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Notes

Electronic Structures of Some Antimicrobial *N*-Chloramines. Possible Existence of Intramolecular Hydrogen Bonding and Its Effect on Germicidal Efficiency

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The photoelectron spectra of eight *N*-chloramines and *N,N*-dichloramines derived from either α-aminoisobutyric acid or 2-amino-2-methylpropanol have been measured. The lone-pair ionization potentials obtained from the photoelectron spectra have been interpreted to indicate that a substantial intramolecular interaction exists between the N–H function and the various oxygen lone pairs of the *N*-chloramines. Such an intramolecular interaction for the *N*-chloramines can explain at least in part why these molecules are less potent as antimicrobial agents than are their *N,N*-dichloramine analogues for which a similar intramolecular interaction is impossible.

Comparative antimicrobial studies of *N*-chloramines and *N,N*-dichloramines derived from α-aminoisobutyric acid or 2-amino-2-methylpropanol have shown that the antimicrobial activities of the compounds are influenced by several factors, including the degree of chlorination, the presence of denaturant, and the polarity of the N–Cl bond.[1] Of particular interest are the observations[1] that *N*-chloramines with highly polar N–Cl bonds are readily denatured, whereas those with relatively nonpolar N–Cl bonds are not, and that *N,N*-dichloramines have antimicrobial activities which are virtually unchanged by the presence of denaturant. This lack of deactivation by denaturant is supportive of the observation that *N,N*-dichloramines are more effective antimicrobial agents than are their *N*-chloramine analogues.

Ultraviolet photoelectron spectroscopy is the best means available for studying the electronic structures of complex molecules. It is particularly useful for investigating the energies and interactions of nonbonding ("lone pair") electrons, for the nonbonding molecular orbitals usually lie at somewhat higher energies than do the bonding MO's and thus normally give rise to identifiable, well-resolved, low-energy ionization bands in the photoelectron spectra. A detailed study of the lone-pair bands in the spectra of the *N*-chloramines and *N,N*-dichloramines should be especially illuminating given that the polarity of the N–Cl function is deemed to be of importance in determining the activity of the antimicrobial agents. It has been demonstrated previously that photoelectron spectroscopy is a viable tool for rationalizing pharmacological activity.[2,3]

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	X	Y	R
1A	H	Cl	$CH_2CH_2CH_3$
1B	Cl	Cl	$CH_2CH_2CH_3$
1C	H	Cl	$C(CH_3)_3$
1D	Cl	Cl	$C(CH_3)_3$
2A	H	Cl	$(CH_2)_5CH_3$
2B	Cl	Cl	$(CH_2)_5CH_3$
2C	H	Cl	$(CH_2)_7CH_3$
2D	Cl	Cl	$(CH_2)_7CH_3$

Figure 1. Compounds included in this investigation.

Table I. Ionization Potentials in Electron Volts

Compd	n_N[a]	n_{CO}	n_O	n_{Cl}	n_{Cl}
1a	9.48	10.29	10.74	11.08	
1b	9.52	10.27	10.53	11.02	11.62
1c	9.38	10.05	10.79	11.19	
1d	9.56	9.98	10.69	11.06	11.65
2a	9.42	10.55	10.77	11.20	
2b	9.54	10.41	10.60	11.15	11.66
2c	9.35	10.48	10.77	11.20	
2d	9.59	10.35	10.62	11.19	11.70

[a] See text for explanation of these orbital designations.

This study will provide further support for use of photoelectron spectroscopy in studies of molecules of biological and pharmaceutical importance.[4]

The compounds studied in this work are shown in Figure 1. Representative spectra for a given *N*-chloramine–*N*,*N*-dichloramine pair (compounds **1a** and **1b**) are depicted in Figure 2. A complete listing of all "low-energy" ionization potentials for the eight compounds is presented in Table I. Band assignments are also given in Table I.

