SCF *AB INITIO* MOLECULAR ORBITAL STUDY ON THE RELATIVE AFFINITIES OF PEPTIDE AND ESTER CARBONYL GROUPS FOR Na^+ AND K^+ IONS

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1. Introduction

The alkali ion binding and transport capacity of cyclic peptides, depsipeptides and macrotetrolides has become a fundamental tool for the investigation of the physicochemical basis of membrane functioning [1–3]. The cationic affinities and selectivities of the ionophores are generally considered as determined by the architectural (conformational) properties of the carriers and the differential interaction energies of the metal cations with the liganding oxygens available on the carrier and with water [1–9].

A quantum mechanical investigation of the conformational properties of the cyclic antibiotics is being developed in our laboratory and results have been presented recently for enniatin B [10]. We have undertaken a parallel series of quantum mechanical studies on the binding between the cations and the ionophores. In this introductory study, we discuss the intrinsic relative affinities and binding characteristics of Na^+ and K^+ for the carbonyl oxygens of the peptide and ester groups, and for water.

2. The method

We have here adopted the "supermolecule" approach, computing the binding energy as the difference between the energy of the complex considered as a single unit and the sum of the energies of its isolated components evaluated in the same approximation.

In order to avoid the uncertainties inherent to semi-empirical methods, we have utilized an *ab initio* self-consistent molecular orbital procedure, where all the electrons are considered in the field of all the nuclei of the system, the molecular orbitals being developed as linear combinations of a basis set of atomic orbitals [11], conveniently expressed in terms of gaussian functions. The choice of the atomic basis fixes the limits for the accuracy of the results but also for the feasibility of computations on large systems. In order to be able to treat model systems large enough to be representative, we have limited ourselves, in this exploratory study, to the use of a relatively small basis of gaussian orbitals, the more so as we were interested rather in the general and *relative* characteristics of the interactions than in the absolute numbers. For this purpose, an STO 3G basis [12, 13] appropriately chosen [14] proved convenient. The computations have been performed with the program Gaussian 70 [15]. The STO 3G basis for Na^+ was reoptimized starting from the molecular standard exponents of reference [13] and the corresponding basis for K^+ was optimized starting from the atomic STO 3G basis [16]. Although it is known that minimal basis sets of the type utilized yield too large values of the interaction energies and too short distances of approach in intermolecular complexes of the kind studied [17, 18] the relative ordering of the values and the general relative features of the binding appear correctly reproduced (*vide infra*).

N-methylacetamide and methylacetate were chosen as model compounds for the peptide and ester groups. They were set in their most stable conformations found in a previous *ab initio* study of their rotational barriers [19], namely a *trans* conformation of the extreme methyl groups, the CH_3 substituent on carbon eclipsing the CO bond, the CH_3 substituent on the hereoatom staggered with respect to CO.

In this configuration, a linear approach of the cation

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(Na^+ or K^+) was performed along the CO_2 direction in the amide or ester plane; then in the most stable position a rotation of the ion around the carbonyl oxygen was allowed in the amide or ester plane (rotation θ). Furthermore, the rotation of the cation was studied in the plane containing the CO bond and perpendicular to the previous one, maintaining fixed the distance of the ion to the carbon end of the carbonyl group (rotation ϕ). A similar out-of-plane rotation maintaining fixed the distance to the oxygen was also studied (rotation ϕ').

The interaction of both cations with one molecule of water was computed in the same fashion for comparison.

3. Results

Fig. 1a and 1b give the variation of the interaction energy with distance for Na^+ and K^+, respectively, approaching the model compounds and water. Fig. 2 gives the corresponding in-plane angular variation for the two model compounds and fig. 3 shows the influence of the out-of-plane angular displacement ϕ.

Fig. 4 gives an example of the rotation ϕ'. Table 1 summarizes the binding characteristics.

Examination of this set of results permits to formulate the following observations:

i) At the minimal distance of approach of the cations the intrinsic affinities of both carbonyl groups are appreciably smaller for K^+ than for Na^+, as shown by the relative depths of the minima and the relative slopes of the potential curves. At the same time the corresponding equilibrium distance in the complex is larger for K^+ than for Na^+. Both the binding energies and equilibrium distances follow the order of the corresponding quantities for the hydration of Na^+ and K^+. As already stated the numerical values of the binding energies are too large and the equilibrium distances too short as shown by the comparison of computed and experimental values for hydration given in table 1. The relative ordering of these quantities is, however, correctly reproduced. Moreover, the ratios of our equilibrium values of ΔE and d with the corresponding quantities obtained in a very recent computation of near Hartree-Fock accuracy [21] are seen to be the same for the two ions indicating a presumably correct ordering of the other results.

