BRIEF COMMUNICATION

COMPLETE NEGLECT OF DIFFERENTIAL OVERLAP

STUDY OF THE BINDING OF SALTS TO

N-METHYL ACETAMIDE

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ABSTRACT The complete neglect of differential overlap method is used to investigate the binding of LiF, LiCl, NaF, and NaCl to N-methyl acetamide (NMA) as a model for these ions binding to a peptide moiety. The cation-----O═C—N—H----anion interaction is shown to result in a net residual charge on NMA, which becomes less positive as the difference in electronegativity between the anion and cation of the salt present increases. A residual charge of smaller magnitude is also found on a water molecule in the analogous system cation---O—H---anion, which displays this same dependence.

INTRODUCTION

In a recent paper, Renugopalakrishnan and Urry (1), using the complete neglect of differential overlap (CNDO/2) method, investigated theoretically the binding of Na^+ and Mg^{+2} to the carbonyl group of N-methyl acetamide (NMA), as a model for these ions binding to a peptide moiety. They noted the interesting fact that the charges on the cations were significantly reduced, leaving a residual positive charge on NMA. This finding is of particular relevance to the proposition made in 1942 by Laki (2, 3) that the effect of salts on some of the properties of proteins, such as their isoelectric points, may be explained if one assumed these salts to create a residual charge on the protein by interacting with the —C—N— units of the backbone. It is also relevant to Szent-Györgyi's electronic theory of cancer (4). Several studies have presented evidence for the existence of ion-peptide unit interactions in solutions of high salt concentration (5–7 and references therein.).

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In this paper we use the CNDO/2 method to estimate the residual charges (if any) on NMA when it interacts with the monovalent salts LiF, LiCl, NaF, and NaCl.

METHODS AND RESULTS

The molecular orbital calculations are performed by using the CNDO/2 method (8). The geometry of NMA used is that obtained from the electron diffraction study of Kitano et al. (9). The cations are initially assumed to approach the carbonyl oxygen of NMA along a path making an angle of 180° with the C═O bond, and the anions are also assumed to initially approach the amide group hydrogen in a direction making an angle of 180° with the N—H bond. The binding of the anions at the imide nitrogen and the cations at the carbonyl oxygen are consistent with earlier suggestions (5, 7, 16) as well as with crystal structure studies (6). The optimum distances of approach of the ions along the above paths are then obtained by varying these distances for each ion-NMA system until the energy minimum is located, assuming that the geometry of NMA remains as in the isolated molecule.

Table I gives the resulting optimum distances as well as the corresponding interaction energies and the charge transferred to NMA. It is interesting to note the significant amount of charge transferred to NMA in the case of Li^+, Na^+, and F^-, and the much stronger interaction of NMA with Li^+ compared with Na^+ and with F^- compared with Cl^-.

Although the results in Table I for Li^+ and Na^+ agree with earlier CNDO/2 calculations on these systems (10, 1), their dependence on the approximate quantum mechanical method used to estimate them should be pointed out. This may be seen by comparing the values in Table I with those we have calculated by a minimal basis (Slater-type orbitals-3 G) *ab initio* Hartree-Fock procedure, using the Gaussian 70 program with its internal parameters (11), for the systems Li^+---NMA and F^---NMA. The values of d, Q, and ΔE thus obtained with the same geometry input are, respectively, 1.57 Å, +0.43, and −105 kcal/mol for the former system, and 2.2 Å, −0.37, and −110 kcal/mol for the latter system. A more extended Gaussian basis set specially parameterized for Li^+ was found by Hinton et al. (12) to yield 1.75 Å, +0.06, and −51 kcal/mol, respectively, for d, Q, and ΔE in the similar system Li^+---N-methyl formamide. An STO-3G calculation by A. Pullman (14) for the system Na^+---NMA, using optimized exponents for Na^+, yielded an interaction energy of −49.7 kcal/mol at the minimum d of 1.95 Å. The STO-3G basis with its internal parameters for the cations has been shown by Pullman et al. (15, and references therein) to result in a strong

TABLE I
CNDO/2-DETERMINED OPTIMUM PARAMETERS FOR THE INTERACTION
OF NMA WITH Li^+, Na^+, F^-, AND Cl^-

	Cation		Anion	
	Li^+	Na^+	F^-	Cl^-
*d	2.16	2.6	2.2	2.8
‡Q	+0.27	+0.22	−0.32	−0.08
§ΔE	−83	−65	−82	−34

*Optimum distance of approach (Å) to the O of NMA for cations, and to the N atom for anions.
‡Electronic charge on NMA as obtained from Mulliken population analysis.
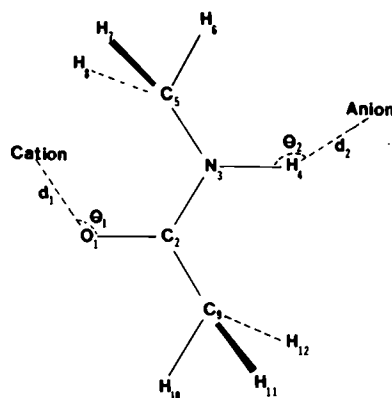§Interaction energy of the ion with NMA (kcal/mol).

