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Conformational Analyses of 9-[3-(3-Indolyl)propyl]adenine and 9-[3-(3-Indolyl)-propyl]-1-methyladeninium by Empirical Energy Calculations,[1] a Model Study for the Intramolecular Stacking Interaction of Indole Ring with Adenine Base and with *N*(1)-Methylated Adenine Base

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In order to elucidate the energetically stable conformations of 9-[3-(3-indolyl)propyl]adenine and 9-[3-(3-indolyl)propyl]-1-methyladeninium, as intramolecular stacking models for the indole–adenine and indole–adeninium interactions, respectively, empirical energy calculations considering nonbonded, electrostatic and torsional energies were carried out. Two or one out of four kinds of stacking modes were considered to be energetically stable for the former or latter molecule, respectively. These stacking modes were significantly stabilized by the orbital interaction between the highest occupied molecular orbital of the indole ring and the lowest unoccupied one of the adenine or the adeninium ring.

Keywords——9-[3-(3-indolyl)propyl]adenine; 9-[3-(3-indolyl)propyl]-1-methyladeninium; empirical energy calculation; stacking mode

The mutual recognition between protein and nucleic acid is in part a result of specific interactions, such as electrostatic, hydrogen bonding and π–π stacking interactions,[2,3] among their constituent chemical groups. Therefore, the elucidation of these interaction modes at the atomic level is expected to be very valuable for understanding the recognition mechanism.

Tryptophan, among aromatic amino acids, is especially important for the π–π stacking interaction with nucleic acid bases because of the π-donating character of the indole side chain.[4] While information concerning its binding mode in the solution state has been accumulated, few detailed studies have been done at the atomic level.

Spectroscopic studies of 9-[3-(3-indolyl)propyl]adenine (IC3A) and 9-[3-(3-indolyl)-propyl]-1-methyladeninium (IC3MA), as simple models for the indole–adenine and indole–adeninium interactions, respectively, showed the existence of intramolecular π–π stacking interactions in solution.[5,6] In order to elucidate the energetically stable stacking modes of these molecules and to investigate to what extent protonation or methylation of the adenine ring actually affects the interaction with the indole ring, we carried out conformational analyses by using the empirical PPF (partitioned potential energy function) method,[7] and investigated the characteristics of the energetically stable stacking modes by the CNDO/2 (complete neglect of differential overlap) molecular orbital method.[8] Such studies should provide informations as to the geometrical requirements for the π–π stacking interaction between the tryptophanyl residue and the natural or methylated (or protonated) adenine base in protein–nucleic acid association.

Experimental

Model Building and Notation of Variable Torsion Angles——The requisite structural parameters of IC3A and IC3MA molecules were obtained from X-ray analyses.[6,9] The atomic numbering and notation used to designate the

