Gas-Phase Cl^+ Affinities of Pyridines Determined by the Kinetic Method Using Multiple-Stage (MS^3) Mass Spectrometry

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Abstract: The relative gas-phase halogen cation affinities of a group of substituted pyridines have been ordered, and absolute Cl^+ affinity values have been estimated. The Cl^+-bound dimer of two pyridines is generated in an ion/molecule reaction using mass-selected Cl—C≡O$^+$ as the chlorinating agent, and its competitive fragmentations to yield the Cl^+—pyridine monomers are monitored by multiple-stage (MS^3) experiments. These data yield approximate Cl^+ affinities which show an excellent linear correlation with literature proton affinity (PA) values. The relationship Cl^+ affinity (kcal/mol) = 0.83PA – 42.5 between the two affinities is derived, and both slope and intercept are rationalized in terms of the greater polarizability of Cl^+ ion. While proton affinities are unaffected by hindrance near the bonding site in the corresponding proton-bound dimers, the affinities for the larger Cl^+ ion are significantly decreased by *intra*molecular steric effects in those Cl^+-bound dimers which involve ortho-substituted pyridines. Electronic effects are separated from steric effects by comparing the fragmentation of the Cl^+- and H^+-bound dimers composed of a hindered and an unhindered pyridine. In this way, ortho substituents are ordered in terms of the magnitudes of their steric effects. The intramolecular steric effects of ortho substituents, defined here as a gas-phase steric parameter S^k, are found to increase, not only with the size of the substituent but also as the Cl^+ affinity of the pyridine increases, due to shortening of the N–Cl^+ bond. The S^k values are found also to fall in the same order as the corresponding S^0 steric parameters obtained by solution kinetic measurements. Exceptions occur for 2-methoxypyridine and quinoline, where an additional, through-space electronic interaction between the electron-rich substituent and Cl^+ is proposed. The methodology used to order Cl^+ affinities can be extended to Br^+ and I^+ affinities, and, in the cases examined, the magnitude of the steric effect falls in the order $Br^+ > I^+ \simeq Cl^+ \gg H^+$. The intramolecular steric effect in the I^+-bound dimers is reduced because of the long N–I bond. The quality of the data obtained is such that it is possible to predict with an estimated uncertainty of 2 kcal/mol Cl^+ affinities for compounds which were not examined. To check further on the experimental data and predictions, semiempirical AM1 molecular orbital calculations are used to estimate absolute values of Cl^+ affinities. An excellent correlation is obtained between the experimental values and the AM1 Cl^+ affinities of unhindered pyridines. The calculation overestimates the Cl^+ affinities of the hindered pyridines, and this confirms that steric, not electronic, effects are responsible for the decreases observed in the Cl^+ affinities of ortho-substituted pyridines. *Ab initio* MP2/6-31G(d,p)//6-31G(d,p) molecular orbital calculations are used to confirm that Cl^+ addition to pyridine occurs at the nitrogen and that the lowest energy structure of the Cl^+-bound dimer is the N–Cl^+–N-bound species.

Introduction

Electron-deficient species, often highly reactive and difficult to characterize, are of considerable interest in chemistry.[1] The systematic study and characterization of these species, including measurements of their thermochemical properties, is of growing concern. The halogen cations fall into this class; they are encountered in plasmas and other high-energy environments and used in materials processing,[2] but there are few systematic studies of their chemical properties.[3] Among the very few published studies of their gas-phase ion chemistry is a report on the reactions of positive and negative halogen cations with Cl_2 and Br_2.[3e] In another study an ion trap is used to study the mechanism of chlorine addition to aromatic compounds in the gas phase.[3f] The possible existence of nonclassical bridged halogenium ions is a topic of continuing interest in solution chemistry.[3g] The present investigation of the Cl^+ affinities of pyridines is motivated by an interest in the nature of the N–Cl bond in isolated Cl^+/pyridine clusters, and another aim is to provide thermochemical data to investigate parallels to the corresponding proton affinities.

The thermochemical information is obtained using the kinetic method,[4] an alternative to the equilibrium technique,[5,6] for the measurement of relative thermochemical quantities. It is an approximate method, based on the kinetics of dissociation of ionic clusters (or incipient clusters) typified by proton-bound dimers

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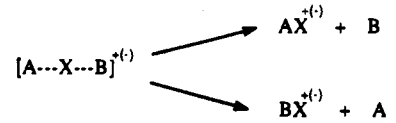
Scheme 1



of simple amines. Since it was proposed in 1977,[4] the method has been employed to compare and determine the gas-phase affinities of neutral molecules toward several types of ionic species. Most studies have investigated proton affinity[7-9] (PA), providing data in good agreement with those determined by equilibrium measurements in the limited number of cases where comparisons have been made. Features of the kinetic method are its applicability to compounds of low volatility or purity[7-9] and the fact that it has been shown to be capable of distinguishing proton affinity differences smaller than 1 kcal/mol.[9]

Affinities are determined from the relative rates of the competing unimolecular dissociations of ion-bound dimers. The method is based on the postulate that, under appropriate conditions, when a loosely bound dimer of two different molecules dissociates competitively (Scheme 1), the difference in the X^+ affinities of the two molecules is given by

$$\ln\frac{[AX]^+}{[BX]^+} = \frac{\Delta(\text{X affinity})}{RT_{\text{eff}}} \qquad (1)$$

In the case of proton affinities this becomes

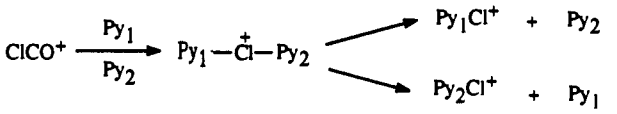
$$\ln\frac{[AH]^+}{[BH]^+} = \frac{\Delta\text{PA}}{RT_{\text{eff}}} \qquad (2)$$

where $[AH]^+$ and $[BH]^+$ are the abundances of the two protonated molecules and T_{eff} is the effective temperature[4] of the proton-bound dimer. The most precise results are expected for chemically similar species, since the method assumes that entropy effects cancel, and this is best satisfied when compounds of similar size and functional groups are compared. In order to determine rather than simply order ion affinities, the effective temperature of the dimer (T_{eff}) must be estimated or measured by examining compounds of known ion affinity and using them to develop a linear correlation between $\ln([AX]/[BX])$ and Δ(X affinity).[7,10]

Recently, it was observed that protonated chloramine (NH_3Cl^+) and the chloroacylium ion $Cl{-}C{\equiv}O^+$ are efficient gas-phase Cl^+ transfer agents,[11] and this raises the possibility that they might be used to generate Cl^+-bound dimers which could be used to measure Cl^+ affinities by the kinetic method (Scheme 2).

Products of Cl^+ addition to (and of substitution on) aromatic compounds are formed by low-energy ion/molecule reactions, and the MS^3 capabilities of a pentaquadrupole mass spectrometer

Scheme 2



allow determination of the site of chlorination in the ion/molecule reaction product. Pyridine readily undergoes chlorination with these reagents, and, in addition to the Cl^+ addition product, an ion/molecule product corresponding to the Cl^+-bound pyridine dimer $[Py{\cdots}^{35}Cl{\cdots}Py]^+$ at m/z 193, is generated. This cluster ion becomes one of the major peaks in the MS^2 ion/molecule product spectrum of the Cl^+ reagent/pyridine mixture when the partial pressure of pyridine in the reaction chamber is raised.

