-1} for **1** and **2**, respectively. If there is an equilibrium mixture of **1** and **2**, this corresponds to 82% of **2** and 18% of **1** at 298 K. As the temperature increases, the relative amount of **1** would also increase. Such an equilibrium mixture is entirely feasible since the transition state **TS 1-2** is found to lie only ~3 kcal·mol^{-1} above the stable minima. The enthalpies of complexation found here are significantly smaller than those obtained by Dougherty and co-workers[51a] (26.9 and 27.4 kcal·mol^{-1} for structures corresponding to **1** and **2**, respectively).

The largest aromatics considered by Dougherty and co-workers[51] are naphthalene and azulene. Sodium complexes of even larger aromatics have also been computed. For instance, Sygula and Rabideau[54] compared the binding of Na^+ to the concave and convex faces of triindenotriphenylene at the HF/6-31G*//HF/3-21G level and found a slight preference for the concave face of 1.2 kcal·mol^{-1}. Calculations have also been reported on endohedral and exohedral Na^+ complexes of the $C_{36}H_{36}$ spheriphane[55a] and of C_{60}.[55b]

Imidines. The interactions of several cations with imidines $XC(NH)NH_2$ have been investigated as prototypical bidentate bases of biological importance by Tortajada, Yanez, and co-workers[56,57] using high-level ab initio calculations. The interaction beween Na^+ and formamidine (X = H) has been computed at the G2(MP2) level, leading to a ΔH_{298} of 32.6 kcal·mol^{-1}. Interactions with acetamidine (X = CH_3) and guanidine (X = NH_2), as well as with NH_3, have been investigated at the B3LYP level with an extended G2-type basis set. While the value for NH_3 appears to be slightly overestimated, it is clear that the interactions with the imidines are very strong (298 K binding energies corrected to ΔH_{298} values of 39.7 and 40.1 kcal·mol^{-1}, respectively). In all cases, the sodium ion is bound to the imine nitrogen, as in CH_2NH-Na^+, and the increase of the binding energy follows that of the dipole moment and the polarizability.

Glycine. The only experimental absolute value for sodium binding to any amino acid comes from the threshold CID measurement of Klassen et al.[11] for glycine (Gly). The recommended ΔH_{298} value is 36.6 kcal·mol^{-1}. However, as with all

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threshold CID measurements, the data must be corrected to 298 K. This relies on the use of estimated vibrational frequencies which, in the case of larger, flexible molecules, leads to an increased uncertainty due to the difficulty in accurately assigning values for the low-frequency modes. The authors assigned error bars of ±2.3 kcal·mol^{-1} based on the uncertainty of the fitting procedure alone. Thus, ±3 kcal·mol^{-1} might be considered to be a typical total uncertainty for the ΔH_{298} value. Early computations by Bouchonnet et al.[58] established the most stable structure for the Gly-Na^+ complex and yielded a D_e value of 45 kcal·mol^{-1} at the MP2/6-31G*//HF/3-21G level. A more extensive survey of the potential energy surface, together with the use of a larger basis set, led Jensen[59] to a D_e value of 38.5 kcal·mol^{-1}, which corresponds to a ΔH_{298} of 37.6 kcal·mol^{-1}. Slightly refined computations by Hoyau et al.[32] give a very similar ΔH_{298} of 36.9[60] kcal·mol^{-1}. This series of computations highlights the important role of diffuse functions in deriving accurate thermochemical values. For Gly, this leads to a reduction of binding energy of ca. 10 kcal·mol^{-1} from the MP2/6-31G* result. Based on this body of results, a sodium binding energy of glycine of 37 ± 2 kcal·mol^{-1} may be recommended. However, given the excellent agreement between experiment and theory, the experimental value of 36.6 kcal·mol^{-1} has been used to anchor relative values for other compounds based on the kinetic method (see below).

Other Amino Acids. Using the kinetic method, Bojesen et al.[18] have obtained sodium ion affinities for alanine (Ala) and valine (Val) which are greater than that for Gly by 1.5 and 3.1 kcal·mol^{-1}, respectively. Using 36.6 kcal·mol^{-1} as the reference affinity of Gly, this leads to 38.1 and 39.7 kcal·mol^{-1} for Ala and Val, respectively. The former is in excellent agreement with the computed difference of 2.0 kcal·mol^{-1} obtained by Jensen[59] for the Gly-Ala pair.

