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A Molecular Orbital Study on Tetranactin-NH_4^+ Complex

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The inclusion complex of NH_4^+ with tetranactin increases the fluxes of ions across thin lipid membranes. When NH_4^+ is inserted into the ionophore of tetranactin, the conformation changes greatly; this structural change is called an "induced fit." When the conformation change of tetranactin is induced by the approach of NH_4^+, the four ether oxygens of the tetrahydrofuran rings and the four carbonyl oxygens of the ester groups function to include NH_4^+ in the molecule. The ether oxygens rotate inwards to hold NH_4^+ inside tetranactin, and the carbonyl oxygens rotate inwards to prevent NH_4^+ from escaping. The four ether oxygens form linear hydrogen bonds with NH_4^+. Although the four carbonyl oxygens approach NH_4^+ at distances similar to those of the four ether oxygens, the carbonyl oxygens do not form linear hydrogen bonds with NH_4^+. In order to clarify the induced fit mechanism of the ionophore, in this paper, the inclusion complex of NH_4^+ with tetranactin was studied with regard to the arrangement of NH_4^+ in the tetranactin molecule from a quantum-chemical point of view. Since tetranactin is too large for double zeta *ab initio* SCF calculations, functional groups which have large contributions to the insertion of NH_4^+ were selected as a model for the tetranactin; the model consisted of four HCHO molecules and four H_2O molecules. The model was in good accord with the actual result, and thus appears to be appropriate.

Tetranactin is composed of four homonactinic acid moieties, and the interaction energy between each of them and NH_4^+ is significant for the arrangement of NH_4^+. The interaction energy between NH_4^+ and the four ether groups was -73.2 kcal/mol, and the interaction energy between NH_4^+ and the four carbonyl groups was -39.4 kcal/mol. The interaction energy between NH_4^+ and the ether groups was thus about 1.9 times larger than that between NH_4^+ and the ester groups. The interaction energy between NH_4^+ and the eight ether and ester groups was -109.0 kcal/mol.

From the results of geometry optimizations, the interaction energy between NH_4^+ and CH_3OCH_3 was larger than that between NH_4^+ and HCOOH by 5.8 kcal/mol due to the electrostatic interaction energy. Therefore, even though the four carbonyl groups may move to accommodate NH_4^+ in tetranactin, the four ether groups of tetranactin will interact more strongly with NH_4^+ than the four carbonyl groups, and NH_4^+ will orient to the ether groups.

Moreover, when perturbation of the ionophore by the rotation of NH_4^+ is neglected, the rotational inhibition energy of NH_4^+ in tetranactin was calculated to be 9.8 kcal/mol; thus, NH_4^+ is expected to orient to the four ether oxygens.

Keywords——MO study; structure; tetranactin; nonactin; *ab initio*; quantum chemistry; inclusion complex; ammonia; molecular complex

Nonactins, which are macrotetrolide antibiotics, are known to increase the fluxes of ions across thin lipid membranes.[2] Tetranactin, one of the nonactins, forms ion complexes. The molecular structures of several tetranactin and nonactin complexes have been determined from

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X-ray diffraction data.[3)]

The molecular shape of the uncomplexed tetranactin is fairly flat, elongated and twisted.[3g)] When NH_4^+ approaches, the oxygen atoms of the tetrahydrofuran rings rotate inwards to hold NH_4^+ in the molecule, and the carbonyl oxygen atoms rotate inwards to prevent NH_4^+ from escaping.[3k)] By the movements of these atoms, the tetranactin is able to include NH_4^+. In the process of approach of the four ether oxygens and the four carbonyl oxygens, it is interesting to speculate why the four ether oxygens bind NH_4^+ and the four carbonyl oxygens prevent NH_4^+ from escaping.

The four hydrogens in NH_4^+ do not fit with the four carbonyl oxygens of tetranactin, but do fit with the four ether oxygens. If the interaction energy between NH_4^+ and an ether oxygen is more stable than that between NH_4^+ and a carbonyl oxygen, the structure in which tetranactin includes NH_4^+ would be formed by the interaction forces between NH_4^+ and the ether oxygens of tetranactin. After being included in the tetranactin, NH_4^+ would not be able to rotate to accommodate the four carbonyl oxygens, since it would bind to the four ether oxygens more strongly than to the four carbonyl oxygens.

In this paper, the rotation of NH_4^+ in the tetranactin-NH_4^+ complex is studied from a quantum-chemical point of view, in connection with the interaction energies of NH_4^+ with ether oxygen and carbonyl oxygen.

The entropy change may be very small, if the four hydrogens of NH_4^+ rotate from the position fitting the four ether oxygens to that fitting the four carbonyl oxygens. Moreover, even though displacements of the hydrogens in NH_4^+ are caused by the rotation, the tetranactin structure should not be greatly changed by the perturbation occurring with the rotation of NH_4^+. X-ray diffraction analyses have shown that the ammonium hydrogen atoms form hydrogen bonds with tetrahydrofuran ether oxygens, and that no signs of rotational disorder were detected for the NH_4^+ ion.[3)] Further, no strong interaction was observed between NH_4^+ and carbonyl oxygen atoms in the infrared (IR) and Raman spectra.[4)] Accordingly, quantum-chemical studies on the arrangement of NH_4^+ in the tetranactin-NH_4^+ complex should give useful information on the nature of the complex.

Method

Molecular orbital calculations have been carried out within the closed-shell-LCAO-SCF approximation by the *ab initio* and semiempirical methods on HITAC 8700 and 8800 computers in the Tokyo University Computer Center and HITAC M-180 Computer in the Institute for Molecular Science. *Ab initio* calculations were performed using the GAUSSIAN 70 program.[5)] The basis sets used were 4-31G and STO-3G.[6)] The basis set was 4-31G, unless otherwise stated. Semiempirical calculations were performed by the CNDO/2 method.[7)] In the CNDO/2 method, the total energy, E, is conveniently divided into intra- and interatomic terms, giving