The pentaquadrupole mass spectrometer[12] allows selection of this dimer, and subsequent activation by collision in the second reaction region of the instrument yields a form of MS^3 spectrum known as the sequential product scan.[13] When a mixture of two different pyridines is introduced, the reagent ion $Cl{-}C{\equiv}O^+$ (or NH_3Cl^+) reacts to form the unsymmetrical Cl^+-bound dimer, among other products. Given the ability to fragment the mass-selected dimer, it should be possible to determine the relative order of Cl^+ affinities of pyridines by applying the kinetic method. From competitive dissociation of the unsymmetrical dimer, the Cl^+ affinity can be estimated using eq 3, which is analogous to eq 2 above:

$$\ln\frac{[Py_1Cl]^+}{[Py_2Cl]^+} = \frac{\Delta(Cl^+\text{ affinity})}{RT_{\text{eff}}} \qquad (3)$$

This paper describes these experiments and for the first time orders the halogen cation affinities of a series of compounds. Electronic and intramolecular steric effects of the ortho substituents greatly influence Cl^+ affinities, and they allow the development of a set of gas-phase steric parameters for ortho substituents. Semiempirical (AM1) calculations are performed and used with the experimental data to estimate the absolute values of Cl^+ affinities. They are also used to estimate vibrational frequencies in the complex, since this is an independent source of information on its structure. Results for a limited number of *ab initio* calculations, reported at MP2/6-31G(d,p)//6-31G-(d,p) level, are aimed at elucidating the lowest energy structure of the product of Cl^+ addition to pyridine and of the cluster ion.

Experimental Section

The MS^2 and MS^3 experiments were performed using a pentaquadrupole mass spectrometer[12] comprised of three mass-analyzing quadrupoles (Q1, Q3, Q5) and two reaction quadrupoles (Q2, Q4). For the MS^2 experiments, the isotopically selected reagent ions $^{35}Cl{-}C{\equiv}O^+$ and $^{79}Br{-}C{\equiv}O^+$ were generated by 70-eV electron ionization of acetyl chloride and acetyl bromide, respectively, and mass-selected using Q1. After ion/molecule reactions were conducted in Q2 with a mixture of two pyridines, Q3 was scanned to record the ion/molecule product spectrum, while Q5 was operated in the nonanalyzing RF-only mode. The composition of the pyridine mixture was varied to maximize the abundance of the mixed dimer in which Cl^+ (or Br^+) is simultaneously bound to one molecule of each pyridine, and relative abundances of 20% or more were typically achieved. The nominal acetyl halide pressure was typically 5×10^{-6} Torr, and it increased to 5×10^{-5} Torr on addition of the pyridine mixture; pressures were monitored by a single ionization gauge located in the vacuum chamber. The ion source region was differentially pumped

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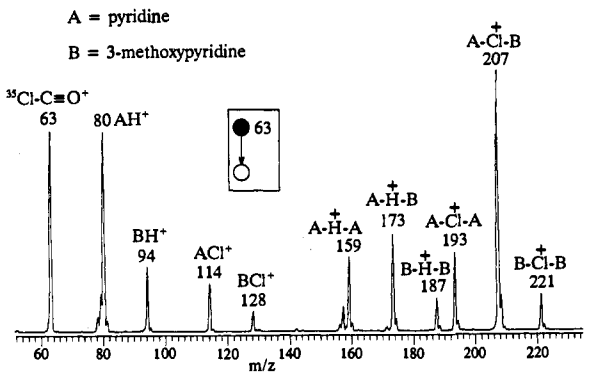

Figure 1. MS^2 ion/molecule product spectrum for mixture of pyridine and 3-methylpyridine, showing several ionic products corresponding to protonation or Cl^+ transfer to the molecules and showing the H^+- and Cl^+-bound dimers.

from the analyzer region. Instrument parameters such as quadrupole and lens potentials were adjusted to maximize the abundance of the ion/molecule reaction products. The I^+-bound pyridine dimer was generated by chemical ionization using I_2 as the reagent, a mixture of two pyridines being introduced into the ion source. In this experiment, Q1 and Q2 were operated in the RF-only mode, and the dimer was mass-selected using Q3 and dissociated in Q4, with Q5 being scanned to record the fragmentation products.

For the MS^3 experiments, the reactant ion of interest, generated in the ion source, was mass-selected using Q1 and reacted with the mixture of pyridines in Q2, and the unsymmetrical Cl^+-, Br^+-, or H^+-bound dimer produced was mass-selected in Q3. This ion was then subjected to collision-induced dissociation (CID) in Q4 using argon as target gas, while Q5 was scanned to record the sequential product MS^3 spectrum. Relative Cl^+ affinity values were obtained by taking the logarithm of the abundance ratio of the fragment ions. The experimental error was calculated as the average standard deviation of relative chlorine affinity using data from all chlorine-bound pairs, for some of which multiple measurements were made. The collision energy, calculated as the voltage difference between the ion source (grounded) and the collision quadrupole, was typically near 0 eV in Q2 for ion/molecule reactions and 10 eV in Q4 for CID in both MS^2 and MS^3 experiments.

The AM1[14] calculations were carried out using the MOPAC6 program.[15] Full geometry optimizations starting from several different conformations were performed on all the neutral pyridines studied and on their N–Cl^+ ionic forms. Upon determination of the heats of formation for the species in their most stable geometries, Cl^+ affinities were calculated from the negative for the enthalpy change for the Cl^+ addition reaction. Since AM1 gives a poor estimate of the heat of formation of Cl^+ (356.2 kcal/mol), the experimental value (329.4 kcal/mol)[16] was used in calculating Cl^+ affinities. The *ab initio* calculations were performed using the GAMESS program.[17] Structural optimizations using gradient techniques were performed at the Hartree–Fock (HF) level of theory using the 6-31G(d,p) basis set. Improved energies were obtained by using single-point calculations at MP2/6-31G(d,p)//6-31G(d,p) level including valence electron correlations calculated by second-order Møller–Plesset perturbation theory.

Results and Discussion

Figure 1 shows a typical MS^2 ion/molecule product spectrum for reactions between $^{35}Cl—C\equiv O^+$ and a mixture of two pyridines, in this case pyridine itself (Py) and 3-methylpyridine (3-MePy). The $Cl—C\equiv O^+$ reactant ion, m/z 63, was selected using Q1 and reacted with the pyridine mixture in the first reaction region of the instrument (Q2). Ion/molecule reactions lead to formation of several products which are assigned as the protonated molecules $[PyH]^+$, m/z 80, and $[3\text{-}MePyH]^+$, m/z 94; the $^{35}Cl^+$ addition products $[Py^{35}Cl]^+$, m/z 114, and $[3\text{-}MePy^{35}Cl]^+$, m/z 128; the two symmetrical proton-bound dimers $[Py\cdots H\cdots Py]^+$, m/z 159, and $[3\text{-}MePy\cdots H\cdots 3MePy]^+$, m/z 187; the unsymmetrical proton-bound dimer $[Py\cdots H\cdots 3MePy]^+$, m/z 173; and most importantly, the $^{35}Cl^+$-bound dimers $[Py\cdots{}^{35}Cl\cdots Py]^+$, m/z 193, $[3\text{-}MePy\cdots{}^{35}Cl\cdots 3MePy]^+$, m/z 221, and $[Py\cdots{}^{35}Cl\cdots 3MePy]^+$, m/z 207. The source of the protons in these experiments was not investigated; they are likely formed by an initial charge-exchange reaction between the mass-selected reagent ion and pyridine. The MS^3 sequential product spectrum of each ionic product was recorded to confirm these assignments, although it does not distinguish between possible isomeric structures. To do this, *ab initio* calculations of the most thermodynamically favorable product were carried out. The results (Table 1) showed that, at the MP2/6-31G(d,p)//6-31g(d,p) level, the N–Cl addition product (I) is by far the most stable product when compared to all three (II–IV) possible ring addition products (Chart 1).