Calculations were also carried out in the present work for three other amino acids: serine (Ser), cysteine (Cys), and proline (Pro). In the first two cases, the side chains have a basic group (CH_2OH and CH_2SH, respectively) which can fold toward the sodium ion, leading to tridentate binding rather than bidentate as with Gly. This is not possible with Pro, which is therefore expected to bind to sodium in a manner similar to that of Gly. The low-energy conformations of Ser and Cys have been discussed in detail previously by Gronert and O'Hair,[61] while those of Pro have been studied by Hoyau and Ohanessian.[62] The low-energy isomers of the sodium complexes were based on similar studies for Cu^+ complexes.[30,62]

Six isomers were determined at the HF/6-31G* level for Ser-Na^+ (see Figure 5) and Cys-Na^+ (see Figure 6), and four for Pro-Na^+ (see Figure 7). Their relative energies at the HF/6-31G* and MP2/6-31G*//HF/6-31G* levels are reported in Tables 3−5. For both Ser-Na^+ and Cys-Na^+, the lowest energy isomer is **1**, which involves tridentate binding between nitrogen, the carbonyl oxygen, and the side-chain heteroatom. The second most stable isomer is **5**, which involves interaction of Na^+ to the carboxylate end of zwitterionic serine or cysteine, but with different patterns of internal hydrogen bonding within the amino acid. The energy of **5** relative to **1** is 5.9 and 2.7 kcal·mol^{-1} for Ser-Na^+ and Cys-Na^+, respectively. Because of the small energy difference in the latter case, **5** was also computed at the MP2/6-311+G(2d,2p)//MP2/6-31G* level, as was **1** (see below). The energy differences at this level were computed to be 2.4 and 1.9 kcal·mol^{-1}, respectively, depending on whether BSSE corrections were included or not. Therefore, the energy ordering in Tables 3−5 essentially carries over to higher levels of calculation. Other isomers, which involve either bidentate or tridentate binding to sodium, are higher in energy. For instance, **3**, which corresponds to the interaction of Na^+ to nitrogen, the hydroxy oxygen, and the side-chain heteroatom, is found to lie 6.0 and 6.5 kcal·mol^{-1} higher in energy than **1** for Ser-Na^+ and Cys-Na^+, respectively. This stability difference between Na^+ attachment to carbonyl and hydroxy oxygens is reminiscent of results previously obtained for glycine isomers.[32] Comparison with analogous copper complexes shows some significant differences. In particular, tridentate complexation is found to be generally more favorable in copper than in sodium complexes, with a stronger interaction of copper with the amino site. The copper ion affinities[30] are all significantly larger than their sodium analogues. This is due to the contribution of charge transfer in copper binding, which is much smaller with sodium.

In contrast, the stability order of the low-energy isomers of the sodium complex of proline is notably different (see Table 5). The most stable isomer involves attachment of the sodium ion to the carboxylate moiety of zwitterionic proline, **6**. This isomer is more stable than **1** by 7.8 kcal·mol^{-1} at the MP2/6-31G*//HF/6-31G* level, and refined energetics at the MP2/6-