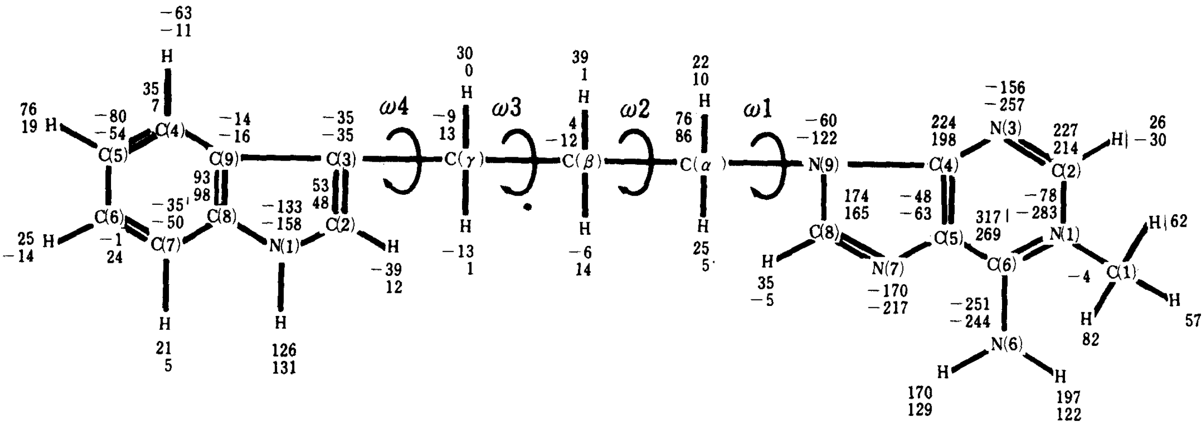


Fig. 1. Atomic Numbering, Notation of Torsion Angles [ω_1: C(8)–N(9)–C(α)–C(β), ω_2: N(9)–C(α)–C(β)–C(γ), ω_3: C(α)–C(β)–C(γ)–C(3), ω_4: C(2)–C(3)–C(γ)–C(β)] and Net Electronic Charges ($\times 10^3$) (in Electronic Unit) for IC3MA (Upper Values) and IC3A (Lower Values)

rotations about the four bonds of the IC3MA molecule are presented in Fig. 1; these were also used for the IC3A molecule. The definition of torsion angles, ω_1—ω_4, follows the proposal of Klyne and Prelog:[10] a torsion angle was defined as positive if, when looking along the front bond B–C in the A–B–C–D bond sequence, the far bond (C–D) rotates clockwise relative to the near bond (A–B), and as negative if counterclockwise. The positive and negative torsion angles were limited to 0—180 and 0— – 180°, respectively.

Energy Calculation——The total energy (E_{tot}) in kcal/mol has been calculated as the sum of the nonbonded (E_{nb}), electrostatic (E_{el}) and torsional (E_{tor}) contributions:

$$E_{tot} = E_{nb} + E_{el} + E_{tor} \tag{1}$$

where

$$E_{nb} = \sum_{i<j}\sum(-A_{ij}r_{ij}^{-6} + B_{ij}r_{ij}^{-12}) \tag{2}$$

$$E_{el} = \sum_{i<j}\sum 332.0 \times Q_i \times Q_j \times r_{ij}^{-1} \times \varepsilon^{-1} \tag{3}$$

$$E_{tor} = \sum_{k=1}^{4} 0.5 \times V_k \times (1.0 + \cos X\theta_k) \tag{4}$$

In Eqs. (2) and (3), r_{ij} is the distance (in Angstroms) between atoms i and j. Parameters used in the Lennard–Jones "6—12" potential function (Eq. (2)) were obtained from the literature,[11-14] and were listed in an earlier report.[15] The Coulombic charge on atom i(Q_i) in Eq. (3) was calculated by the CNDO/2 method; these values are also shown in Fig. 1. The dielectric constant (ε) was taken as 4.0, close to the experimental values for biomolecules in polar media.[11,12] V_k in Eq. (4) is the energy barrier potential for internal rotation about the k-th torsion angle (θ_k), and was taken as 2.5 kcal/mol for a C–C single bond, but was considered to be negligible for the C–N bond in accordance with Lakshminarayanan and Sasisekharan.[11] X is the periodicity of the barrier and was taken as 3 for ω_2 and ω_3, and 6 for ω_1 and ω_4.

Procedure——As each starting torsion angle, the most reasonable values were selected on the basis of the rotation barriers of sp^3–sp^3 or sp^2–sp^3 covalent bonds: ω_1 and $\omega_4 = \pm 30$, ± 90, and $\pm 150°$; ω_2 and $\omega_3 = \pm 60$ and 180°. Thus 324 different conformations were calculated for the IC3A and IC3MA molecules, respectively.

Minimization of the energy, with each torsion angle as a variable parameter, was done by using the Powell algorithm.[16] The minimization was carried out by the parabola approximation with 4° intervals and no angle was permitted to vary by more than 12° at each step.

CNDO/2 Molecular Orbital Calculation——The molecular orbital calculations for the 1,9-dimethyladeninium cation, 9-methyladenine and 3-methylindole were carried out by using their standard coordinates[17] in order to obtain the atomic charges, the vectors of dipole moments, and the atomic orbital coefficients of the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) of these molecules. The electronic energy for each molecule was converged by the iterative self-consistent field method.

All numerical calculations were carried out on an ACOS-900 computer at the Computation Center of Osaka University.