The photoelectron spectra of the *N*-chloramines contain four prominent low-energy ionization events. Extensive work in these laboratories on numerous similar compounds and model compounds having N, O, Cl, and carbonyl functional groups has shown that the lowest ionization process must correspond to the nitrogen lone pair, n_N, when there can be no mesomeric interaction between the N and carbonyl functions, as for all compounds considered in this study.[2,5,6] Likewise, the higher ionization processes should be assigned in the order n_{CO} (carbonyl oxygen lone pair) < n_O (ester oxygen lone pair) < n_{Cl} (chlorine lone pairs). It had been noted previously that the ionization potential corresponding to the ester oxygen lone pair is always higher than that for the carbonyl oxygen lone pair,[7] and we have always observed this ordering also. The chlorine lone pairs have different symmetries and are subject to spin–orbit coupling[8] and thus could correspond to several bands in the photoelectron spectrum. However, we detect only one Cl lone-pair band in the spectra of the *N*-chloramines, so we must conclude that any splitting caused by the difference in symmetries of the lone pairs and/or spin–orbit coupling must be too small to be resolved for these complex molecules.

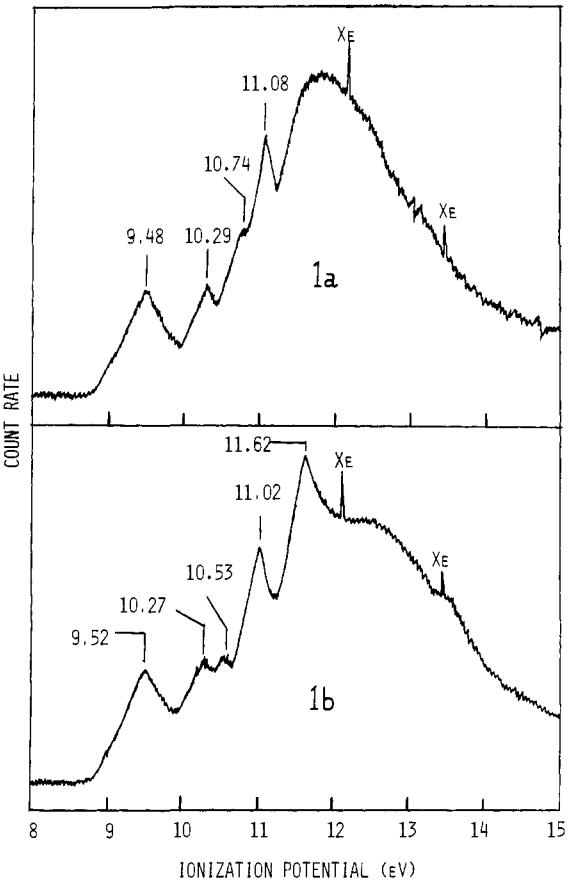

Figure 2. The photoelectron spectra of a pair of *N*-chloramine–*N*,*N*-dichloramine analogues.

Table II. Differences in Ionization Potential (eV) between Analogous *N*-Chloramines and *N*,*N*-Dichloramines

	Δn_N	Δn_{CO}	Δn_O
1b-1a	+0.04	−0.02	−0.21
1d-1c	+0.18	−0.07	−0.10
2b-2a	+0.12	−0.14	−0.17
2d-2c	+0.24	−0.13	−0.15

The photoelectron spectra of the *N*,*N*-dichloramines contain five lone-pair ionization bands. The ordering of the bands is the same as for the *N*-chloramines, i.e., n_N < n_{CO} < n_O < n_{Cl}, except that a fifth band appears which must correspond to a second n_{Cl} component. The two chlorine lone-pair components for the *N*,*N*-dichloramines probably result from a through-space interaction between the two chlorine functions. However, given that each chlorine has lone pairs of different symmetries and the possibility of spin–orbit coupling, the nature of this interaction is too complex to be further delineated. Bunzli et al. have observed two chlorine lone-pair bands for methylene chloride and three for 1,1-dichloroethene.[9]

The data in Table II represent the differences in the lowest three ionization energies between each *N*,*N*-dichloramine and its *N*-chloramine analogue [e.g., n_N(*N*,*N*-dichloramine) − n_N(*N*-chloramine)]. In the absence of unusual circumstances, the addition of a second chlorine function to an *N*-chloramine should cause an increase in all of the lone-pair ionization energies because of a destabilizing inductive effect on the various ionic states. The magnitude of the increase, of course, should decrease as the number of bonds between the chlorine and the heteroatom (N, O, CO) increases. As can be seen in Table II, this is clearly not the case. The ionic states corresponding