Table 1. *Ab Initio* MP2/6-31G(d,p)//6-31G(d,p)//6-31G(d,p) Total Energies (hartrees) and Relative Energies (kcal/mol) from Structure Optimization Calculations of the Cl^+ Addition Products to Pyridine (I–IV) and the Pyridine–Cl^+–NH_3 Adducts (IX–XI)

ionic product	HF/6-31G(d,p) (hartrees)	MP2/6-31G(d,p)/6-31G(d,p) (hartrees)	relative energies[a] (kcal/mol)
I	−705.915 43	−706.856 96	0
II	−705.863 07	−706.787 38	43.7
III	−705.880 74	−706.797 93	37.0
IV	−705.844 63	−706.779 76	48.4
IX	−762.132 50	−763.269 36	0
X	−762.092 10	−763.226 66	26.8
XI	−762.097 67	−763.230 48	24.4

[a] I–IV relative to I; IX–XI relative to IX. Relative energy is calculated using MP2/6-31G(d,p)//6-31G(d,p).

The assignment of the ion, m/z 207, as the Cl^+-bound pyridine dimer V is based on the following facts. (i) The ion fragments readily under collision energy and pressure conditions which dissociate proton-bound dimers but cause little dissociation of covalently bound ions. (ii) The π-bound structure VI is found by semiempirical AM1 molecular orbital calculations not to exist in a potential well but to collapse to a less stable structure than V. (iii) The most reasonable covalent structures, VII and VIII, are expected to rearomatize by HCl elimination, a process which is not observed. (iv) Semiempirical AM1 molecular orbital calculations show V to be by far (17.2 kcal/mol) the most stable of the four structures.[18] (v) Finally, *ab initio* calculations[19] for ions IX–XI of the model system $PyNH_3Cl^+$ (analogues of ions V, VII, and VIII, respectively, Chart 1) show the $[Py\cdots Cl\cdots NH_3]^+$ dimer IX to be the most stable dimer when compared to the C2 (X) and C4 (XI) ring addition products (Table 1). In addition, *ab initio* calculations for another model system, $(NH_3)_2Cl^+$, show an energy barrier along the N–Cl–N reaction coordinate which maximizes when the two N–Cl bond lengths are equal.[20] This behavior is analogous to that observed for proton-bound dimers which show energy barriers along the N–H–N reaction coordinate.[21]

When the unsymmetrical $^{35}Cl^+$-bound dimer, m/z 207, is mass-selected in Q3 and fragmented by CID with argon in the second reaction region (Q4), the sequential product spectrum shown in Figure 2 is recorded by scanning Q5. The only fragments observed in this simple spectrum correspond to Cl^+ addition products of each pyridine, as expected for a loosely bound dimer.[7,22] Comparison of the relative abundances of these two fragments

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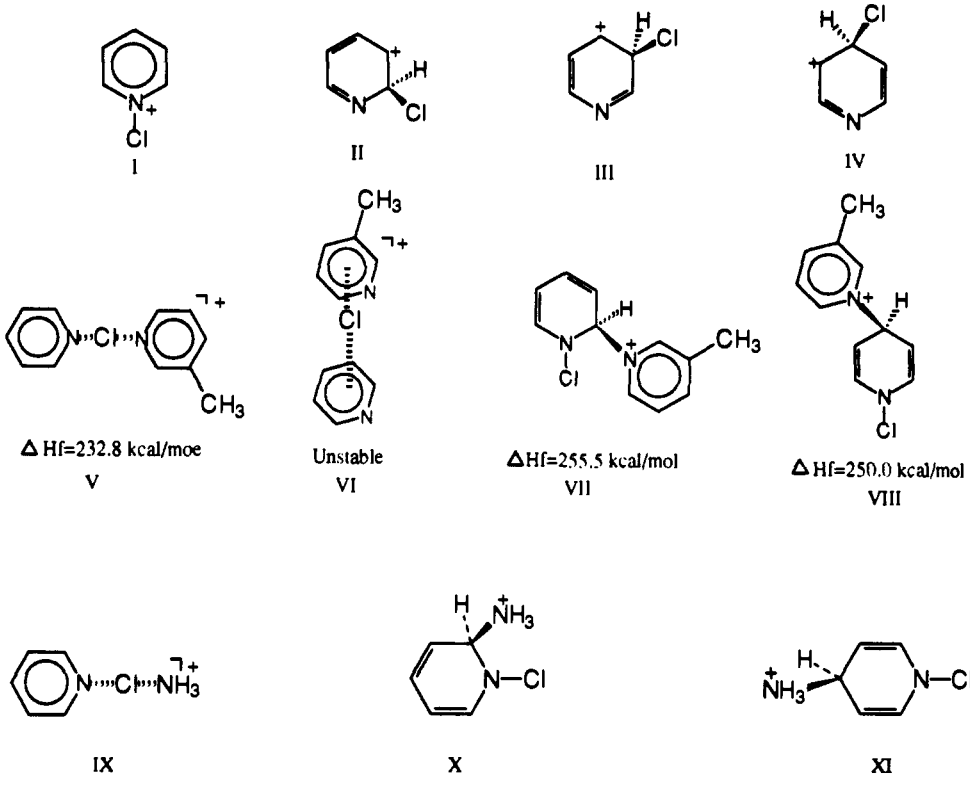
Chart 1



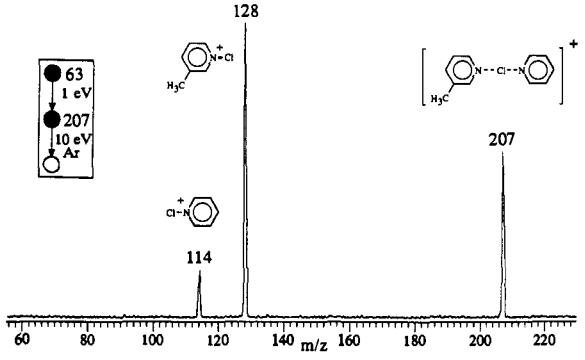


Figure 2. MS^3 sequential product spectrum showing the CID fragmentation of the Cl^+-bound dimer, m/z 207, formed by ion/molecule reaction between $ClCO^+$ and a mixture of pyridine and 3-methylpyridine. The greater relative abundance of m/z 128 than m/z 114 indicates a higher Cl^+ affinity for 3-methylpyridine.