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3) *a*) M. Dobler, J.D. Dunitz, and B.T. Kilbourn, *Helv. Chim. Acta*, **52**, 2573 (1969); *b*) Y. Nawata and K. Kondo, *Acta Cryst.*, **B27**, 1680 (1971); *c*) M. Dobler, *Helv. Chim. Acta*, **55**, 1371 (1972); *d*) Y. Iitaka, T. Sakamaki, and Y. Nawata, *Chemistry Letters*, **1972**, 1225; *e*) M. Dobler and R.P. Phizackerley, *Helv. Chim. Acta*, **57**, 664 (1974); *f*) Y. Nawata, T. Sakamaki, and Y. Iitaka, *Acta, Cryst.*, **B30**, 1047 (1974); *g*) *Idem*, *Chemistry Letters*, **1975**, 151; *h*) T. Sakamaki, Y. Iitaka, and Y. Nawata, *Acta Cryst.* **B32**, 768 (1976); *i*) K. Neupert-Laves and M. Dobler, *Helv. Chim. Acta*, **59**, 614 (1976); *j*) T. Sakamaki, Y. Iitaka, and Y. Nawata, *Acta Cryst.*, **B33**, 52 (1977); *k*) Y. Nawata, T. Sakamaki, and Y. Iitaka, *ibid.*, **B33**, 1201 (1977).

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6) *a*) W.J. Hehre, R.F. Stewart, and J.A. Pople, *J. Chem. Phys.*, **51**, 2657 (1969); *b*) R. Ditchfield, W.J. Hehre, and J.A. Pople, *ibid.*, **54**, 724 (1971).

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$$E = \sum_{r} E_r + \sum\sum_{r<s} E_{rs}$$

where r and s represent atoms. The second term on the right was divided into two terms (intra- and intermolecular terms). If i and j, and k and l represent atoms in the A and B molecules, respectively, we have

$$\sum\sum_{r<s} E_{rs} = \sum_{i}\sum_{k} E_{i_A k_B} + \Big(\sum\sum_{i<j} E_{i_A j_A} + \sum\sum_{k<l} E_{k_B l_B}\Big)$$

where $\sum_{i}\sum_{k} E_{i_A k_B}$ is the total intermolecular two-atom energy.

Energy decomposition analyses in our *ab initio* calculations were carried out using the method of Morokuma *et al.*[8] The intermolecular interaction energy ΔE was divided into five terms: electrostatic (ES), exchange repulsion(EX), polarization(PL), charge transfer(CT), and a mixing term (MIX).

The results described in this paper for the insertion of NH_4^+ into tetranactin were obtained using a model.

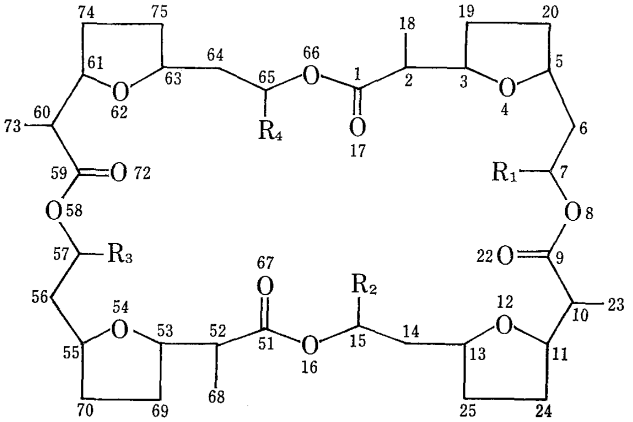

Fig. 1. Structure of Tetranactin. R_1, R_2, R_3, and R_4 are Ethyl Groups

Table I. Coordinates for Various Arrangements of NH_4^+ in the Tetranactin-NH_4^+ Complex in Å

Atom	x	y	z
N	7.11852	5.23169	2.24562
NH_4^+ (I)			
H^1	6.92537	5.85099	3.04824
H^2	6.27316	4.68310	2.02326
H^3	7.38373	5.80169	1.42721
H^4	7.89161	4.59087	2.48371
NH_4^+ (II)			
H^1	7.53473	5.86595	2.94526
H^2	6.34945	4.69770	2.67969
H^3	6.75031	5.78477	1.45596
H^4	7.83949	4.57845	1.90138
NH_4^+ (III)			
H^1	7.91330	5.84003	2.49711
H^2	6.89518	4.61170	3.03981
H^3	6.29659	5.81442	2.02229
H^4	7.36919	4.66073	1.42329

Geometries——The coordinates of carbon, nitrogen and oxygen were obtained from the results of X-ray analyses.[3k] The NH distance for NH_4^+ was 1.032 Å.[9] The structure and atom numbering are shown in Fig. 1. For the arrangement of NH_4^+ in tetranactin, three structures, I, II, and III, were considered. First the structure in which the four ammonium hydrogens form hydrogen bonds with tetrahydrofuran ether oxygens was constructed. When the four angles of $N-H\cdots O^4$, $N-H\cdots O^{12}$, $N-H\cdots O^{54}$ and $N-H\cdots O^{62}$ approached 180°, it was assumed that the most stable structure had been reached. This structure is called the "ether fit model," and the coordinates are shown in Table I. The arrangement of NH_4^+(I) was very close to the structure reported from X-ray diffraction data. This is, the interaction energy between NH_4^+ and tetranactin in the "ether fit structure" is minimum. The method mentioned above is appropriate for identifying the local minimum of the interaction energies between the four carbonyl oxygens and the four NH bonds of NH_4^+ and between the four middle points mentioned below and the four NH bonds of NH_4^+.

Secondly, the structure in which the four ammonium hydrogens approach the middle points M^1, M^2, M^3, and M^4 between O^4 and O^{17}, between O^{62} and O^{72}, between O^{54} and O^{67}, and between O^{12} and O^{22}, respectively, was considered. This structure is called the "middle fit model." The distance between O^4 and O^{17} of a homonactinic acid moiety is 3.21 Å; the distances between O^{62} and O^{72}, between O^{54} and O^{67}, and between O^{12} and O^{22} are 3.18, 3.18, and 3.16 Å, respectively. The distances between the two oxygens in each pair are shorter than the distance between either of the two oxygens in a pair and any other oxygen. Therefore the selection of the rotational models seems appropriate.