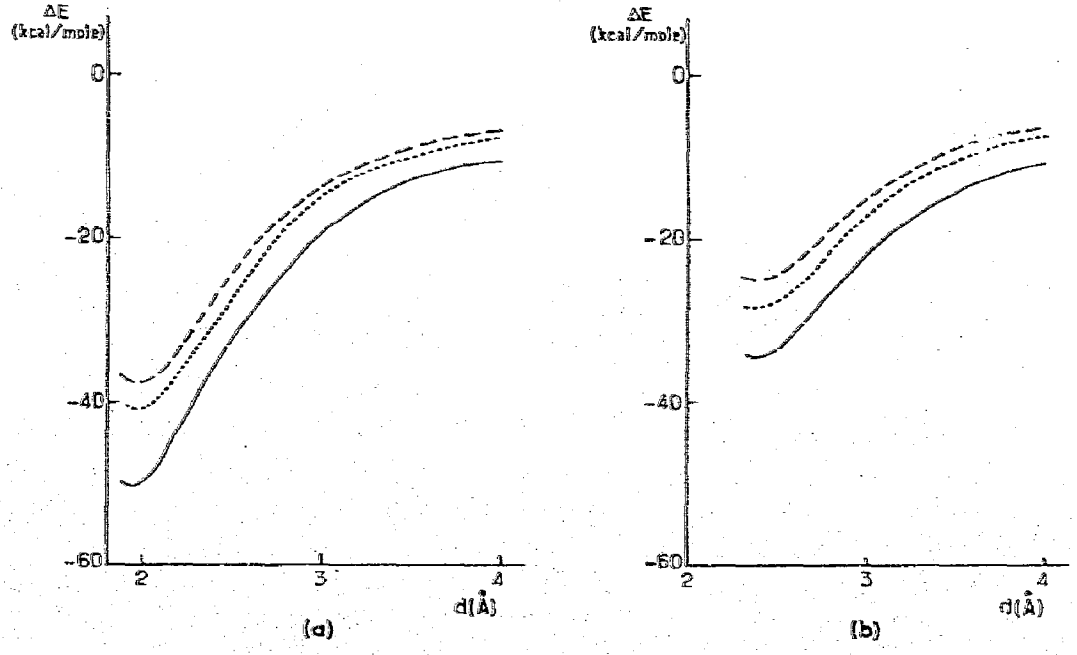

Fig. 1. Binding energies for (a) Na^+ and (b) K^+ interaction with: (——) the peptide group, (– – –) the ester group (linear approach of the cation toward the carbonyl oxygen along the C=O axis), (·····) water (approach towards the O atom along the bissectrix of the HOH angle).

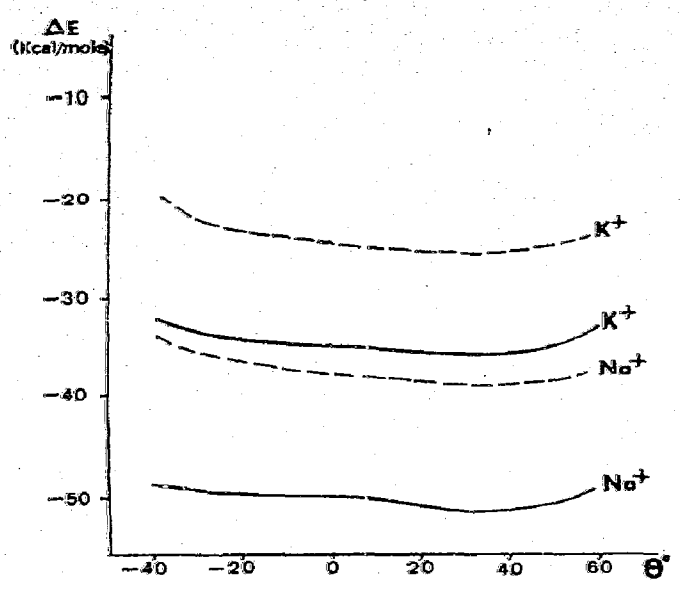

Fig. 2. Variation of the binding energy with the angular displacement (θ) of the cation in the plane of the amide or ester groups at the equilibrium distance of fig. 1.
(——) Interaction of the amide with the cation as indicated.
(– – –) Interaction of the ester with the cation as indicated.