Results and Discussion

1. IC3A Molecule

Energy calculations for 324 different conformers indicated that the energetically stable conformations could be roughly divided into two groups, *i.e.*, the open and folded forms. Five sets of starting and final torsion angles giving open conformations are given in Table I, along with their final energies. The conformations with ω_2 and ω_3 both having 180° as their starting angles were converged to the open forms irrespective of the remaining torsion angles, and have energy values of $-7\sim-8$ kcal/mol. There is little difference among their energy values, implying that these open forms are energetically metastable, because there is no steric hindrance to the rotations of ω_1 and ω_4 in the state of the *trans* zig-zag orientation of ω_2 and ω_3. The conformation of IC3A observed in its crystal structure[9] also belongs to this group with the energy of -7.23 kcal/mol (see Table I). Figure 2 shows the open conformation of Set No. 1 in Table I and the conformation observed in the crystal structure. It is interesting to note that the conformers having 180° as the starting angle of either ω_2 or ω_3 were also converged to the open forms with energy values of $-7\sim-9$ kcal/mol, although they are slightly more stable compared with those having *ca.* 180° for both ω_2 and ω_3.

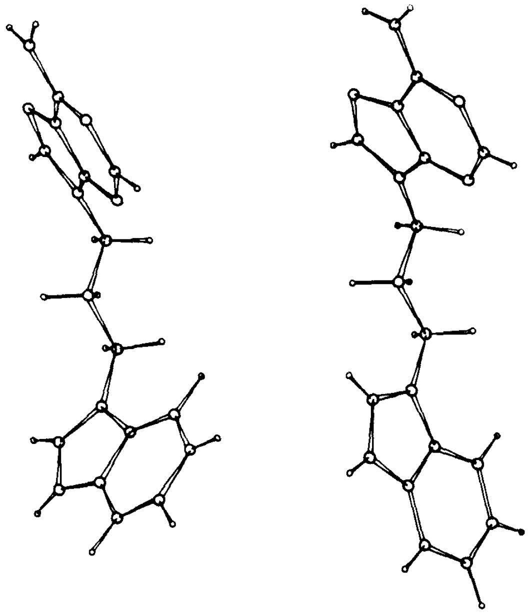
On the other hand, the energetically more stable conformations were the folded forms, especially those in which the indole and adenine rings are directly stacked on each other.

TABLE I. The Starting and Final Torsion Angles and Their Energy Values for the Energetically Stable Open Conformations of the IC3A Molecule, along with the Angles Observed in the Crystal Structure

Starting angle (°)				Final angle (°)				Energy (kcal/mol)	Order
ω_1	ω_2	ω_3	ω_4	ω_1	ω_2	ω_3	ω_4		
−90	180	180	90	−119.3	181.4	178.5	90.9	−7.785	1
−150	180	180	90	−119.5	181.0	179.8	90.1	−7.783	2
90	180	180	−90	113.5	179.5	181.0	−90.8	−7.714	3
150	180	180	−90	113.5	179.3	180.2	−90.5	−7.712	4
−90	180	180	−30	−119.6	180.8	180.6	−30.0	−7.527	5
				−107.0	−167.0	179.3	2.8	−7.231	Crystal

TABLE II. The Starting and Final Torsion Angles and Their Energy Values for the Energetically Stable Folded Conformations of the IC3A Molecule

Starting angle (°)				Final angle (°)				Energy (kcal/mol)	Order	Type
ω_1	ω_2	ω_3	ω_4	ω_1	ω_2	ω_3	ω_4			
−90	−60	60	30	−80.9	−55.3	69.9	37.4	−18.19	1	A
−30	−60	60	90	−35.4	−70.5	58.5	83.1	−18.10	2	A
30	60	−60	−90	32.1	69.9	−61.1	−86.5	−18.05	3	A′
90	60	−60	−30	80.8	55.2	−71.0	−37.4	−18.01	4	A′
−150	60	−60	90	−135.0	66.9	−54.8	101.3	−17.66	5	A
30	60	−60	90	44.4	75.4	−33.6	97.1	−17.36	6	B
−30	−60	60	30	−86.2	−65.3	74.5	30.0	−17.30	7	A
150	−60	60	−90	131.2	−67.0	51.8	−104.3	−17.21	8	A′
30	60	−60	−30	84.7	67.0	−73.2	−29.6	−17.14	9	A′
−90	60	−60	150	−115.0	72.9	−64.6	132.7	−16.75	10	A