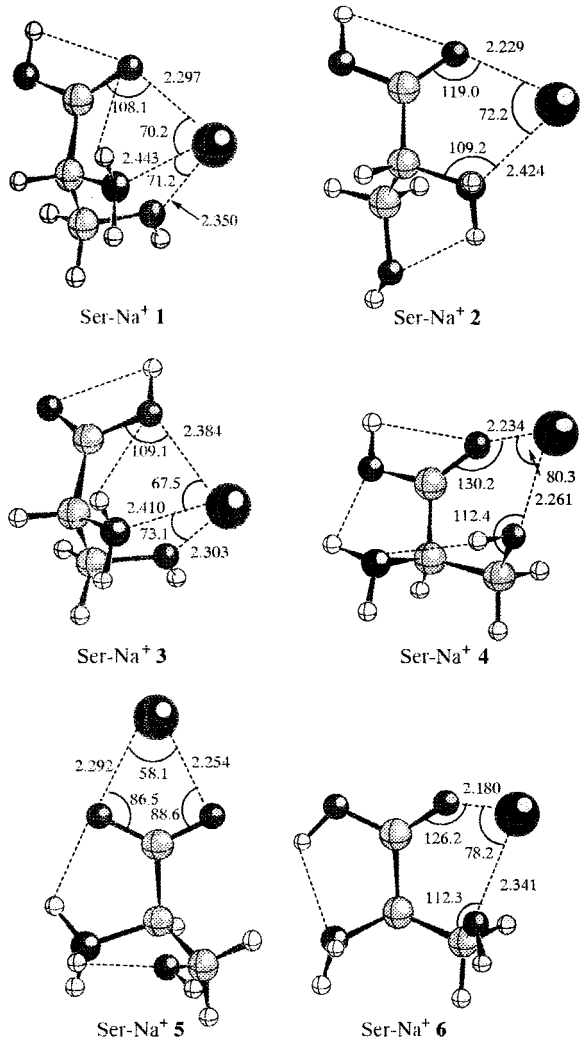

Figure 5. Optimized structures of the low-energy isomers of serine-Na^+ at the HF/6-31G* level.

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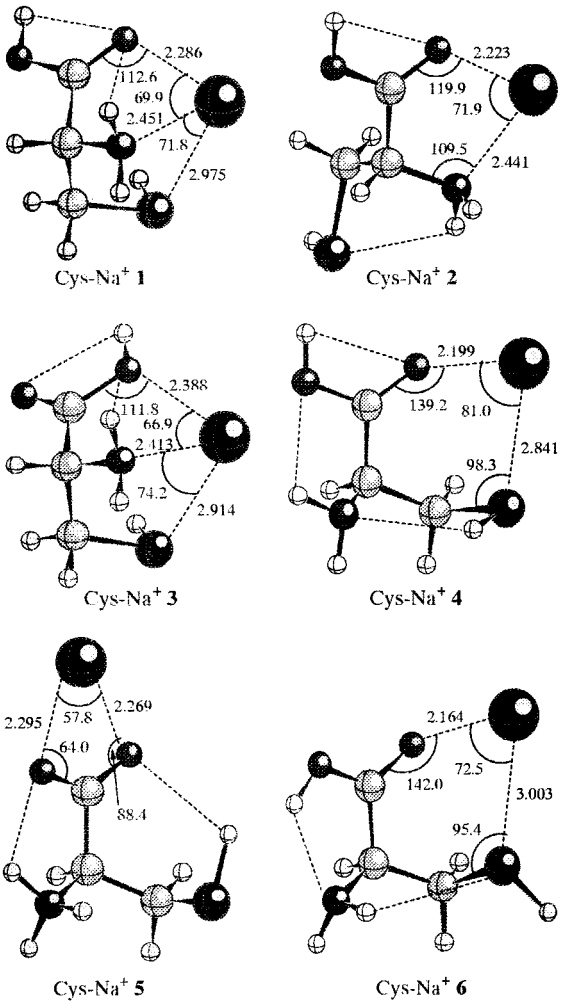

Figure 6. Optimized structures of the low-energy isomers of cysteine-Na^+ at the HF/6-31G* level.

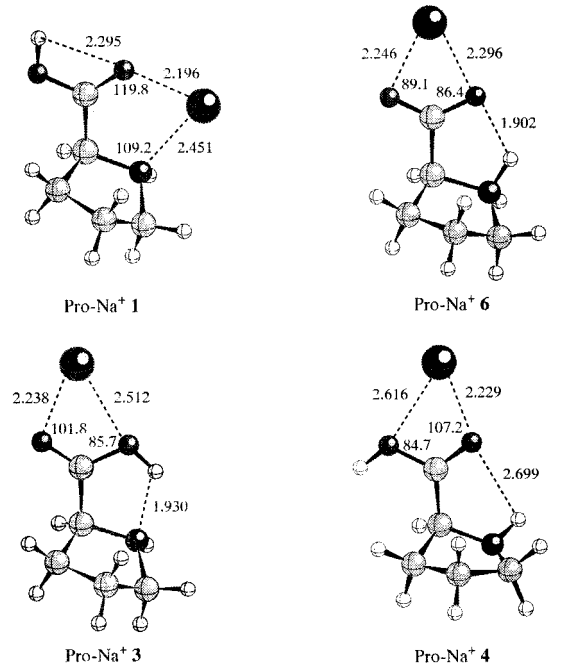

Figure 7. Optimized structures of the low-energy isomers of proline-Na^+ at the HF/6-31G* level.