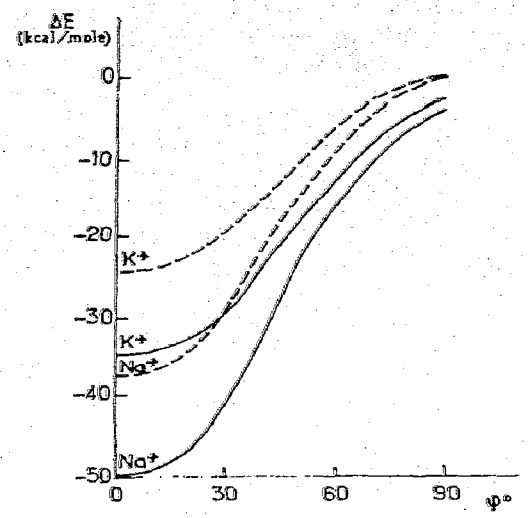

Fig. 3. Variation of the binding energy with the out-of-plane displacement ϕ (at a fixed distance of the carbonyl).
(——) Interaction of the amide with the cation as indicated.
(– – –) Interaction of the ester with the cation as indicated.

ii) The rotation of the cation out of the plane of the amide or ester bond has a stronger effect on the binding energy than the in-plane rotation, the Na^+ interaction showing a sharper decrease than the K^+ interaction with increasing ϕ. It is seen, however, that for both ions, appreciable binding still occurs even for large out-of-plane displacements (at $\phi = 45°$ about one half of the binding energy is conserved).

The other out-of-plane rotation at a constant distance from the oxygen (ϕ') induces a smaller loss in binding energy, half of the binding energy being conserved in the perpendicular position. The maximum binding is, however, clearly in the plane, in contradic-

Table 1
Binding characteristics at equilibrium for Na^+ and K^+ interaction with amide, ester and water.

	Na^+			K^+		
	$-\Delta E$	d	$\theta°$	$-\Delta E$	d	$\theta°$
Amide	49.7	1.95	35	35.1	2.35	35
Ester	38.8	1.99	35	25.5	2.40	35
Water (a)	40.7(27)	1.95(2.2)	0	27.9(18)	2.40(2.65)	0
(b)	25.2	2.25		17.5	2.69	
(c)	0.62	1.13		0.62	1.12	

(a) Present computation.
(b) Near-Hartree-Fock limit [21].
(c) Ratio (a)/(b).
ΔE: binding energy (kcal/mole);
d: minimal distance of approach (A);
$\theta°$: angle of the oxygen–cation direction with the CO bond.
Experimental values [20] in parentheses.

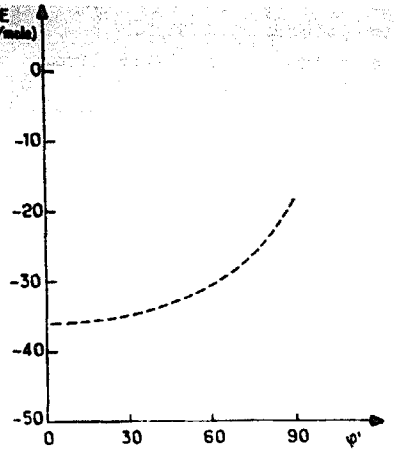

Fig. 4. Variation of the binding energy with the out-of-plane displacement ϕ' at a fixed distance of the oxygen of the carbonyl (example shown corresponds to Na^+ and the ester).

tion with a recent result [25] concluding to the existence of an out-of-plane minimum which is clearly one of the artefacts of the CNDO method [26].

The comparison of the relative binding properties of amide and ester carbonyl groups indicates that, for both cations:

i) the intrinsic affinity of the amide carbonyl is appreciably larger than that of the ester carbonyl, and larger than the corresponding affinity of water (fig. 1);

ii) the intrinsic affinity of the ester carbonyl is close to the corresponding affinity of water but slightly smaller (fig. 1);

iii) the equilibrium distances of approach are practically the same for the ester and water, but shorter for the amide.

This set of results appear to represent a basis for a quantiative differentiation of the relative energies of stabilization corresponding to different modes of interaction of the Na^+ and K^+ cations with the carbonyl groups of depsipeptides. Thus e.g. the finding that the intrinsic affinity of the amide carbonyl is appreciably greater for both ions than that of the ester carbonyl suggests that this factor is responsible at least to a large extent for the decrease in complex stability upon the replacement of the N-methyl peptide group by an ester group in enniatin B [27] or for the increase in complex stability upon the complete replacement of the L-lactic and D-α-hydroxyisovaleric acid residues by L- and D-proline, respectively, in valinomycin [28]. The curves representing the angular dependence of the binding may be of particular utility for the evaluation of the binding energy in the K^+ complex of enniatins in which the K^+···CO arrangement is far from linear and coplanar, in distinction to the complex of valinomycin in which the ester bonds point almost directly to the cation [27]. Similarly the knowledge of the dependence of the binding energy upon the cation··· CO distance offers the possibility of a more precise evaluation of the binding energy of the Na^+ cation in valinomycin in which, because of the small size of the ion with respect to the relatively large size of the cavity, the Na^+-cation is not situated in the center of this cavity but shifts toward its perimeter, thereby giving rise to differing interactions with the various ester groups [28].

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