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[8] *a)* K. Morokuma, *J. Chem. Phys.*, **55**, 1236 (1971); *b)* K. Kitaura and K. Morokuma, *Int. J. Quantum Chem.*, **10**, 325 (1976); *c)* H. Umeyama, K. Kitaura, and K. Morokuma, *Chem. Phys. Letts.*, **36**, 11 (1975); *d)* H. Umeyama and K. Morokuma, *J. Amer. Chem. Soc.*, **98**, 4400 (1976); *e) Idem, ibid.*, **98**, 7208 (1976); *f)* H. Umeyama, K. Morokuma, and S. Yamabe, *ibid.*, **99**, 330 (1977); *g)* H. Umeyama and K. Morokuma, *ibid.*, **99**, 1316 (1977); *h)* K. Morokuma and H. Umeyama, *Chem. Phys. Letts.*, **49**, 333 (1977); *i)* H. Umeyama and S. Nakagawa, *Chem. Pharm. Bull.*, **25**, 1671 (1977).

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Thirdly, the structure in which the four ammonium hydrogens form hydrogen bonds with the ester carbonyl oxygens was constructed. This structure is called the "carbonyl fit model," and the coordinates are shown in Table I. When the four angles N–H···O^{17}, N–H···O^{22}, N–H···O^{67} and N–H···O^{72} were close to 180°, the coordinates were considered to be those of the "carbonyl (ester) fit model." In order to compare the "fit structure" to the structure in which only one N–H···O^{i} bond is 180° and in which the other three N–H···O^{j} bonds are bent similarly (we call this structure the "180° model"), the 180° model was laso calculated. NH_4^+ in the ether fit model, the middle fit model, the carbonyl fit model, the ether 180° model, or the carbonyl 180° model is indicated by NH_4^+(I), NH_4^+(II), NH_4^+(III), NH_4^+(I′) or NH_4^+(III′), respectively. The ionophore structure should be little changed due to induced fit effects. In this paper, however, the perturbation of the ionophore by the rotation of NH_4^+ was neglected.

Coordinates of the hydrogens of tetranactin were determined as follows; r(CH) and r(OH) for HCOOH are 1.097 and 0.972 Å, respectively; r(OH) for H_2O is 0.956 Å; r(CH) for HCHO is 1.097 Å; r(CH) for CH_3OCH_3 is 1.094 Å.[10] Further, r(CH) and r(OH) for CH_3OH are 1.094 and 0.960 Å; and r(CH) for CH_3COOCH_3 is 1.094 Å.[9] The hydrogens mentioned above are placed on the bonds obtained from the X-ray diffraction data. The hydrogens which are not on the bonds were determined as described in another paper.[11]

In this paper, the tetranactin part is broken up to simplify the calculations. When such models are used in place of tetranactin, the conclusions should be unaffected. Since tetranactin is composed of four homonactinic acid moieties, the interaction energy between NH_4^+ and a single homonactinic acid can be considered. The interaction energies between NH_4^+ in the ether fit model and each of the various parts of the homonactinic acid moiety from O^{58} to O^{65} were calculated using an STO-3G basis set. It was found that the contributions of the ether region with O^{62} and the ester region with O^{72} to the interaction energy between NH_4^+ and the homonactinic acid moiety were 78.4% and 11.8%, respectively. Accordingly, tetranactin can be broken into segments without affecting the conclusions obtained in this paper.

In the *ab initio* calculations for tetranactin, the energy of NH_4^+ is first calculated with one ether (HO^{12}H) or with one ester (HCHO^{22}) in a single homonactinic acid moiety. The result is compared with the energy of NH_4^+ calculated with HO^{12}H and HCHO^{22} in the SCF process in connection with the rotational inhibition of NH_4^+. Secondly, the energy of NH_4^+ is calculated with four HOH molecules or with four HCHO molecules in tetranactin. The result is compared with the energy of NH_4^+ calculated with four HOH molecules and four HCHO molecules, in connection with the rotational inhibition of NH_4^+. In the second calculations mentioned above, although NH_4^+, HO^{4}H, HO^{12}H, HO^{54}H, HO^{62}H, HCHO^{17}, HCHO^{22}, HCHO^{67} and HCHO^{72} are included in the SCF calculations, the other molecules except for NH$^+$, HO^{12}H and HCHO^{22} are included as point charges; these point charges were obtained from calculations for each isolated molecule of HOH and HCHO.

Calculations of Rotational Inhibition Energy of NH_4^+——When HO^{i}H and HCHO^{m} molecules are used in place of the ether and ester groups in tetranactin, the energy of rotational inhibition is given by the following equation.

$$\varDelta E_{\mathrm{ROT}} = E_{[\mathrm{NH_4^+(III)}\cdots\sum_i^4\mathrm{HO}^i\mathrm{H}\cdots\sum_m^4\mathrm{HCHO}^m]} - E_{[\mathrm{NH_4^+(I)}\cdots\sum_i^4\mathrm{HO}^i\mathrm{H}\cdots\sum_m^4\mathrm{HCHO}^m]}$$

where $\sum_i^4$HO^{i}H means that the set of the four water molecules is treated as a polyatom. The three dots indicate the complex. Moreover, the above equation can be approximated as follows.

$$\begin{aligned}\varDelta E_{\mathrm{ROT}} = {} & [E_{[\mathrm{NH_4^+(III)}\cdots\sum_i^4\mathrm{HO}^i\mathrm{H}]} + E_{[\mathrm{NH_4^+(III)}\cdots\sum_m^4\mathrm{HCHO}^m]} \\ & -\delta E_{\mathrm{NH_4^+(III)}} + E_{[\sum_i^4\mathrm{HO}^i\mathrm{H}\cdots\sum_m^4\mathrm{HCHO}^m]}] \\ & -[E_{[\mathrm{NH_4^+(I)}\cdots\sum_i^4\mathrm{HO}^i\mathrm{H}]} + E_{[\mathrm{NH_4^+(I)}\cdots\sum_m^4\mathrm{HCHO}^m]} \\ & -\delta E_{\mathrm{NH_4^+(I)}} + E_{[\sum_i^4\mathrm{HO}^i\mathrm{H}\cdots\sum_m^4\mathrm{HCHO}^m]}]\end{aligned}$$

where δE_{M} is the overestimated interaction energy between NH_4^+(I) or NH_4^+(III) and the ionophore. Since both NH_4^+(I) and NH_4^+(III) have two hydrogen bonds to each of the homonactinic acid moieties in tetranactin, $\delta E_{\mathrm{NH_4^+(I)}} \fallingdotseq \delta E_{\mathrm{NH_4^+(III)}}$ may be assumed. Accordingly, the rotational inhibition energy is approximately given by the following equation.