311+G(2d,2p)//MP2/6-31G* level maintain this relative order, with **6** being favored by 6.7 kcal·mol^{-1}. This inverse stability ordering, relative to the Gly-Na^+ complex, is driven by the fact that, in the case of the proline complex, the zwitterion involves protonation of a secondary amine site, whereas for glycine a primary ammonium ion is formed. Other isomers, **3** and **4**, lie significantly higher in energy. This is the first demonstration of greater stability of a zwitterionic (salt bridge) structure for a cationized amino acid.

Table 3. Relative Energies (D_e) of Serine-Na^+ Isomers (kcal·mol^{-1})

isomer	HF/6-31G*	MP2/6-31G*//HF/6-31G*
Ser-Na^+ **1**	0.0	0.0
Ser-Na^+ **2**	8.9	10.6
Ser-Na^+ **3**	7.6	6.0
Ser-Na^+ **4**	8.0	9.7
Ser-Na^+ **5**	10.1	5.9
Ser-Na^+ **6**	11.2	12.1

Table 4. Relative Energies (D_e) of Cysteine-Na^+ Isomers (kcal·mol^{-1})

isomer	HF/6-31G*	MP2/6-31G*//HF/6-31G*
Cys-Na^+ **1**	0.0	0.0
Cys-Na^+ **2**	5.6	7.6
Cys-Na^+ **3**	8.6	6.5
Cys-Na^+ **4**	9.4	11.8
Cys-Na^+ **5**	7.1	2.7
Cys-Na^+ **6**	9.0	10.0

Table 5. Relative Energies (D_e) of Proline-Na^+ Isomers (kcal·mol^{-1})

isomer	HF/6-31G*	MP2/6-31G*//HF/6-31G*
Pro-Na^+ **1**	2.5	7.8
Pro-Na^+ **3**	7.0	10.7
Pro-Na^+ **4**	19.3	39.2
Pro-Na^+ **6**	0.0	0.0

To derive accurate thermodynamic parameters, the geometry of the most stable isomer of each complex was reoptimized at the MP2/6-31G* level. There is no chemically significant difference between HF and MP2 structures. The largest is for the Na−S distance in Cys-Na^+, which was found to be reduced by 0.1 Å when electron correlation was included. Single-point energies were obtained at the MP2/6-311+G(2d,2p) level and further corrected for BSSE. Using the HF/6-31G* frequencies, the sodium complexation enthalpies were finally obtained as ΔH_{298} values of 44.9, 40.1, and 44.2 kcal·mol^{-1} for Ser, Cys, and Pro, respectively. The values for Ser and Pro are close enough that their ordering cannot be conclusively determined from these results. The affinity ordering found here, Gly < Cys < Pro < Ser, is modified to Gly < Cys < Ser < Pro when free energies of complexation are considered. Since it is this quantity which is probed in the kinetic method experiments of Bojesen et al.,[18] the experimental and theoretical results are consistent.

The ordering is different from that found for Cu^+ complexes: Gly < Ser < Pro < Cys. This reversal between the sodium and copper ion affinities of Ser and Cys is the equivalent of that for H_2O and H_2S.[30] For these simple models of the side chains of Ser and Cys, reversal has been explained in terms of the dominance of the electrostatic interaction with the dipole moment of H_2O for Na^+, while charge transfer makes the interaction between H_2S and Cu^+ larger than that with H_2O.[31] Calculations show that all four amino acids bind Cu^+ in a non-zwitterionic form. Thus, kinetic method experiments are less likely to involve any dissociation barriers, and the true thermodynamic stability order should be revealed. Consistent with this, excellent agreement has been found between the

kinetic method experiments of Cerda and Wesdemiotis[63] and calculations with the same method as described here.[30,62]

The kinetic method study of Bojesen et al.[18] established an affinity ordering of all other amino acids, although no quantitative ladder was determined.