(Figure 2) suggests that 3-methylpyridine has a higher affinity for Cl^+ than does pyridine. Since it is not possible to measure the effective temperature (T_{eff}) of the dimer (see eq 1) due to lack of experimentally known values of Cl^+ affinities, the absolute Cl^+ affinity values of these pyridines cannot be directly extracted from the MS^3 data although they can be reasonably estimated using AM1 calculations (see below). However, it is possible to compare the relative magnitudes of the Cl^+ affinities using the $\ln([Py_1Cl]^+/[Py_2Cl]^+)$ values which, from eq 3, are equal to $(\Delta Cl^+ \text{ affinity})/RT_{eff}$ and therefore directly proportional to the Cl^+ affinities. The relative Cl^+ affinities obtained for the pyridine/3-methylpyridine dimer and for a series of pyridines (**1–17**) examined in similar experiments are displayed in Table 2. To obtain the relative Cl^+ affinity values shown in Table 2, the Cl^+ affinity of 2-fluoropyridine, the compound that displays the lowest value, was set arbitrarily to zero. For comparison, literature values of the PAs of the set of pyridines are also shown in Table 2.

If one considers that the same electronic effects known to influence proton affinities[23] might also affect Cl^+ affinities, and if these effects parallel each other, then the same order for both Cl^+ affinities and PAs is to be expected. This was tested by plotting the relative Cl^+ affinities versus the PAs as shown in Figure 3. This plot shows that an excellent correlation exists between the two ionic affinity values for pyridines having no ortho substituents (unhindered pyridines). The quality of this correlation also provides evidence that the kinetic method is an appropriate method of obtaining halogen cation affinities. The results for the ortho-substituted pyridines are noteworthy. For the compounds bearing electron-withdrawing halogens in the ortho position (2-fluoropyridine and 2-chloropyridine) which therefore display relatively low Cl^+ affinities, the correlation with proton affinity is also very good. However, as the Cl^+ affinity of the hindered pyridines increases due to electron-donating effects of the ortho groups, the correlation becomes worse, showing a lower than expected Cl^+ affinity for these compounds. Such behavior can best be understood as being the result of steric effects of the ortho group(s) in the dimer. The steric hindrance between the ortho group and the large Cl^+ ion can cause a lengthening of the N–Cl^+ bond which consequently decreases its strength and hence decreases the Cl^+ affinity of the hindered pyridine.[24] This steric effect of ortho groups not only reduces the observed values of Cl^+ affinities but in a few cases also causes inversions when compared to the PA order, as the following discussion shows.

Proton affinity measurements carried out by several methods[7,23] show that 2- and 4-methylpyridine have similar PAs which are higher than that of 3-methylpyridine, i.e., 3-Me < 2-Me = 4-Me (Table 2). In the case of Cl^+ affinity, however, the present results show a different order within the series, i.e., 3-Me = 2-Me < 4-Me. Note the relative decrease for the ortho-substituted pyridine (2-Me). This same trend is observed for the ethylpyridines and also for the dimethylpyridines. For the ethylpyridines, the PA order is 3-Et < 2-Et = 4-Et, while the Cl^+ affinity order is 3-Et = 2-Et < 4-Et, again indicating steric hindrance due to

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(24) It is suggested that the steric effect is an intramolecular effect intrinsic to the interaction of Cl^+ and the pyridine. It is not a consequence of using the Cl^+ dimer to measure Cl^+ affinities.

Table 2. Cl^+ Affinities and Proton Affinities of Pyridines

entry	pyridines	$Py_1:Py_2$[a]	relative Cl^+ affinities,[b] $\ln[(Py_1Cl^+)/(Py_2Cl^+)]$	proton affinities[c] (kcal/mol)	AM1 affinities (kcal/mol)	absolute Cl^+[d] affinities (kcal/mol)
1	2-F		0	211.8	134.3	133.7
2	2-Cl	2:1	2.0	214.8	136.7	135.9
3	3-Cl	4:3	2.8	215.7	135.8	136.8
4	2-MeO	4:2	6.0	221.3	140.2	140.3
5	pyridine	5:4	6.2	220.4	140.5	140.5
6	2-Me	6:5	8.2	223.7	143.8	142.7
7	3-Me	7:5	8.2	222.8	142.1	142.7
8	4-Me	8:5	8.6	223.7	143.5	143.1
9	2-Et	9:8	9.0	224.9	144.3	143.6
10	3-Et	10:8	9.0	223.9	142.8	143.6
11	4-Et	11:8	9.8	224.6	144.3	144.5
12	2-Prop^n	12:9	9.6	225.6[e]	145.0	144.2
13	quinoline	13:8	10.1	225.8[f]	145.5	144.4
14	2,6-diMe	14:8	10.0	227.1	146.7	144.7
15	3,5-diMe	15:8	10.3	225.5	143.8	145.0
16	2,3-diMe	16:8	10.4	226.3	145.2	145.1
17	2,4,6-triMe	17:11	12.2	230.3[g]	149.5	147.1

[a] The entry number of the pyridines forming the Cl^+-bound dimer used to estimate the Cl^+ affinity. [b] Values, obtained from dissociation (MS^3 spectra) of the ionic dimer, are directly proportional to the Cl^+ affinities; see eq 3. [c] Data from ref 23, unless otherwise noted. [d] The absolute Cl^+ affinities were obtained applying eq 3 and by using experimental and theoretical results, i.e., the experimental values of $\ln(Py_1Cl^+/Py_2Cl^+)$, the T_{eff} extracted from the plot shown in Figure 7, and the AM1 Cl^+ affinity value for pyridine. [e] Estimated assuming an inductive plus resonance effect for a 2-*n*-prop group as being intermediate (5.2) between that of 2-ethyl (4.2) and 2-*tert*-butyl (6.0); see ref 23. [f] Data from ref 7a. [g] Estimated using the inductive plus resonance effect of 3.2 for a 4-methyl group (see ref 23 and 2-methyl- and 2,4-dimethylpyridine) and by adding this value to the PA of 2,6-dimethylpyridine.

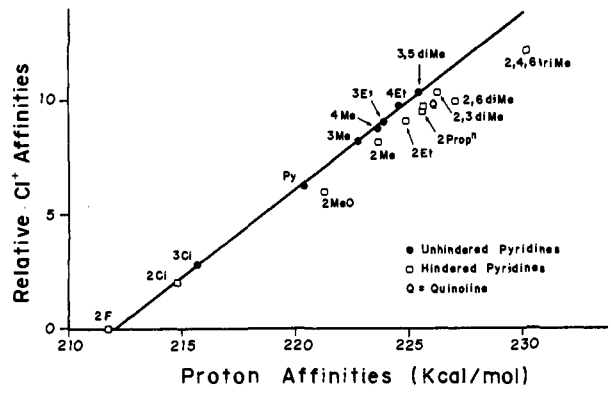

Figure 3. Plot of the experimental relative Cl^+ affinities versus PAs of the pyridines studied, showing the very good correlation for the unhindered molecules. For hindered pyridines, the correlation becomes poorer as the size of the ortho group and/or the Cl^+ affinity of the pyridine increases.