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FIGURE 1   Nomenclature for the system cation---NMA---anion.

exaggeration of ΔE and of the closeness of approach. The sum of the van der Waals radius for O and the ionic radius of the cation yields 2.08 Å for Li^+ and 2.37 Å for Na^+, while that of N and the anion gives 2.83 Å for F^- and 3.31 Å for Cl^- (13).

Using the optimum distances given in Table I as a starting point, supermolecule calculations were performed on the system cation---O=C—N—H---anion for each of the four salts, simultaneously minimizing the cation---O distance, d_1, the H---anion distance, d_2,

the cation---O $\overset{\diagup C}{}$ angle, θ_1, and the N—H $\overset{\diagup anion}{}$ angle, θ_2 (Fig. 1). The distance variation was in increments of 0.05 Å and the angle variation in increments of 5°. The results are shown in Table II. The following observations may be made: (a) the minimum d_1 value for a particular cation is almost insensitive to the nature of the anion, and similarly for d_2; (b) although the anion remains almost linear with H—N, the cation has a θ_1 of 120° ± 5° in the four cases; (c) a significant residual positive charge on NMA, Q_{NMA}, is found for all the salts considered; (d) the charges on the cations and anions are quite different from the corresponding ones in the four salt molecules at their optimum interionic distances, which are given in Table III.

Table IV shows the electronic charge densities on the various atoms of NMA when isolated, and when in the presence of each of the four salts in the minimum energy conformations of Table II. The salt ions are seen to affect the charge densities on all of the atoms in NMA (not just those closest to them), with the H in —N—H losing, and the N gaining, the most electrons.

DISCUSSION

The present CNDO/2 study shows that the interaction of salts with NMA leads to significant positive residual charges on the latter. This makes NMA an active partner in deciding how the electrons distribute themselves among the three species, rather than a passive transmitter of

TABLE II

CNDO/2 MINIMUM CONFORMATION PARAMETERS FOR CATION---
NMA---ANION SYSTEMS*

Salt	LiF	NaF	LiCl	NaCl
d_1 (ångströms)	2.25	2.70	2.25	2.75
	(2.25)‡			
[N − H + d_2] (ångströms)	2.15	2.15	2.80	2.80
	(2.20)			
Θ_1 (degrees)	115	125	115	125
	(115)			
Θ_2 (degrees)	185	180	180	180
	(190)			
Q_{NMA}	+0.201	+0.076	+0.425	+0.294
	(+0.274)			
Q_{cat}	+0.389	+0.526	+0.423	+0.570
	(+0.374)			
Q_{an}	−0.590	−0.602	−0.848	−0.868
	(−0.648)			
ΔE (kcal/mol)	−370	−303	−294	−231
	(−360)			

*The conformational parameters d_1, d_2, Θ_1, and Θ_2 are as defined in Fig. 1; Q_{NMA}, Q_{cat}, and Q_{an} are the net residual charges of NMA, the cation, and anion, respectively; ΔE is the interaction energy of the three component supermolecule system, calculated as the difference between the total energy of the latter and the sum of the energies of the three isolated components: NMA, cation, and anion.
‡Values obtained using the intermediate neglect of differential overlap method.

charge from the anion to the cation. If similar interactions take place with the peptide backbond units in a protein, a pronounced effect on the conductivity of the protein could result.

Note that the present calculations are for systems in vacuum and do not take into account the presence of the solvent. The presence of strong ion-solvent interaction, as in a dilute aqueous system, for example will disfavor this type of interaction, as pointed out earlier (1, 6). Table V shows the minimum energy distances and charge densities on the three species in the
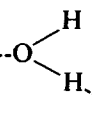
analogous system cation---O⟨H / H··· anion   for the four salts. As in the case of NMA, one

TABLE III

CNDO/2 MINIMUM CONFORMATION PARAMETERS FOR
THE CATION ... ANION SYSTEMS*

Salt	NiF	NaF	LiCl	NaCl
d(ångströms)	2.16	2.63	2.29	2.50
Q_{cat}	+0.562	+0.610	+0.428	+0.306
ΔE (kcal/mol)	−229	−193	−238	−295

*d is the interionic distance; Q_{cat} is the charge on the cation which is equal and opposite in sign to the charge on its conjugate anion; ΔE is the interaction energy of the cation and anion, calculated as the difference between the total energy of the system, and the sum of the energies of its two composite anion and cation.
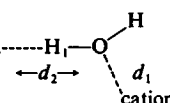
TABLE IV
CNDO/2 CHARGE DENSITIES ON THE VARIOUS ATOMS OF NMA IN THE ABSENCE AND PRESENCE OF SALTS AT THE MINIMUM CONFORMATIONS OF TABLE II