$$\begin{aligned}\varDelta E'_{\mathrm{ROT}} = {} & [E_{[\mathrm{NH_4^+(III)}\cdots\sum_i^4\mathrm{HO}^i\mathrm{H}]} + E_{[\mathrm{NH_4^+(III)}\cdots\sum_m^4\mathrm{HCHO}^m]}] \\ & -[E_{[\mathrm{NH_4^+(I)}\cdots\sum_m^4\mathrm{HO}^i\mathrm{H}]} + E_{[\mathrm{NH_4^+(I)}\cdots\sum_m^4\mathrm{HCHO}^m]}]\end{aligned}$$

Determination of Models for Tetranactin by the CNDO/2 Method——The structure of tetranactin is shown in Fig. 1. Only the atoms positioned near NH_4^+ were included in the calculations. Four structures of the form

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10) G. Hertzberg, "Electronic Spectra of Polyatomic Molecules," Van Nostrand, New York, N.Y., 1966.

11) S. Nakagawa and H. Umeyama, *J. Amer. Chem. Soc.*, 100, 7716 (1978).

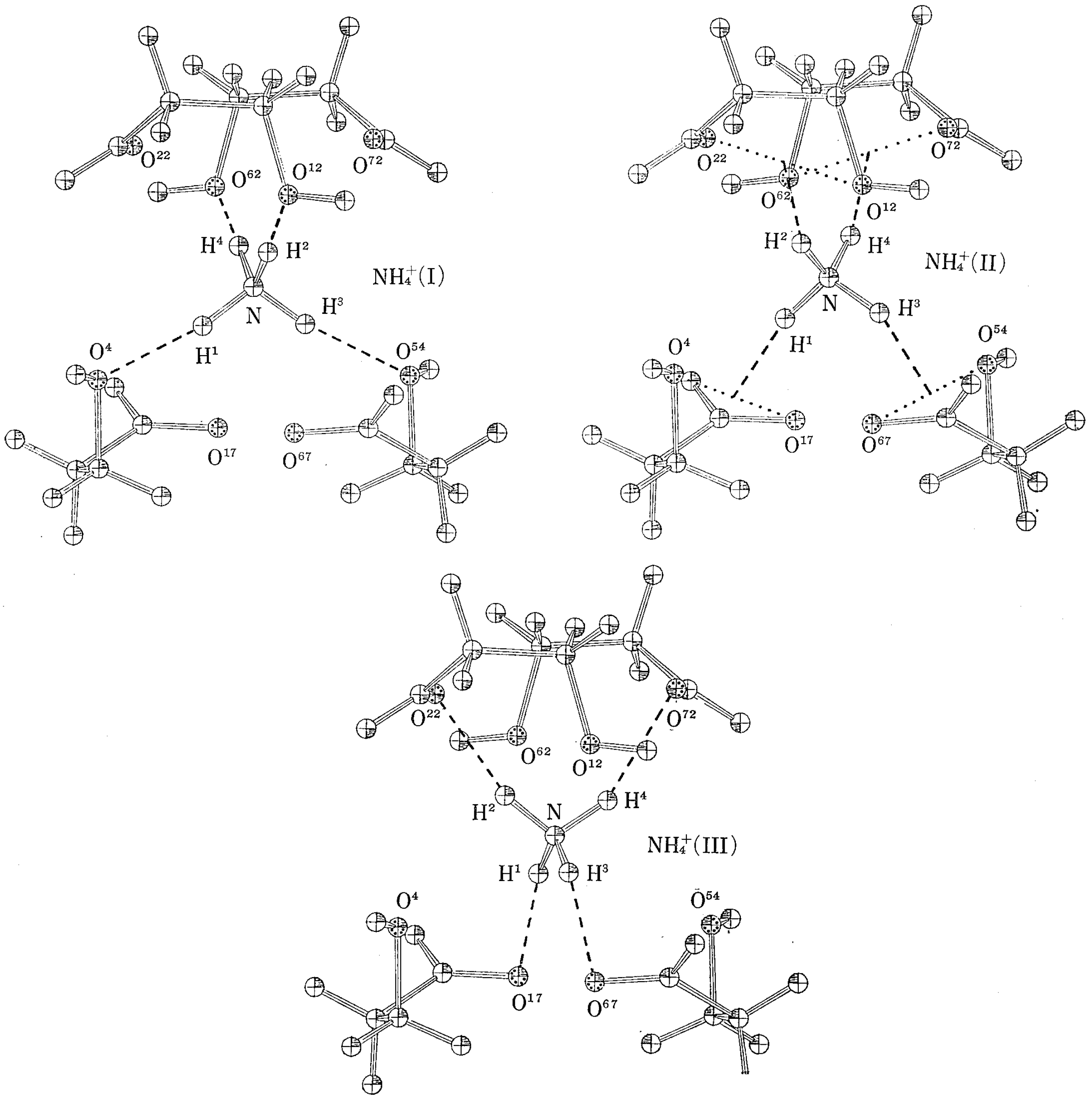

Fig. 2. Inclusion Complex Structures of Tetranactin and NH_4^+

Homonactinic acid is represented by $HOCH_2CH_2CHO$.
NH_4^+(I), NH_4^+ (II), and NH_4^+ (III) indicate the ether, middle, and ester fit models, respectively.

$HO^{i}C^{j}H_2C^{k}H_2C^{l}HO^{m}$, in which the symbols (i,j,k,l,m) are (4,3,2,1,17), (12,11,10,9,22), (54,53,52,51,67), or (62,61,60,59,72) occur in Fig. 1. Fig. 2 shows the structure. The interaction energy between the tetranactin model and NH_4^+(I) is more stable than that between the tetranactin model and NH_4^+(III) by 8.9 kcal/mol. The middle fit model is on the path of rotation of NH_4^+ from the ether fit model to the carbonyl fit model, and it is less stable than the ether fit and the carbonyl fit models by 10.2 and 1.3 kcal/mol, respectively. From the intermolecular total two-atom terms, the ether fit model was more stable than the carbonyl fit model by 20.8 kcal/mol. In these models, each of the four N–H bonds interacts with an ether oxygen or a carbonyl oxygen of each of the four homonactinic acid moieties. The contribution of the homonactinic acid moiety can be considered in terms of the total intermolecular two-atom energies. The total intermolecular two-atom energies of the homonactinic acid fragment, $HO^{i}C^{j}H_2C^{k}H_2C^{l}HO^{m}$, for NH_4^+(I) were more stable than those for NH_4^+(III). The larger and smaller values of the difference were 9.4 and 1.9 kcal/mol, respectively, for the following reasons.