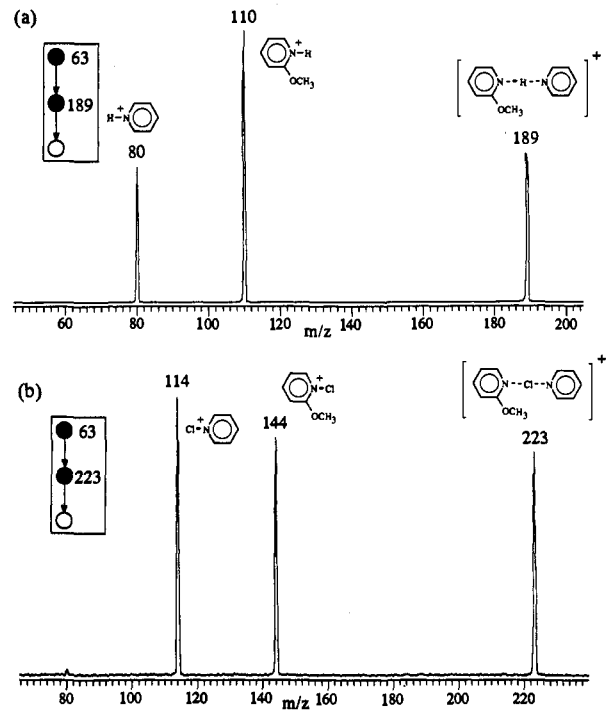

Figure 4. MS^3 sequential product spectrum showing the CID fragmentation of (a) the H^+-bound dimer, m/z 189, and (b) the Cl^+-bound dimer, m/z 223, formed by ion/molecule reactions between $^{35}ClCO^+$ and a mixture of pyridine and 2-methoxypyridine. The inversion observed in the relative abundance of the two fragments in both spectra is attributed to the decrease in the Cl^+ affinity of 2-methoxypyridine caused by the steric effect of the ortho group.

the 2-ethyl group. Within the dimethylpyridine series, 2,6-dimethylpyridine, which has two methyl groups in ortho positions, is expected from a consideration of only electronic effects[7,23] to have the greatest cation affinity. This expectation is met for the proton, for which this compound indeed displays the highest affinity within the dimethyl series (Table 2). However, the steric hindrance of the two methyl groups moves 2,6-dimethylpyridine to the *lowest* value of Cl^+ affinities among the dimethylpyridine isomers investigated (Table 2). The intramolecular steric effect associated with 2-methyl substituents is also observed for 2,3-dimethylpyridine, which shows a Cl^+ affinity approximately equal to that of 3,5-dimethylpyridine. By contrast, the PA of 2,3-dimethylpyridine is 0.8 kcal/mol greater than that of 3,5-dimethylpyridine. For 2-*n*-propylpyridine, the greater steric hindrance of the large 2-substituent is also easily seen in the fact that it displays a lower Cl^+ affinity than the para-substituted *lower* homologue, 4-ethylpyridine. One would expect the opposite order on the basis of electronic effects alone. Of course, electronic effects operate and can be observed within the homologous series of ortho-substituted hindered pyridines. The Cl^+ affinity order 2-Me < 2-Et < 2-*n*-Pr occurs as predicted on the basis of polarizabilities.

An interesting case of inversion in the expected affinity order is presented by 2-methoxypyridine in relation to pyridine. Since reactions with Cl—C≡O$^+$ yield both the H^+- and the Cl^+-bound dimers, it is possible to make an excellent comparison between the proton and Cl^+ affinities of two pyridines by the kinetic method using the pentaquadrupole instrument. Both unsymmetrical ionic dimers can be prepared simultaneously and examined under very similar experimental conditions. The only change that must be made to acquire both spectra is the selection of the appropriate ion in Q3. This experiment was performed for 2-methoxypyridine and pyridine (and also for several other cases, see below), and the results are presented in Figure 4. The higher abundance of m/z 110 (protonated 2-methoxypyridine) compared to m/z 80 (protonated pyridine) in the MS^3 spectrum of the proton-bound

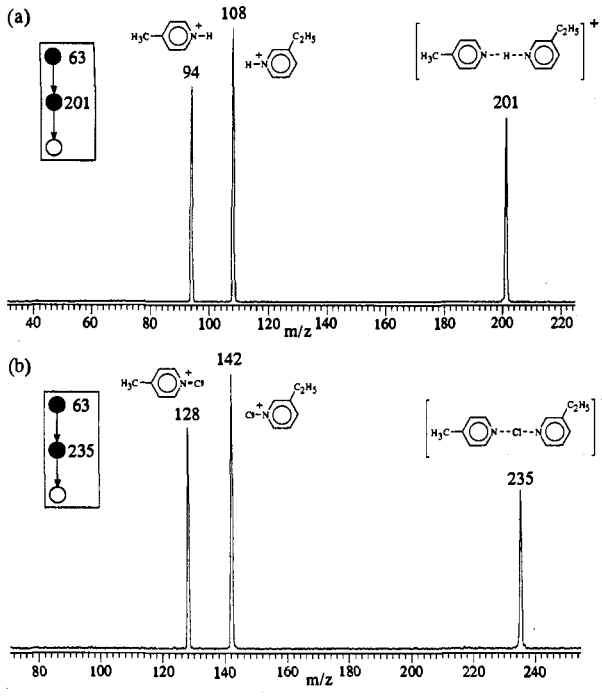

Figure 5. MS^3 sequential product spectrum showing the CID fragmentation of (a) the H^+-bound dimer, m/z 201, and (b) the Cl^+-bound dimer, m/z 235, formed by ion/molecule reactions between $^{35}ClCO^+$ and a mixture of the unhindered pyridines, 4-methyl- and 3-ethylpyridine. Note the similar relative abundance of the two fragments in both spectra.

dimer (Figure 4a) clearly shows that 2-methoxypyridine has the higher PA, as determined earlier.[23] The MS^3 spectrum for the Cl^+ dimer (Figure 4b), however, shows the opposite result. The abundance of $[2\text{-MeOPyCl}]^+$ (m/z 144) is smaller than that of $[PyCl]^+$ (m/z 114). The lower Cl^+ affinity for 2-methoxypyridine is ascribed to steric and/or electronic interactions of the ortho group with the chlorine cation. Note that such interactions may also occur with the proton, since comparison of the proton affinities of the three isomeric methoxypyridines reveals an anomalous decrease of some 5 kcal/mol in the value for the ortho isomer.[23]