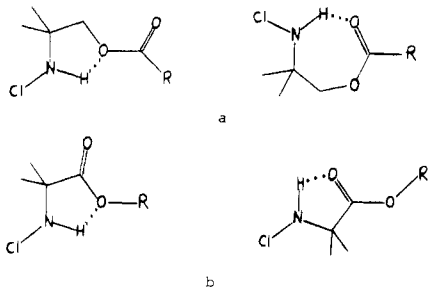

Figure 3. Possible intramolecular interactions for the *N*-chloramines.

to removal of the ester oxygen lone pair and the carbonyl oxygen lone pair actually are *stabilized* upon addition of the second chlorine. This observation can best be explained by postulating a through-space intramolecular interaction between the N–H hydrogen on the *N*-chloramines with the oxygen lone pairs as shown in Figure 3. Such an interaction, which might be viewed as a weak intramolecular hydrogen bond, would stabilize the oxygen lone pairs in the ground state causing an increase in ionization potential for n_{CO} and n_O relative to the *N,N*-dichloramines for which no such interaction is possible. One notes that the interaction seems to be largest for the ester oxygen lone pair in all cases but dramatically more so for the series **1** molecules. This can be rationalized by noting that, in general, five-membered rings are more stable than seven-membered ones. For the series **1** molecules the interaction with the ester oxygen leads to a pseudo-five-membered ring, while the interaction with the carbonyl oxygen is manifest in a pseudo-seven-membered ring. For the molecules in series **2** either interaction forms a pseudo-five-membered ring, and the difference is less pronounced. Hydrogen bonding to an ester oxygen in preference to the carbonyl oxygen has been discussed previously.[10] MINDO SCF–MO calculations on various anhydrides and their protonated forms indicate that protonation on the ester oxygen results in a more stable species than does protonation on the carbonyl oxygen; experimental data support these calculations.[10]

For all pairs of compounds studied the addition of a second chlorine caused an increase in the nitrogen lone-pair ionization potential. There are two rationalizations for this observation. First, chlorine has been observed to inductively destabilize nitrogen lone-pair ionic states to a greater extent than it mesomerically stabilizes them for several *N*-chloropiperidines.[2] Second, the N–H interaction with the oxygen lone pairs would be expected to increase the electron density at nitrogen in the ground state, thus causing a lower nitrogen lone-pair ionization energy for the *N*-chloramines than for the *N,N*-dichloramine analogues. It is this latter effect which we believe to be of primary importance in determining the relative antimicrobial activities of the *N*-chloramines vs. the *N,N*-dichloramines. The N–H···O interaction causes an increase in electron density at nitrogen which, in turn, causes the polarity of the N–Cl bond to increase for the *N*-chloramines. The chloramines having more highly polarized N–Cl bonds are denatured more rapidly by the donation of positive chlorine to the denaturant, rendering them less effective as antimicrobial agents. Photoelectron spectroscopy provides a reasonable rationalization for an increase in N–Cl bond polarity for the *N*-chloramines relative to the *N,N*-dichloramines, and thus this powerful spectroscopic technique aids in our understanding of why *N,N*-dichloramines are more effective antimicrobial agents than are their *N*-chloramine analogues.

We cannot say at this time whether our observed interaction between N–H and the oxygen lone pairs is a true intramolecular hydrogen bond. However, work employing other spectroscopic techniques is in progress in these laboratories which we hope will resolve this point.[11]

Experimental Section

The compounds studied in this work shown in Figure 1 were prepared and purified by methods described previously.[4] The photoelectron spectra were recorded by a Perkin-Elmer PS-18 spectrometer with the He(I) resonance line (584 Å or 21.22 eV) as the excitation source. The samples which were sufficiently volatile were studied at room temperature using the standard volatile inlet probe of the PS-18. Less volatile samples required the use of a heated inlet probe, but extreme caution was employed to ensure that the samples did not decompose upon heating. Xenon and argon were used as internal calibrants for all spectral runs, and the ionization potentials given in the text represent the average of at least four sets of data for each compound.

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