Amino Acid Derivatives. Bojesen's kinetic method scale of sodium ion affinity[18] also included sarcosine (*N*-methylglycine), for which a corrected value of 39.9 kcal·mol^{-1} can be assigned. This does not appear to be in very good agreement with the computed D_e value of Jensen[59] of 44.8 kcal·mol^{-1}, in contrast to the good agreement found for alanine. Bojesen has also obtained a sodium ion affinity of α-aminobutyric acid of 39.0 kcal mol^{-1}, and Jensen has computed a D_e of 40.5 kcal·mol^{-1} for the sodium complex of the methyl ester of glycine. Kebarle[11] has also obtained threshold CID Na^+ affinities for succinamide and glycinamide of 44.5 and 41.4 kcal·mol^{-1}, respectively. However, the thermal corrections for these measurements are potentially very large, leading to significant uncertainties for these values (≥5 kcal·mol^{-1} for succinamide).

Nucleobases. Cerda and Wesdemiotis[19] used their modified kinetic method to obtain the Na^+ affinities of the five bases present in nucleic acids. If the affinity for the reference for their scale, glycine, is corrected to the Kebarle[11] value, the sodium ion affinities obtained are, in kcal·mol^{-1}, 42.1 for guanine, 40.9 for cytosine, 39.7 for adenine, 33.0 for thymine, and 32.3 for uracil. From the evaluation of differences in complexation entropies, it was concluded that exocyclic amino groups are involved in cation binding, either directly (for adenine) or through resonance effects (for guanine and cytosine). Thymine and uracil, which lack such substituents, are slightly more weakly bound. Threshold CID results were reported in preliminary form by Rodgers and Armentrout.[64] Good agreement was obtained with the above results for the affinities of guanine (42.8 kcal·mol^{-1}), thymine (33.2 kcal·mol^{-1}), and uracil (31.3 kcal·mol^{-1}), while a significantly smaller affinity was determined for adenine (31.3 kcal·mol^{-1}). A computational study of the binding of several atomic ions to guanine and adenine has also been reported.[65] Complexation was shown to follow approximately the direction of the dipole moment in both cases. Compared to both sets of experiments, the affinity of guanine appears to be largely overestimated, while the opposite holds for that of adenine. Restriction to planar complexation may explain the latter effect.

Dipeptides. For the simplest dipeptide, glycylglycine (GlyGly), there have been three independent determinations of the sodium ion affinity. Klassen et al.[11] have proposed a value of 42.9 kcal·mol^{-1} based on threshold CID determinations. However, the uncertainty in this value is rather large, due to the kinetic shift correction, which depends strongly on the number and magnitude of low-frequency modes of the complex. As noted above for succinamide, molecules of this size may have an uncertainty as large as ±5 kcal·mol^{-1}. Cerda et al.[20] report a sodium ion affinity of GlyGly of 42.3 kcal·mol^{-1} based on kinetic method experiments. This is in good agreement with the threshold CID value. However, if this kinetic method scale is anchored to Kebarle's affinity of glycine[11] as noted above, then this value is reduced to 40.9 kcal·mol^{-1}. It should also be noted that the reference bases used are nucleobases, which do not necessarily bind Na^+ in the same way as dipeptides and can lead to increased uncertainty. These authors also reported a computed affinity of 46.0 kcal·mol^{-1}.[60] Based on all of these results, the best estimate of the affinity of GlyGly is 43 ± 5 kcal·mol^{-1}. Kinetic method measurements were also made for the linear and cyclic dipeptides based on Gly and Ala and for some derivatives (see Table 2).[20]

There have been two kinetic method measurements of the affinity of *N*-acetylglycine as a model for dipeptide binding. Cerda et al.[20] obtain a value of 39.7 kcal·mol^{-1} if the affinity for the reference of their scale, glycine, is corrected to the Kebarle[11] value. Feng et al.[22] also obtained a value of 37.7 kcal·mol^{-1} by using the Kebarle reference value of *N*,*N*-dimethylacetamide for their scale and assuming no significant entropy change. These authors have also examined the affinities of 12 other *N*-acetyl amino acids. Based on recent computations of the low-energy isomers of the sodium complex of diglycine,[20] it may be expected that these *N*-acetyl derivatives bind the ion through the two carbonyl oxygens, with some additional contributions due to interaction with the side chains. The reported ΔG_{298} difference of only 6.6 kcal·mol^{-1} between the largest (*N*-acetyl-Trp) and smallest (*N*-acetyl-Gly) values may correspond to greater ΔH_{298} values when the unfavorable entropic effect of such side-chain binding is accounted for. Feng et al.[22] also studied a series of *N*-glycyl amino acids and obtained sodium binding free energies 3−4 kcal·mol^{-1} larger than those of the corresponding *N*-acetyl derivatives. This is attributable to an additional interaction with the N-terminal amino group. Dipeptides were also studied by Cerda and Wesdemiotis,[21] who obtained an ordering of sodium ion affinities different from that obtained by Feng et al.[22] This is presumably due to the attempt to take account of entropic effects.