Quantitative Treatment of Steric Effects. Studies of steric effects of substituents must always deal with the difficult task of separating steric from electronic (inductive and resonance) effects.[25] In the present case, it is noted that for pairs of unhindered pyridines, the ratios of the two fragments obtained by CID of the H^+- and Cl^+-bound dimers are very similar, as shown for 4-methylpyridine and 3-ethylpyridine in Figure 5. Given this, and since both H^+- and Cl^+-bound dimers fragment under very similar experimental conditions as just discussed, it is reasonable to suggest that when a pair consisting of a sterically hindered, ortho-substituted pyridine (Py^h) and an unhindered pyridine (Py^u) is studied, the decrease in the relative abundance of the $[Py^hCl]^+$ fragment, compared to the relative abundance of $[Py^hH]^+$, is due mainly to the steric effect of the ortho group, i.e., the interaction between the halogen and the ortho substituent. Owing to the very small size of the proton, such steric effects are expected to be negligible in proton-bound dimers. It is therefore possible to efficiently separate electronic from steric effects and to treat quantitatively the steric effect of the ortho groups by comparing proton and chlorine relative cation affinities. This was done for several hindered pyridines, and the results are displayed in Table 3, where a steric parameter S^k is assigned to each case. This parameter reflects the steric hindrance of the ortho group(s) by measuring the extent to which the logarithm of $[Py^hCl]^+/[Py^u\text{-}Cl]^+$ (the reference compound is pyridine itself) decreases in comparison to the logarithm of $[Py^hH]^+/[Py^uH]^+$. For mono-ortho-substituted pyridines, bound to pyridines lacking ortho substituents, the measured S^k value can be assigned as the steric parameter of the ortho substituent. For instance, a steric parameter S^k of –0.84 is attributed to the 2-methoxy group because the $[2\text{-MeOPyCl}]^+/[PyCl]^+$ ratio of 0.86 in Figure 4b (m/z 144)/(m/z 114) is 2.3 times lower than the $[2\text{-MeOPyH}]^+/[PyH]^+$ ratio of 2.0 in Figure 4a (m/z 110)/(m/z 80).

For comparison, the ortho steric parameters S^0 are also included in Table 3. These parameters (S^0) are determined from the kinetics of quaternization of pyridines in solution by methyl iodide,[25,26] a reaction which is used as the basis for this scale of ortho steric effects. Interestingly, the same relative order of S^k and S^0 is obtained for all groups except for 2-MeO and the 2,3-fused ring compound quinoline. Excluding these two cases, the S^k order is also identical to that expected from consideration of the size of the groups.[27] For example, the steric parameter for the 2-Me group in 2-methylpyridine is slightly lower than that for the 2-Me group in 2,3-dimethylpyridine due to the buttressing effect of the 3-Me group.[25] It is interesting to note the very high intramolecular steric effect of the two ortho methyl groups in both 2,6-dimethyl- and 2,4,6-trimethylpyridine (steric parameters S^k of –1.6 and –1.7, respectively). These values are more than twice as great as that of a single ortho methyl group ($S^k = -0.41$). This may be explained in part by considering that the steric effect of a 2-substituent should increase as the Cl^+ affinity of the pyridine increases. This follows because the higher Cl^+ affinity will tend to shorten the N–Cl bond and therefore intensify the steric effect. Both 2,6-dimethyl and 2,4,6-trimethylpyridine have Cl^+ affinities considerably greater than that of 2-methylpyridine (Table 2), and hence the steric effect of each methyl group in the former pyridines is expected to be greater. The steric parameter S^k of –1.6 for 2,6-dimethylpyridine gives a steric parameter of approximately $-1.6/2 = -0.8$ for each ortho methyl group, while for 2,4,6-trimethylpyridine each ortho methyl would contribute $-1.7/2 = -0.85$ to the overall S^k value of –1.7. In view of this, the larger Cl^+ affinity of 2,3-dimethylpyridine relative to that of 2-methylpyridine can also be used, in conjunction with the buttressing effect, to explain the higher steric effect of the 2-methyl substituent in 2,3-dimethylpyridine.

We now turn to the anomalous cases, the 2,3-(fused benzene ring) in quinoline and the 2-MeO group. The static peri-hydrogen (Cα–H) of the fused benzene ring results in a steric parameter (S^k) which is lower than that for 2-methylpyridine (Table 3), while the opposite is true of the S^0 parameter, i.e., for quinoline S^0 is more negative. The same inversion in S^k and S^0 values is observed for 2-MeO and 2-Et substituents and confirmed by direct comparison between these two pyridines (see below). The 2-MeO and 2,3-fused benzene ring groups are electron rich, and their lower than expected steric effects may be accounted for by an extra, spatial electronic interaction with the Cl^+ ion, as represented in Chart 2. This electronic interaction will tend to increase the Cl^+ affinity of the 2-substituted pyridine and therefore reduce to some extent the intramolecular steric effect of the ortho group. Note that an analogous phenomenon has been suggested to explain the unexpectedly large gas-phase basicity of the formate anion.[28] A similar case has been reported by Squires and co-workers in measuring gas-phase acidities of carboxylic acids and alcohols from collision-induced dissociation of dimer cluster ions using the kinetic method.[29]

The measurement of the steric parameters was also undertaken between two hindered pyridines; the purpose was to compare the steric parameter from this experiment with the steric parameters reported in Table 3. In this experiment, the steric parameter for

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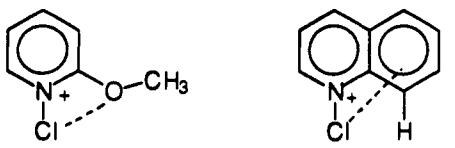
Table 3. Experimental and Derived Values of Abundance Ratios and Steric Parameters

Py_1	Py_2	$(Py_1H)^+/(Py_2H)^+$ [a]	$(Py_1Cl)^+/(Py_2Cl)^+$ [a]	$(Py_1H)^+/(Py_2H)^+$ [b]	$(Py_1Cl)^+/(Py_2Cl)^+$ [b]	S^k [c]	S^0 [d]
Py	Py	1.0	1	1	1	0	0
2-MeO	Py	2.0	0.86	2	0.86	−0.84	−1.28
2-Me	Py	12	7.8	12	7.8	−0.43	−0.73
4-Me	Py	12	12	12	12	0	
4-Et	4-Me	3.5	3.6	42	42	0	
2-Et	4-Me	4.5	1.6	54	19	−1.1	−1.08
2-*n*-Pr	2-Et	2.1	1.8	113	34	−1.2	−1.2
quinoline	4-Me	5.0	4.1	60	48	−0.22	−0.85
2,3-dimethyl	4-Me	12	6.2	138	72	−0.64	−0.92
2,6-dimethyl	4-Me	18	3.9	214	45	−1.6	−1.98
2,4,6-trimethyl	4-Et	51	11	2124	438	−1.7	

[a] Experimental data. [b] The ratio is normalized to pyridine from experimental data. [c] S^k value is obtained from logarithm of the normalized chlorine-bound dimer ratio vs normalized proton-bound dimer ratio. [d] S^0 is obtained from refs 25 and 26.

Chart 2



an 2-ethyl group was found to be 0.64 more negative than that of a 2-methyl group, a result which is very close to that recorded in Table 3 (steric parameters of −1.1 and −0.41, respectively). In a further attempt to separate steric and electronic effects, the relative rates of fragmentation of 2,4-dimethylpyridine and 2,6-dimethylpyridine were compared. The proton- and chlorine-bound dimers comprised of 2,4-dimethylpyridine and 2-methylpyridine showed a relative S^k value of −0.32, and hence, from the known S^k value of 2-methylpyridine −0.43 (Table 3), the S^k value for 2,4-dimethylpyridine is −0.75. This is to be compared to the values of −1.6 and −0.64 for 2,6-dimethylpyridine and 2,3-dimethylpyridine, respectively, viz., to values of −0.8 and −0.64 per ortho methyl group. Note the similarity in the effect per ortho methyl substituent between the three compounds. Note also that the value for the *o,p*-isomer is greater than that for the *o,m*-isomer, consistent with the expectation that the higher the Cl^+ affinity, the greater the steric effect.