(a) (b)

Fig. 2. Perspective Views of the Most Energetically Stable Open Conformation in Table I [(a)] and the Conformation Observed in the Crystal Structure [(b)] of the IC3A Molecule

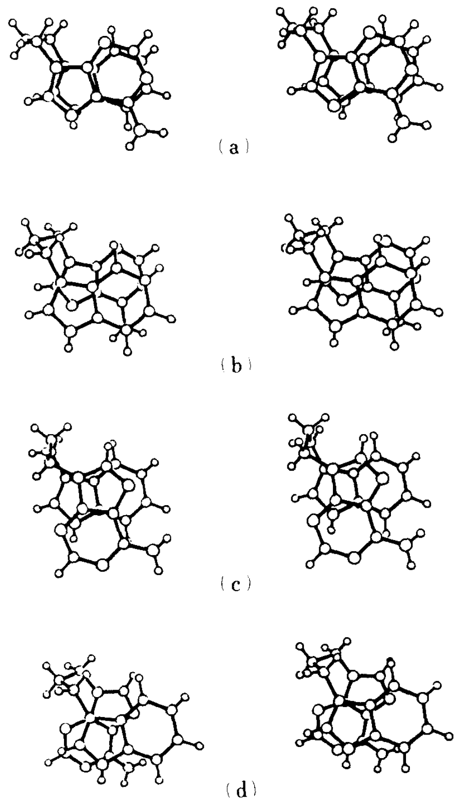


Fig. 3. Stereoscopic Views of the Four Kinds of Most Energetically Stable Stacked Conformations of the IC3A Molecule, Projected onto the Indole Ring [(a): Type A, No. 1 in Table II; (b): Type A′, No. 3; (c): Type B, No. 6; (d): Type B′, No. 18]

These have energies of $-17 \sim -18$ kcal/mol and are more stable by *ca.* 10 kcal/mol than the open forms. Ten energetically stable conformers are listed in Table II, along with their starting angles and final energies. As is obvious from Table II, the stable folded conformations of the IC3A molecule, as well as the open forms, depend largely on the combination of the starting angles of ω_2 and ω_3: the (ω_2, ω_3) starting set of either (60, -60°) or (-60, 60°) produces the energetically stable stacked conformers.

The folded conformers listed in Table II could be further grouped into four kinds on the basis of their stacking modes, and are designated by letters A, A′, B, and B′ in Table II; the order No. of the first emergence corresponding to conformer B′ is 18, and is therefore not listed in Table II. Figure 3 illustrates these four kinds of most energetically stable conformers, in which the respective molecules are projected onto the indole ring. Conformers A and B or A′ and B′ could be differentiated by the orientation of the adenine ring with respect to the indole ring: the long axes of the indole and adenine rings are nearly parallel to each other in conformers A and A′, while in conformers B and B′ they are orientated with angles of about 45°.

Although conformers A and A′ or B and B′ are quite similar to each other in stacking mode, a significant difference exists in the stacking site of the adenine ring with respect to the indole ring: in conformers A and B, the adenine rings are stacked from above the indole ring, while in conformers A′ and B′, the rings are stacked from below.

Conformational calculations for the IC3A molecule resulted in the following conclusion: conformers A and A′, among four kinds of stacking modes, are the most energetically stable forms, and the adenine ring could stack well with the upper side as well as with the lower side of the indole ring; in other words, the indole ring can interact with both sides of the adenine bases of nucleic acids with the same stacking force.

2. IC3MA Molecule

From the energy calculations for 324 different conformers, it became apparent that the characteristics of the energetically stable conformations are quite similar to those in the IC3A molecule, irrespective of the modification of the adenine ring by the *N*(1)-methylation; the energy minimizations coverged to both open and folded conformations as stable forms of the IC3MA molecule.