Sugars. Cerda and Wesdemiotis[66] have used their modified kinetic method to investigate Na^+ binding to the pentoses arabinose (Ara), xylose (Xyl), and ribose (Rib), the hexoses glucose (Glc), galactose (Gal), and mannose (Man), and the disaccharides melibiose (Mel), gentibiose (Gen), and lactose (Lac). The reference bases were either nucleobases, small peptides, or both. If the affinities for these references are corrected as described in previous paragraphs, i.e., if the Na^+ affinity of glycine, on which all are based, is taken from the threshold CID work of Kebarle and co-workers,[11] then the sugar affinities range from 39.2 kcal·mol^{-1} for Ara to 47.4 kcal·mol^{-1} for Lac, as detailed in Table 2. Comparison of nucleobases and dipeptides as reference bases helps us to understand entropy trends and their relation to structural trends. Tri- or tetradentate attachment was proposed for the monosaccharide complexes, and tetradentate for the disaccharides, in agreement with the large affinities.

Recommended Na^+ Affinities. Based on the many results described above, a critical appraisal of the current state of gas-phase Na^+ affinities emerges. Past HPMS experiments based on a nonpulsed ionization process often led to overestimated enthalpies and entropies. This appears to be the case for all HPMS enthalpies, for which reliable values exist for comparison, except for those of water[5] and methane.[7,9] PHPMS measurements, whenever possible, provide the most reliable affinities, with error bars as low as ±0.2 kcal·mol^{-1}. The method is, however, severely limited in its range of applications, since the neutral molecule must be sufficiently volatile and the sodium signal is difficult to generate over a wide range of temperatures. Threshold CID results are reliable, provided that a sophisticated fitting procedure is used and that vibrational frequencies are available. For some of the largest molecules considered above, amides and small amino acids, the error bars can be as large as

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(66) Cerda, B. A.; Wesdemiotis, C., manuscript submitted for publication.

±5 kcal·mol^{-1}. It is therefore likely that this method will be mostly restricted to small molecules. Kinetic method determinations are reliable, provided that molecules with similar binding sites are involved. This reliability is also enhanced if a modified procedure is used in which several effective temperatures are modeled through the use of metastable fragmentations plus CID with several collision gases. Therefore, the main limitation of this method lies in the availability of references with accurately known sodium affinities. This is also the case for ligand-exchange equilibria, for which a deconvolution of entropic contributions is also necessary. This is precisely what quantum chemical calculations can bring. Since electron correlation effects are small for electrostatic and polarization interactions, the MP2 level is ideally suited for accurate yet tractable calculations. Still, a large fraction of computed values in the literature are overestimations due to limitations in the one-electron basis set used and the lack of correction for BSSE. Adding diffuse functions to moderately large bases appears to yield affinities with an accuracy of ∼1 kcal·mol^{-1} at a small computational cost for molecules with 5−10 non-hydrogen atoms. Larger cases may still be tractable, perhaps with the restriction of geometry optimization at the Hartree−Fock level. It is also possible that future development of density functional methods will permit the computation of sodium affinities for yet larger molecules.

We therefore recommend that the values presented in Table 1 be adopted as the basis for a quantitative sodium ion affinity scale. This combination of experimental and computational values seems to be very promising for widely extending the scale of sodium affinities soon.