(1) Since the distance, 2.08 Å, between the carbonyl oxygen O^{72} and H of NH_4^+(III) was longer than the three other distances between O^{m} and H by 0.06 to 0.12 Å, the energy between the homonactinic acid region with O^{72} and NH_4^+(III) was smaller than the three other energies.

(2) Since the distance, 1.91 Å, between the ether oxygen O^{4} and H of NH_4^+(I) was longer than the three

other distances between O^i and H by 0.03 to 0.07 Å, the energy between the homonactinic acid region with O^4 and NH_4^+(I) was smaller than the three other energies. The values of the energy differences are all positive, and hence only the interaction energy between a single homonactinic acid region and NH_4^+ need be considered to discuss the arrangement of NH_4^+ in the tetranactin-NH_4^+ complex. When the interaction energies between a homonactinic acid fragment ($HCO^{22}OH+CH_3O^{12}CH_3$) and NH_4^+ were calculated, the interaction energy with NH_4^+(I) was larger than those with NH_4^+(II) and NH_4^+(III) by 3.7 and 1.9 kcal/mol, respectively. The results confirm the significance of the interaction energy between the homonactinic acid fragment and NH_4^+.

Since the results should not be changed by a different selection of atoms of tetranactin, $C^hH_3O^iH$ and $HC^lO^mO^nH$ were used in place of the tetrahydrofuran ether and ester groups, where the symbols (h,i) are (5,4), (13,12), (55,54), or (63,62), and (l,m,n) are (1,17,66), (9,22,8), (51,67,16), or (59,72, 58). If the results obtained from the calculations using $HO^iC^jH_2$- and $C^hH_3O^iH$ are similar, these groups may be used in place of the tetrahydrofuran ether. Futhermore, if the results obtained using $-CH_2C^lHO^m$ are similar to those obtained using $HC^lO^mO^nH$, the carbonyl moiety C=O of the ester will be significant. Figure 3 shows the structure. The results are all very similar to those obtained using $HO^iC^jH_2C^kH_2C^lHO^m$. By comparison between the two models for tetranactin, the following points were confirmed. (1) Two isolated molecules of ester and ether can be used in place of a homonactinic acid fragment without changing the conclusions. (2) For the ether moiety it is possible to use an OH group in place of the $-CH_2O-$ group of $-CH_2OCH_2-$, since the results using $HO^iC^jH_2-$ and $C^hH_3O^iH$ are almost the same. (3) For the ester moiety it is possible to use a carbonyl group (–CO–) in place of the ester, –COO–, since the results using $-C^kH_2C^lHO^m$ and $HC^lO^mO^nH$ are almost the same. As the number of coordinated groups increases around NH_4^+, the increase of the interaction energy is not thought to be additive. If charge transfer from one coordinated group to NH_4^+ occurs, the vacant MO's of NH_4^+ will accept electrons from the occupied MO's of the first coordinated group. Thus, charge transfer from the second coordinated group to NH_4^+ will occur differently. In order to study the effects of the number of coordinated groups, the interaction energies between NH_4^+ and the ether or ester moiety of tetranactin were calculated. The sum, −61.2 kcal/mol, of four interaction energies between $C^hH_3O^iC^jH_3$ and NH_4^+(I) was larger than the interaction energy between the four ether groups and NH_4^+(I) by 8.1%. The sum, −52.8 kcal/mol, of four interaction energies between $C^kH_3C^lO^mO^nC^oH_3$ and NH_4^+(III) was larger than the interaction energy between the four ester groups and NH_4^+(III) by 7.4%. An additive relationship was not obtained, as discussed above. The interaction energy between $CH_3O^{12}CH_3$ and NH_4^+(I′) was almost the same as that between $CH_3O^{12}CH_3$ and NH_4^+(I), since the angle, 176.1°, of $O^{12}\cdots H-N$ for NH_4^+(I) was near 180°. On the other hand, the interaction energy, −15.5 kcal/mol, between $CH_3CO^{22}OCH_3$ and NH_4^+(III′) was similar to that between $CH_3CO^{22}OCH_3$ and NH_4^+(III), although the $O^{22}\cdots H-N$ angle, 163.6°, for NH_4^+(III) results in a bent hydrogen bond in comparison with the $O^{22}\cdots H-N$ angle, 180°, for NH_4^+(III′). Moreover, the interaction energy between the tetranactin model and NH_4^+(III′) was similar to that between the tetranactin model and NH_4^+(III) (the difference was 1.0 kcal/mol). This result means that NH_4^+(III) is very close to the local minimum.[12,13]

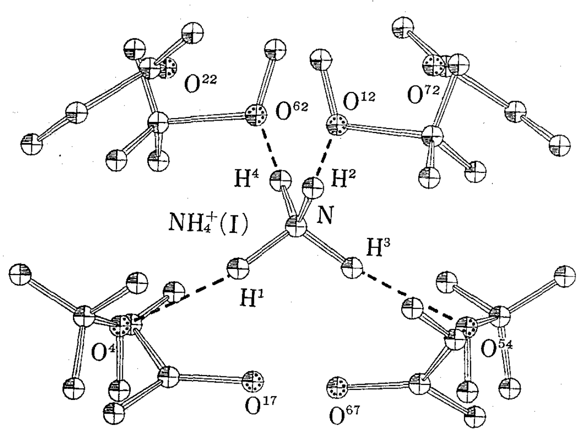

Fig. 3. Inclusion Complex Structure of Tetranactin and NH_4^+

Homonactinic acid is represented by HCOOH and $HOCH_3$.

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12) The electrostatic term contributes to the interaction energy between HCOOH and NH_4^+, so the distance $r(H\cdots O)$ of $N-H\cdots O=C$ is very significant. It seems clear that the carbonyl fit structure will be very close to the local minimum, since the four hydrogens of NH_4^+ approach the carbonyl oxygens in the carbonyl fit model.