NMA atom no.*	Isolated NMA	$Li^+\ldots NMA\ldots F^-$	$Na^+\ldots NMA\ldots F^-$	$Li^+\ldots NMA\ldots Cl^-$	$Na^+\ldots NMA\ldots Cl^-$
1	−0.338	−0.369	−0.392	−0.341	−0.362
2	+0.350	+0.387	+0.383	+0.397	+0.392
3	−0.220	−0.374	−0.378	−0.274	−0.277
4	+0.110	+0.310	+0.311	+0.274	+0.269
5	+0.105	+0.124	+0.120	+0.127	+0.122
6	−0.005	+0.021	+0.007	+0.053	+0.037
7	−0.001	+0.029	+0.001	+0.047	+0.019
8	−0.001	+0.029	+0.001	+0.047	+0.019
9	−0.088	−0.083	−0.085	−0.090	−0.091
10	+0.029	+0.013	+0.008	+0.027	+0.020
11	+0.029	+0.057	+0.050	+0.079	+0.073
12	+0.029	+0.057	+0.050	+0.079	+0.073

*The numbering of the atoms is that shown in Fig. 1.

TABLE V
CNDO/2 MINIMUM CONFORMATION PARAMETERS FOR THE SYSTEMS CATION---H_2O---ANION*

Salt	LiF	NaF	LiCl	NaCl
d_1 (ångströms)	2.55	3.05	2.60	3.00
$[O - H + d_2]$ (ångströms)	2.10	2.15	2.55	2.55
Q_0	−0.421	−0.439	−0.323	−0.343
	[−0.285]			
Q_{H_1}	+0.322	+0.314	+0.305	+0.297
	[+0.142]			
Q_{H_2O}	−0.040	−0.075	+0.077	+0.051
Q_{cat}	+0.681	+0.759	+0.718	+0.745
Q_{an}	−0.641	−0.684	−0.795	−0.796
ΔE (kcal/mol)	−220	−185	−155	−133

*The conformational parameters d_1 and d_2 are defined as follows: anion------H_1—O⟨^{H}, in which the cation lies

←d_2→ d_1 cation

along the bisector of the H—O⟨$_H$ angle and the anion along the extension of the O—H bond; Q_0 and Q_{H_1} are the charge densities of the O and H_1 atoms in the presence of the salt, with those corresponding to an isolated H_2O molecule being shown in square brackets (a fixed experimental O—H distance of 0.9572 Å and an H—O⟨^{H} angle of 104.52° are assumed); Q_{H_2O}, Q_{cat}, and Q_{an} are the net residual charges on the H_2O, the cation, and the anion, respectively; ΔE is the interaction energy of the three species in the supermolecule system, calculated as in Tables II and III.
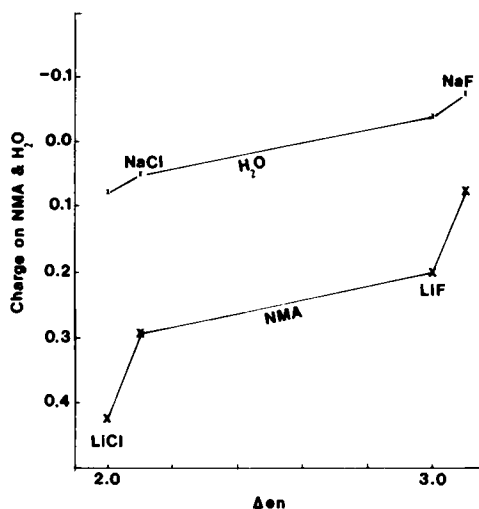
FIGURE 2   The variation of the residual charges on NMA and H_2O with the difference in electronegativity between the anion and cation of the salt present for the four salts considered for the system cation---NMA (H_2O)---anion.

observes net residual charges on the water molecule in the presence of the salts, although they are of much smaller magnitude. The charges on the cations and anions are also seen to be different from those in Tables II and III. The presence of many water molecules around each ion in a dilute aqueous system will greatly enhance the salt-water interaction energies of Table V. The ion-peptide unit interactions considered here are expected to become more favorable in a nonaqueous environment (such as in membranes or the interior of a protein), as well as in aqueous solutions of high salt concentratin (1, 6, 7).

The residual charges on NMA (Table II) are plotted against the difference in electronegativity, Δen, of the cation and anion of the particular salt present in Fig. 2. This figure reveals a tendency for the residual charge on NMA to become less positive as Δen increases. This correlation may offer a possible explanation for the increase in the isoelectric point of casein with the Δen of various added salts that was observed by Laki (2, 3). As the salt-induced charge on the protein becomes less positive, less hydroxyl ions will be required from the solution to neutralize it and maintain it at the isoelectric point, which leads to an increase in the measured pH of the solution. The similar correlation obtained between the residual charge on the water molecule (Table V) and Δen, plotted in Fig. 2, may also be a contributing factor to the increase in the isoelectric point of casein with Δen by the same above logic.

Note that the present conclusions are based on the use of the CNDO/2 method and hence are subject to all of its limitations.

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