Entropies and Structure of Na^+ Complexes. The HPMS experiments carried out here yield entropy changes for the clustering reactions in addition to the enthalpies of association. As well, the ab initio calculations generate all of the parameters required in order to carry out statistical thermodynamic treatments of the entropy of each species studied. Thus, a comparison of experimental and theoretical entropies provides a good check on both types of data. As can be seen from the data in Table 1, there is excellent agreement between experimentally determined and theoretically calculated values. The largest difference between the two is 1.3 cal·mol^{-1}·K^{-1}, well within the smaller experimental error bars of ±2 cal·mol^{-1}·K^{-1}. In addition, the magnitude of the entropy change for a clustering reaction can give an intuitive indication of the gross structural and vibrational properties of the complex.

In the present case of clustering of an atomic ion with a polyatomic neutral molecule, three translational degrees of freedom are lost, which accounts for the greatest part of the negative entropy change for the reaction ($\Delta S = -35$ cal·mol^{-1}·K^{-1}). This is counterbalanced, to a certain extent, by the fact that three new vibrational modes are created. Since these are generally of very low frequency because the new bond is relatively weak, this gives a significant additional entropy to the cluster ion. In addition, most notably for the smaller molecules studied, the addition of Na^+ results in a significant increase in the moments of inertia of the cluster relative to the neutral molecule, and thus an increase in the rotational contribution to the entropy. As can be seen from Table 1, with the exception of the amino acids, the entropy changes for addition of Na^+ are nearly all within the range of 22 ± 2 cal·mol^{-1}·K^{-1}. Electrostatic (charge−dipole and charge−quadrupole) and polarization (charge−induced dipole) interactions are expected to dominate the bonding in sodium complexes. This is illustrated by the structural differences between the sodium complexes of acetone, methyl acetate, and *N*,*N*-dimethylformamide shown in Figure 8. Deviations from 180° in the Na−O−C angles are seen to follow the contributions of carbonyl substituents to the molecular dipole moment. Also consistent with this, the least negative entropy changes for association are found for those species which bind sodium the most weakly, i.e., CH_4, CO_2, C_2H_2, C_2H_4, and H_2S. The low bond strengths correspond to long bonds, which then result in larger moments of inertia and greater rotational entropies. Similarly, the low bond strengths give rise to lower vibrational frequencies and thus also to greater vibrational entropies. As noted above, the methane complex has C_{3v} symmetry, with the Na^+ equidistant to three hydrogen atoms. However, there are two other minima, with double and single Na^+−H interactions of C_{2v} and C_{3v} symmetry, respectively. If the barriers between the three minima are sufficiently small, then the Na^+ may have considerable freedom to move about the CH_4 molecule, and the true entropy change might be even less negative than that calculated here. It is also interesting to compare the Na^+ complexes of C_2H_2 and C_2H_4. Both species involve a Na^+ sitting above the center of the C−C multiple bond, with distances from Na^+ to the bond center of 2.63 and 2.66 Å for acetylene and ethylene, respectively. It seems somewhat surprising that this distance for the acetylene complex is less than that for the ethylene complex, even though the latter binds sodium more strongly. In both cases, the binding is not in the direction of maximum polarizability, and thus the geometry is largely determined by the molecular quadrupole moments. The quadrupole moment of C_2H_2 is more than double that of C_2H_4, which compensates for the smaller perpendicular polarizability of acetylene relative to ethylene. It is also interesting to note that, in the acetylene complex, the two hydrogen atoms are pushed ∼5° away from the C−C bond axis, while in the ethylene adduct no change in the C_2H_4 moiety

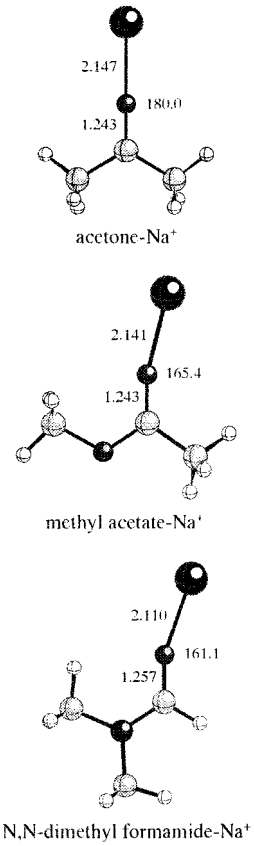

Figure 8. Optimized structures of the sodium complexes of acetone, methyl acetate, and *N*,*N*-dimethylformamide at the MP2/6-31G* level.