13) In order to determine the sensitivity of the results to structural change, the tetranactin structure was slightly modified by applying strain to the crystals. The strain was introduced by the use of 90.0 degrees in place of the angle 90.48 degrees of monoclinic crystals. Displacements of the coordinates were 0.039, 0.014, 0.023, 0.035, 0.002, 0.024, 0.013, 0.003, and 0.019 Å for O^4, O^{12}, O^{17}, O^{22}, O^{54}, O^{62}, O^{67}, O^{72}, and N, respectively. Moreover, the coordinates corresponding to NH_4^+(I), NH_4^+(II), and NH_4^+(III) were different. The values corresponding to ΔE's in Table IV were −67.8, −57.0, and −60.1 kcal/mol for NH_4^+(I), NH_4^+(II), and NH_4^+(III); these values are almost the same as the values in Table IV. Therefore, a slight change of the tetranactin structure does not affect the results obtained in this paper.

Results and Discussion

Tetranactin is constructed from four homonactinic acid moieties. The energy of rotation from NH_4^+(I) to NH_4^+(III) in the interacting field within the ionophore may be determined from the change of the interaction energies between each of the homonactinic acid moieties and NH_4^+. Since the total intermolecular two-atom energy change (4.6 kcal/mol) in the rotation from NH_4^+-(I) to NH_4^+(III) for $HO^{12}C^{11}H_2C^{10}H_2C^9HO^{22}$ is close to the average (5.2 kcal/mol) of the four values (1.9, 4.6, 4.8, and 9.4 kcal/mol), the homonactinic acid region containing O^{12} and O^{22} was used in the *ab initio* calculations. In order to develop an approximate method for calculating the rotational inhibition, $HCHO^{22}$ and $HO^{12}H$ were used in place of the ester and ether groups. The interaction energies between NH_4^+ and $[HO^{12}H \cdots HCHO^{22}]$, $HO^{12}H$, or $HCHO^{22}$ are shown in Table II. The interaction energy between $[HO^{12}H \cdots HCHO^{22}]$ and NH_4^+(I) was −31.1 kcal/mol. This value was primarily due to *ES* (78.3%). The interaction energy between $HO^{12}H$ and NH_4^+(I) was −23.7 kcal/mol. *ES* (77.9%) and *CT* (13.8%) were the dominant contributors. The interaction energy between $HCHO^{22}$ and NH_4^+(I) was −9.4 kcal/mol, originating largely from *ES* (72.1%). *EX*, *PL*, and *CT* contribute little to ΔE. The interaction energy of the ether group was 2.5 times that of the carbonyl group. Therefore, the interaction energy between the ester and NH_4^+(I) contributes little to the arrangement of NH_4^+(I) in tetranactin. The relationship among (1), (2), and (3) in Table II is given by

Table II. The Interaction Energies in kcal/mol and the Energy Decomposition Analyses between NH_4^+ (I) or NH_4^+ (III) and the Molecules used in Place of Tetranactin obtained by Using a 4-31G Basis Set. The rotational inhibition energy is also given.

	NH_4^+ (I)				NH_4^+ (III)					NH_4^+ (III) $-NH_4^+$ (I)	
	$HO^{12}H$ $+HCHO^{22}$ (1)	$HO^{12}H$ (2)	$HCHO^{22}$ (3)	(a)	$HO^{12}H$ $+HCHO^{22}$ (4)	$HO^{12}H$ (5)	$HCHO^{22}$ (6)	(b)		(c)	(d)
ΔE	−31.1	−23.7	−9.4	−33.1	−26.8	−16.3	−12.2	−28.4	$\Delta\Delta E$	4.3	4.7
ES	−31.2	−24.2	−7.9	−32.1	−25.3	−15.8	−10.4	−26.2	ΔES	5.9	5.9
EX	8.7	7.4	1.4	8.8	6.2	1.9	4.5	6.4	ΔEX	−2.5	−2.4
PL	−4.8	−2.2	−1.7	−3.9	−3.7	−1.0	−2.8	−3.8	ΔPL	1.1	0.0
CT	−3.6	−4.3	−1.4	−5.7	−4.3	−1.5	−3.6	−5.1	ΔCT	−0.7	0.6
MIX	−0.2	−0.4	0.1	−0.3	0.3	0.1	0.2	0.3	ΔMIX	0.5	0.6

(a); (2)+(3).
(b); (5)+(6).
(c); (4)−(1). This term is the rotational inhibition energy.
(d); [(5)+(6)]−[(2)+(3)]; This term is approximately equal to the rotational inhibition energy.

$$E_{[NH_4^+(I)\cdots HO^{12}H\cdots HCHO^{22}]} = E_{[NH_4^+(I)\cdots HO^{12}H]} + E_{[NH_4^+(I)\cdots HCHO^{22}]} - \delta E_{NH_4^+(I)} + E_{[HO^{12}H\cdots HCHO^{22}]}$$

Accordingly,

$$E_{[HO^{12}H\cdots HCHO^{22}]} - \delta E_{NH_4^+(I)} = (1) - (2) - (3)$$

Therefore the energy of the right-hand side is 2.0 kcal/mol. The interaction energy between NH_4^+(III) and $[HO^{12}H \cdots HCHO^{22}]$ was −26.8 kcal/mol, and originated mainly from *ES* (75.8%) and *CT* (13.0%). The interaction energy between $HO^{12}H$ and NH_4^+(III) was −16.3 kcal/mol, and was largely due to *ES* (86.4%). That between $HCHO^{22}$ and NH_4^+(III) was −12.1 kcal/mol. It originated from *ES* (61.9%), *CT* (21.3%) and *PL* (16.8%). Although NH_4^+(III) is the carbonyl fit structure, the interaction energy between $HO^{12}H$ and NH_4^+(III) was larger than that between $HCHO^{22}$ and NH_4^+(III) by 2.0 kcal/mol. Therefore, even though NH_4^+ rotates from NH_4^+(I) to NH_4^+(III), the interaction energy between the ether moiety and NH_4^+ was comparable to that between the ester moiety and NH_4^+. The relationship among (4), (5), and (6) in Table II is given by

$$E_{[\mathrm{HO^{12}H \cdots HCHO^{22}}]} - \delta E_{\mathrm{NH_4^+(III)}} = (4) - (5) - (6)$$