Other Halide Cation Affinities. The fact that and the degree to which the ionic bridging species Cl^+ interacts sterically with ortho substituents have now been discussed. A similar effect occurs for Br^+-bound dimers. This is evident when analyzing the MS^3 spectra for the Br^+-bound and H^+-bound dimers of pyridine and 2-methoxypyridine, displayed in Figure 6. These dimers are formed, among other products, when a mixture of these two pyridines is allowed to react with $^{79}Br—C{\equiv}O^+$. When the Br^+- and H^+-bound dimers are independently mass-selected and dissociated, the intramolecular steric effect of the 2-methoxy group causes the ratio $(m/z\ 188)/(m/z\ 158)$, i.e., $[2\text{-MeOPy}^{79}\text{Br}]^+/[\text{Py}^{79}\text{Br}]^+$, to be 4.0 times lower than the ratio $(m/z\ 110)/(m/z\ 80)$,[30] i.e., $[2\text{-MeOPyH}]^+/[\text{PyH}]^+$). This represents a steric parameter S^k for the 2-methoxy group of −1.3 in the Br^+-bound dimer. This value is much larger than the steric parameter S^k of −0.84 in the Cl^+-bound dimer (Table 3). It is interesting to note that this result indicates that, even though one expects a longer N–Br bond length (1.85 Å)[31] compared to N–Cl (1.67 Å),[32] this effect is not enough to offset the significant increase in the size of the Br^+ ion. However, when the mixed I^+- and H^+-bound dimers are formed from these same pyridines under I_2 chemical ionization conditions and then fragmented, the S^k parameter decreases to −0.91. This indicates that the N–I bond

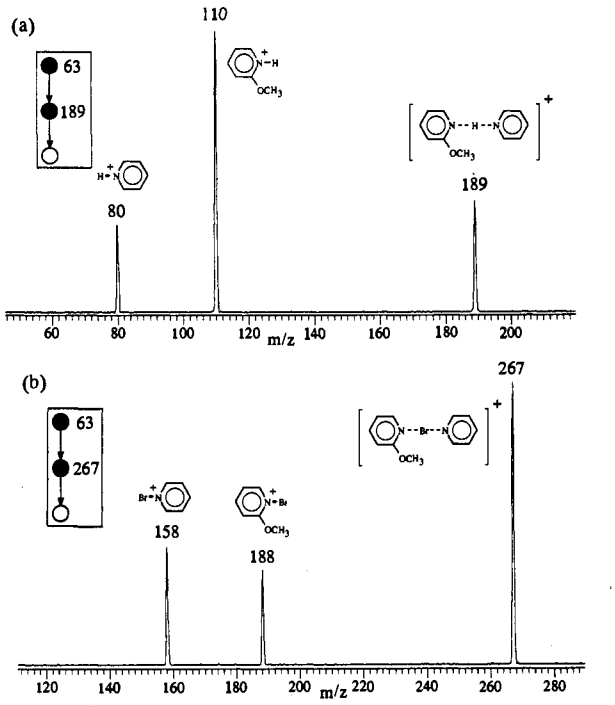


Figure 6. MS^3 sequential product spectrum showing the CID fragmentation of (a) the H^+-bound dimer, m/z 189, and (b) the $^{79}BrCO^+$-bound dimer, m/z 267, formed by ion/molecule reactions between $^{79}BrCO^+$ and a mixture of pyridine and 2-methoxypyridine. The greater reduction in the relative abundance of the $[2\text{-MeOPyBr}]^+$ fragment in spectrum b shows that the steric effect of the 2-methoxy group is increased when binding is performed using larger ions.

(1.98 Å)[31] is sufficiently long to minimize the steric hindrance due to ortho groups.

Theoretical Calculations. The use of semiempirical and *ab initio* MO calculations to confirm the structures of the Cl^+ dimers has already been discussed above. Calculations also provided valuable information on the applicability of the kinetic method since they showed that the two stretching N–Cl bonds within the unsymmetrical chlorine-bound dimer have similar frequencies. This, in turn, strongly supports the validity of the kinetic method in measuring of the chlorine affinity.

Since chlorine cation affinities have not been measured in either the gas or the solution phase and the kinetic method is a

(30) The lower $[2\text{-MeOPyH}]^+/[\text{PyH}]^+$ ratio obtained in Figure 6a when compared to that in Figure 4a is likely the result of a lower effective temperature (T_{eff} in eq 2) for the proton-bound dimer formed by ion/molecule reactions involving $Br—C{\equiv}O^+$ vs $Cl—C{\equiv}O^+$ as reagent.

(31) AM1 calculations for the corresponding N-halogenated pyridine ions give the following lengths for the N–Cl, N–Br, and N–I bonds: 1.67, 1.85, and 1.98 Å, respectively.

(32) For recent examples, see: (a) Shen, M.; Schaefer, H. F., III; Liang, C.; Lii, J.-H.; Allinger, N. L.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1992**, *114*, 497. (b) Sethson, I.; Johnels, D.; Lejon, T.; Edlund, U.; Wind, B.; Sygula, A.; Rabideau, P. W. *J. Am. Chem. Soc.* **1992**, *114*, 953. (c) O'Shea, K. E.; Fox, M. A. *J. Am. Chem. Soc.* **1991**, *113*, 611. (d) Dewar, M. J. S.; Hwang, J. C.; Kuhn, D. R. *J. Am. Chem. Soc.* **1991**, *113*, 735. (e) Kim, K. H.; Martin, Y. C. *J. Med. Chem.* **1991**, *34*, 2056. (f) Lahti, P. M.; Ichimura, A. S. *J. Org. Chem.* **1991**, *56*, 3030. (g) Larumbe, D.; Moreno, M.; Gallardo, I.; Bertrán, J.; Andrieux, C. P. *J. Chem. Soc., Perkin Trans. 2* **1991**, 1437. (h) Katritzky, A. R.; Karelson, M. *J. Am. Chem. Soc.* **1991**, *113*, 1561. (i) Kim, K. H.; Martin, Y. C. *J. Org. Chem.* **1991**, *56*, 2723.

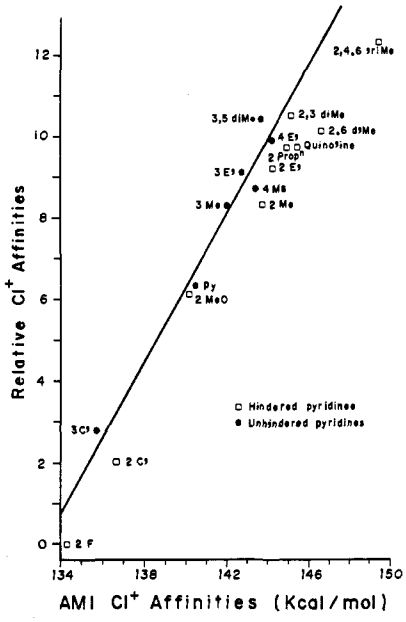


Figure 7. Plot of the experimental relative Cl^+ affinities of pyridines as a function of calculated AM1 Cl^+ affinities. Note the good correlation obtained for the unhindered pyridines and the fact that most hindered pyridines fall below this line, which shows that AM1 overestimates their Cl^+ affinities.

comparative method, it is not possible to obtain absolute values of Cl^+ affinities from the experimental results. Therefore, we used the AM1 method[14] to estimate these values and to compare the relative order to that obtained experimentally. The AM1 method has proven reliable for several problems of chemical interest including the determination of affinities for ionic species.[32] The results have shown the AM1 PAs to agree well with experimentally known values for a large variety of organic compounds.[33] Recently the AM1 method was expanded to include the halogens[34] and used to provide heats of formation for many neutral and ionic halogen-containing species of comparable quality to those for compounds containing only C, H, N, and O.