occurs. Houk et al. have previously observed that bending of hydrogens out of linearity or planarity, respectively, is easier in the case of acetylenes than ethylenes under either electrophilic or nucleophilic attack.[67] Bonding of the Na^+ electrophile to these two π systems described in this work thus provides support for this hypothesis. The binding of Na^+ to benzene is also of interest. Na^+ sits above the center of the ring, with a Na−ring distance of 2.38 Å. This distance is less than that to the C−C bond axis in either acetylene or ethylene, and, consistent with this, the bond to benzene is considerably stronger. It is interesting to note, however, that the sodium-to-carbon distance in all three complexes is very similar, with that for benzene (2.76 Å) only slightly longer than those in ethylene (2.74 Å) and acetylene (2.70 Å). This greater distance permits the Na^+ to undergo better interaction with the entire π system of the ring.

One other notable consequence of the dominance of electrostatic and polarization interactions over covalent ones in sodium complexes is the fact that the Na^+ is always nearly perfectly aligned with the dipole moment of dipolar molecules. Thus, for example, $NaOH_2^+$ is planar rather than pyramidal, and CH_2-ONa^+ has a 180° C−O−Na bond angle rather than being bent. In addition, the noncovalent nature of the bonding can be deduced from the fact that complexation of Na^+ results in, at best, very minor changes in the skeleton of the neutral fragment in the complex.

Another interesting feature of the structures of complexes where Na^+ is bound to an oxygen atom is the constancy of the Na−O distances. If SO_2 is excluded, since it undergoes simultaneous interaction with two oxygen atoms, the 10 remaining complexes have Na−O distances of 2.17 ± 0.1 Å, with the amides having the shortest bond distances (2.11 Å) and CO_2 having the longest bond distance (2.27 Å). The alcohols and ethers have somewhat longer bond distances (2.21 Å) than formic acid (2.18 Å), acetone (2.15 Å), and methyl acetate (2.14 Å), even though, for example, diethyl ether binds Na^+ more strongly than does formic acid and with nearly the same strength as methyl acetate. This thus suggests that the bond distances are determined largely by the sum of effective radii of the participating atoms. The van der Waals radius of oxygen is tabulated as 1.4 Å on the basis of O−O distances in neutral aggregates. It is very likely that this effective radius would be somewhat reduced in the presence of an ionic interaction. Thus, the effective radius of oxygen appears to be less in carbonyl oxygens than in singly bonded oxygens.

As noted above, Na^+ adducts of the amino acids investigated in this work involve interactions with more than one site in the molecule. This gives rise to the enhanced enthalpies of binding to sodium but also results in a more negative entropy of interaction due to the loss of internal degrees of freedom in the complex, such as internal rotations about C−N and C−C single bonds.

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Conclusions

At a time when the determination of gas-phase Na^+ affinities of organic and small biological molecules is a rapidly evolving field, both experimentally and computationally, this work provides a critical survey of existing results. PHPMS experiments and accurate ab initio calculations are used to resolve several conflicts in the literature and to provide a number of new Na^+ affinities for molecules bearing a wide range of functional groups. This enables the first table of reliable gas-phase Na^+ affinities to be set up, thereby forming a reference basis for future determinations of relative affinities, either by the kinetic method or by ligand-exchange equilibria. This work also explores in detail the attachment of sodium to polyfunctional molecules such as amino acids. Altogether, Na^+ affinities determined herein range from 6.1 (for CH_4) to 44.9 kcal·mol^{-1} (for serine). The simple picture of Na^+/molecule interactions dominated by electrostatic and polarization forces nicely explains the structural and energetic results obtained here. The relationship between the structure of Na^+ complexes and the complexation entropy has been discussed in some detail.

Acknowledgment. We thank Profs. S. Gronert and C. Wesdemiotis for communication of results prior to publication. J. E. Szulejko is thanked for performing preliminary measurements of sodium ion clustering onto acetone. This work was supported by a grant of computer time from the Institut de Développement et de Ressources en Informatique Scientifique (project No. 980543). Financial support from the Natural Sciences and Engineering Research Council (Canada) is also gratefully acknowledged. The scientific collaboration of T.B.M. and G.O. was greatly facilitated by a Collaborative Research Grant from NATO (Grant No. CRG 940748).

JA9841198