The energy of the right-hand side is 1.6 kcal/mol. Since the value of (4)—(5)—(6) is almost the same as the value of (1)—(2)—(3), the approximate calculation method for the rotational inhibition energy seems to be in good agreement with the SCF calculation. In Table II, (c) and (d) correspond to ΔE_{ROT} and $\Delta E_{\mathrm{ROT}}'$, respectively. Since those two values are almost the same, it is clear that the rotational inhibition energy can be calculated by using the terms, (2), (3), (5), and (6) in Table II. In term (d), the rotational inhibition energy from NH_4^+(I) to NH_4^+(III) was almost entirely due to ΔES (83.1%). The exchange repulsion energy decreased with structure change from NH_4^+(I) to NH_4^+(III) by 2.4 kcal/mol. The polarization and mixing energies did not change with the rotation.

In order to confirm the results obtained from Table II, the interaction energies in the optimized structures between NH_4^+ and H_2O, CH_3OCH_3, H_2CO or HCOOH were calculated. The

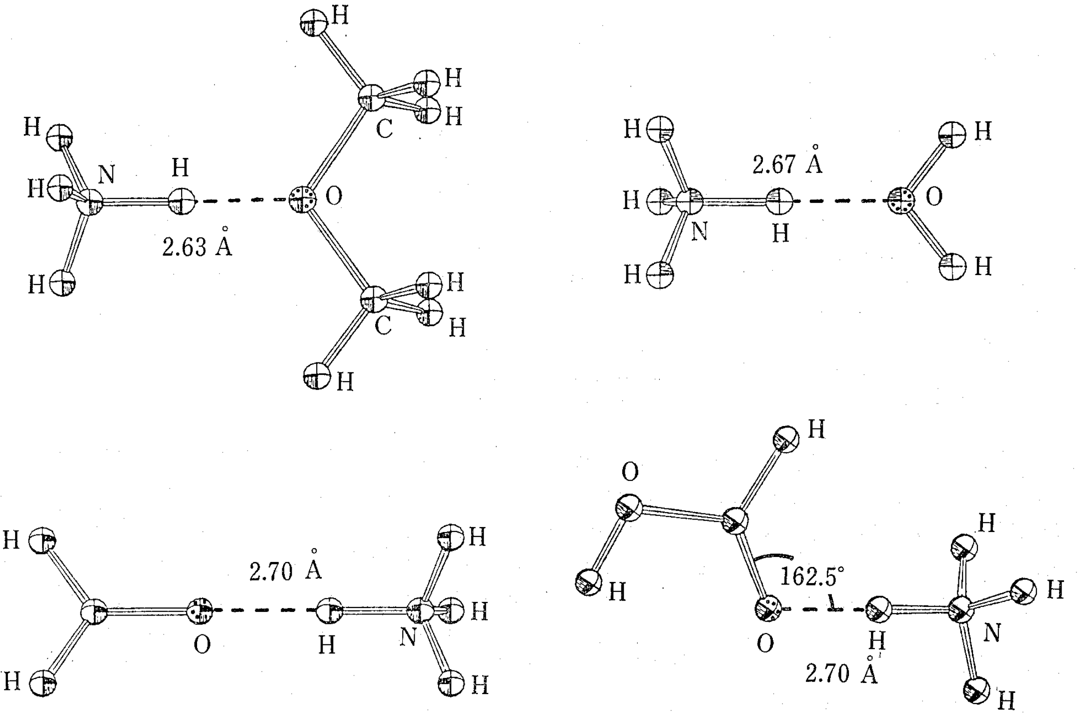

Fig. 4. Optimized Structures for Interaction between NH_4^+ and H_2O, CH_3OCH_3, H_2CO or HCOOH

Table III. The Interaction Energies in kcal/mol and the Energy Decomposition Analyses between NH_4^+ and H_2O, CH_3OCH_3, H_2CO or HCOOH Using a 4-31G Basis Set

	H_2O	CH_3OCH_3	H_2CO	HCOOH
ΔE	−27.7	−28.9	−25.2	−23.1
ES	−34.1	−34.3	−26.6	−24.6
EX	15.9	19.5	12.2	12.1
PL	−4.1	−7.4	−6.7	−6.5
CT	−5.4	−6.5	−4.3	−4.4
MIX	−0.0	−0.2	0.2	0.4

results of geometry optimizations are shown in Fig. 4. The interaction energies and the energy decomposition analyses are shown in Table III. When the interaction energy between CH_3OCH_3 and NH_4^+ was compared with that between H_2O and NH_4^+, the interaction energy of the former was similar to that of the latter. The interaction energy between HCOOH and NH_4^+ was also similar to that between H_2CO and NH_4^+. Since the results obtained from H_2O or H_2CO were very similar to those from CH_3OCH_3 or HCOOH, respectively, H_2O or H_2CO can reasonably be used in place of the ether or ester group. The interaction energy between NH_4^+ and CH_3OCH_3 was larger than that between NH_4^+ and HCOOH by 5.8 kcal/mol, almost entirely due to *ES*. This may explain the fact that the ammonium ion in tetranactin binds with the four ether oxygens rather than the four carbonyl oxygens. The optimized structure between NH_4^+ and CH_3OCH_3 was very similar to the "ether fit model". Although the four carbonyl groups move to accommodate NH_4^+, the interaction energy in the ether fit model is larger than that in the carbonyl fit model judging from the optimized results. In this paper, therefore, movement of the ether groups due to perturbation of the ionophore resulting from the rotation of NH_4^+ was neglected.