The Cl^+ affinity values obtained by the AM1 method for all the pyridines studied here are reported in Table 2. An examination of the AM1 Cl^+ affinity order shows that, with the exception of 2-methoxy and 2-chloropyridine, it coincides with the corresponding PA order. This discrepancy indicates that the AM1 method does not deal adequately with the steric effects caused by ortho groups. This is evident when the AM1 Cl^+ affinities are plotted (Figure 7) against the experimental relative Cl^+ values reported in Table 2. This plot shows a good correlation between the AM1 and the experimental Cl^+ affinities for the unhindered pyridines. However, when a correlation line is drawn using only the points corresponding to the unhindered pyridines, all the hindered pyridines, except for 2-methoxypyridine, fall below the line. In this plot it is clearly seen that the AM1 method overestimates the Cl^+ affinities of hindered pyridines, and this effect is most pronounced for those pyridines that are the most crowded. These results are not surprising taking into account previous reports showing the AM1 method to underestimate spatial repulsions.[14] These results also confirm that the decreases observed for the hindered pyridines in the experimental Cl^+ affinity order (see previous discussion) are not due to electronic effects but are caused by steric effects.

Nevertheless, it is seen in Figure 7 that the AM1 Cl^+ affinities for the unhindered pyridines are in good agreement with the experimental relative Cl^+ affinities. We therefore can use the calibration line for these compounds to estimate the effective temperature of the dimer (T_{eff}). According to eq 3, the slope of this line is equal to $1/RT_{eff}$, and therefore T_{eff} is found to be 555 K. This temperature is in agreement with values of around 600 K obtained experimentally in studies[8-10] on many other systems activated under similar conditions. This agreement is a further indication of the reliability of the AM1 Cl^+ affinities for unhindered pyridines. The AM1-determined effective temperature of 555 K and the derived value for the Cl^+ affinity for pyridine (140.5 kcal/mol) can be used in combination with the experimental $\ln([Py_1Cl]^+/Py_2Cl]^+$ values reported in Table 2. This allows the absolute Cl^+ affinities of the other pyridines to be calculated from eq 3, and the results are shown in Table 2. The decreases caused by the steric effects of ortho groups are taken into account in the experimental results, even though these effects were poorly estimated by the AM1 method.

If the absolute values of Cl^+ affinities are plotted versus PAs of the unhindered pyridines (plot not shown, correlation coefficient 0.9989), a dimensionless slope of 0.83 is found for the correlation line, which crosses the abscissa at –42.5 kcal/mol. This plot makes it possible to formulate eq 4, which correlates Cl^+ affinities with PA values:

$$Cl^+ \text{ affinity (for unhindered pyridines, kcal/mol)} = 0.83PA - 42.5 \quad (4)$$

The estimated uncertainty in individual Cl^+ affinities values, based on this correlation, is 2 kcal/mol. Note that uncertainties in both the present experiments and in the literature values for proton affinities contribute to this quantity. The equation indicates that the Cl^+ affinities increase more slowly than proton affinities, an effect which may be ascribed to the greater polarizability of the Cl^+ ion. Similar results have been reported in studies of methyl cation affinities (MCA). Correlations between PA and MCA have been reported by McMahon and co-workers.[35] In their work, the MCA values follow in general the proton affinities. A plot of PA vs MCA leads to a slope of ~3 for compounds with low MCA values (inert gases), while the slope is close to ~1 for compounds with high MCA values (amines). In another study, Bartmess reported the existence of a correlation between PA and MCA: the slope of the linear correlation is 0.98 when the substrates are amines and alcohols.[36]

Conclusion

The results obtained in this study have the following implications. (i) The general approach used (kinetic method in conjunction with MS^3 or MS^2 experiments) may be applicable in other cases in which thermochemical information is desired on unusual species. (ii) The data given here could probably be obtained by equilibrium measurements in a high-pressure ion source, and comparisons of such experiments with the results of the kinetic method would be worthwhile. (iii) The gas-phase steric parameters derived from this work are of interest for future comparisons with other gas-phase experiments and with solution S^0 parameters. The overall similarities in S^k and S^0 steric parameters observed here are noteworthy, and more extensive comparisons of these isolated and solution-phase parameters are desirable.

Unlike the case of proton-bound dimers, the relative yield of the two chlorinated pyridines formed by dissociation of the corresponding Cl^+-bound dimer is not exclusively dependent on the electronic effects of the substituents. When ortho groups are

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(36) Bartmess, J. E. *Mass Spectrom. Rev.* **1989**, *8*, 297.

present, fragment ion abundances are also sensitive to structure, i.e., to the intramolecular steric effects of the ortho groups.[37] The steric effects cause a substantial decrease in the measured affinity for large ionic species, and they can be quantified on the basis of this effect. In the cases examined, the steric effect of the ortho group is greater for larger bridging ions, i.e., $H^+ \ll Cl^+ < Br^+$, and increases with the cation affinity of the compound. For I^+ the trend reverses, as the effect of its much longer N–I bond more than compensates for the increased atomic size.

An increase in ionic affinity causes a decrease in the length of the molecule–Cl^+ bond, which intensifies the steric effect of the ortho group. This is seen by the fact that the gas-phase steric parameters (S^k) for an ortho methyl group were found to be –0.41, –0.64, –1.6, and –1.7 for 2-methyl-, 2,3-dimethyl-, 2,6-dimethyl, and 2,4,6-trimethylpyridine, respectively. It is therefore possible to predict substantial decreases in affinities for large bridging ions for those pyridines (and presumably other compounds) which display relatively high ionic affinities based on electronic effects but which also bear large groups located in positions which allow steric interactions within the complex. For instance, the Cl^+ affinity of 2-*tert*-butylpyridine is *predicted* to be considerably lower than that of the 4-*tert*-butylpyridine, although the PA of the latter is slightly higher, 218.6 vs 218.3 kcal/mol, respectively.[23] For unhindered pyridines, i.e., those without ortho groups, proton affinity and Cl^+ affinity orders are similar, and therefore Cl^+ affinities can be estimated from the PA values. The same trend is expected to hold true for other classes of compounds and ionic species. For instance, it is possible to predict, based on known PAs,[23] the following Cl^+ affinity order and also the absolute values (shown in parentheses) by applying eq 4 for some 4-substituted pyridines not studied here: 4-NO_2 (PA = 209.5 kcal/mol; Cl^+ affinity = 131.4 kcal/mol) < 4-Cl (217.8; 138.4) < 4-MeO (226.6; 145.9) < 4-NMe_2 (229.9; 148.7). Estimated uncertainties in these predictions are 2 kcal/mol.

(37) These steric effects cause changes in ground-state equilibrium properties, making the separation of steric and electronic effects ambiguous.

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