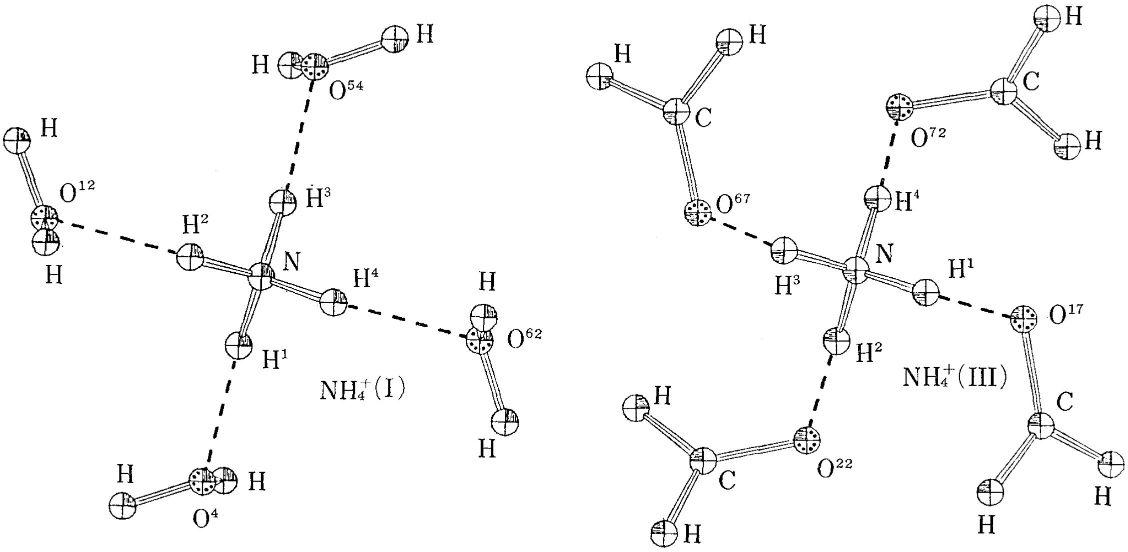

Fig. 5. Interacting Structures of Four Water Molecules and NH_4^+ (I), and between Four Formaldehyde Molecules and NH_4^+ (III)

Since tetranactin is made up of four homonactinic acid moieties, calculations in which the four ether groups and four ester groups were taken into account were carried out. Table IV shows the results. The interacting structures are shown in Figure 5. As shown in Table II, the origin of the rotational inhibition of NH_4^+ is the electrostatic term. In the calculations in Table IV, therefore, molecules other than $HO^{12}H$, $HCHO^{22}$ and NH_4^+ were included as point charges in the SCF calculation process.

The interaction energy between NH_4^+(I) and the ionophore including the four water and the four formaldehyde molecules was calculated to be -109.0 kcal/mol. This was more stable than in the case of NH_4^+(III) by 9.8 kcal/mol. This value is the rotational inhibition energy of NH_4^+ in tetranactin. The value of 9.8 kcal/mol was very close to the value of 8.9 kcal/mol or 7.9 kcal/mol obtained from the CNDO/2 calculations. The CNDO/2 method seems to be reliable for calculations utilizing models. The interaction energy between the four water molecules and NH_4^+(I) was calculated to be -73.2 kcal/mol. This is about 1.9 times the interaction energy between the four formaldehyde molecules and NH_4^+(I). On the other hand, the interaction energy between the four formaldehyde molecules and NH_4^+(III) was comparable to that between the four water molecules and NH_4^+(III). The value of $(5)+(6)-(3)-(4)$ in Table IV was close to that of $(2)-(1)$ and the overestimated energies of $\delta E_{NH_4^+(I)}$ and $\delta E_{NH_4^+(III)}$ are 3.6

TABLE IV. The Interaction Energies in kcal/mol between NH_4^+ (I) and $\sum_{i}^{4} HO^{i}H$, $\sum_{m}^{4} HCHO^{m}$, or $\sum_{i}^{4} HO^{i}H + \sum_{m}^{4} HCHO^{m}$, and between NH_4^+ (III) and $\sum_{i}^{4} HO^{i}H$, $\sum_{m}^{4} HCHO^{m}$, or $\sum_{i}^{4} HO^{i}H + \sum_{m}^{4} HCHO^{m}$ Using a 4-31G Basis Set

	NH_4^+ (I) $\sum_{i}^{4} HO^{i}H + \sum_{m}^{4} HCHO^{m}$ (1)a)	NH_4^+ (III) $\sum_{i}^{4} HO^{i}H + \sum_{m}^{4} HCHO^{m}$ (2)a)	NH_4^+ (III) − NH_4^+ (I) (2) − (1)
ΔE	−109.0	−99.2	9.8

	NH_4^+ (I)			NH_4^+ (III)			NH_4^+ (III) − NH_4^+ (I)
	$\sum_{i}^{4} HO^{i}H$	$\sum_{m}^{4} HCHO^{m}$		$\sum_{i}^{4} HO^{i}H$	$\sum_{m}^{4} HCHO^{m}$		
	(3)b)	(4)c)	(3) + (4)	(5)b)	(6)c)	(5) + (6)	(5) + (6) − [(3) + (4)]
ΔE	−73.2	−39.4	−112.6	−52.6	−50.1	−102.7	9.9

a) Molecules other than $HO^{12}H$ and NH_4^+ are included as point charges.
b) Molecules other than $HCHO^{22}$ and NH_4^+ are included as point charges.
c) Molecules other than $HO^{12}H$, $HCHO^{22}$ and NH_4^+ are included as point charges.

and 3.5 kcal/mol, respectively. Thus, the approximate calculation method for the rotational inhibition energy was shown to be in good agreement with the full SCF calculation.

Conclusion

(1) An approximate method for calculating the rotational inhibition of NH_4^+ in tetranactin was developed. The result obtained by this method was in good agreement with the SCF calculations.

(2) In calculations of the interaction between the homonactinic acid model and NH_4^+(I) or NH_4^+(III), the origin of the rotational inhibition of NH_4^+ from the ether fit model to the ester fit model was clarified. ΔES was shown to be a significant contributor.

(3) The interaction energy in the optimized structure between NH_4^+ and CH_3OCH_3 was larger than that between NH_4^+ and HCOOH. This result explains why, in the induced fit mechanism of tetranactin, the ether oxygens turn inwards by bond rotations to hold NH_4^+ in tetranactin, and why the carbonyl oxygens rotate inwards to prevent NH_4^+ from escaping.[3k]

(4) The structure in which the four hydrogens of NH_4^+ fit with the four ether oxygens of the tetrahydrofuran rings was more stable than that in which the four hydrogens of NH_4^+ fit with the four carbonyl oxygens of the ester groups by 9.8 kcal/mol. This result explains why no signs of rotational disorder in the X-ray diffraction analyses[3k] were detected for NH_4^+.

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