When ω_2 and/or ω_3 took 180° as their starting angles, the molecule was converged to open conformations with energy values of $-6 \sim -8$ kcal/mol. A typical conformation is shown in Fig. 4. On the other hand, the conformers having ω_2 and ω_3 of 60 or -60° as their starting angles were minimized into the folded forms,in which the torsion angle of ω_1 or ω_4 may not have any significant effect on the determination of the energetically stable conformations because of the nearly equal appearance of stable conformers having ω_1 and ω_4 of about ± 30, ± 90, and ± 150°. Among these many folded conformations, those having stacked rings are especially stable, and the energy values range from -16 to -18 kcal/mol. The starting and final torsion angles for ten stable conformers are listed in Table III. As in the case of the IC3A molecule, the combination of (ω_2, ω_3) torsion angles is very important for the determination of the stable stacked forms. The most favorable combination are (60, -60°) and (-60, 60°). The conformers having (-60, -60°) as (ω_2, ω_3) starting angles,

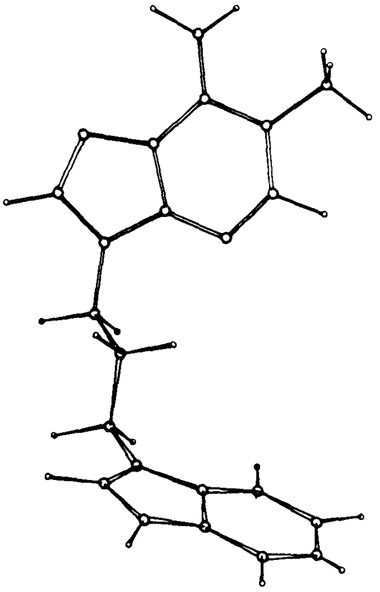


Fig. 4. Perspective View of a Typical Open Conformation of the IC3MA Molecule

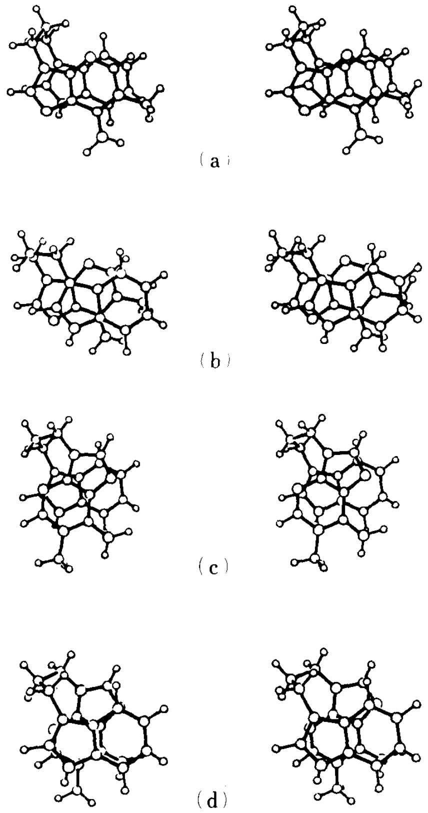


Fig. 5. Stereoscopic Views of the Four Kinds of Most Energetically Stable Stacked Conformations of the IC3MA Molecule, Projected onto the Indole Ring [(a): Type A, No. 5 in Table III; (b): Type A′, No. 1; (c): Type B, No. 9; (d): Type B′, No. 10]

Table III. The Starting and Final Torsion Angles and Their Energy Values for the Energetically Stable Folded Conformations of the IC3MA Molecule, along with the Angles Observed in the Crystal Structure

Starting angle (°)				Final angle (°)				Energy (kcal/mol)	Order	Type
ω_1	ω_2	ω_3	ω_4	ω_1	ω_2	ω_3	ω_4			
90	60	−60	−30	84.1	52.0	−66.3	−36.5	−18.51	1	A′
150	−60	60	−90	135.0	−63.1	55.0	−96.5	−18.25	2	A′
30	60	−60	−90	35.9	65.7	−59.6	−84.6	−17.80	3	A′
30	60	−60	−30	82.5	67.0	−67.4	−34.5	−17.55	4	A′
−150	60	−60	90	−139.0	60.9	−57.4	98.9	−17.00	5	A
−30	−60	60	90	−43.1	−64.2	52.5	84.8	−16.94	6	A
−90	−60	60	30	−90.3	−57.2	65.2	36.2	−16.87	7	A
90	−60	60	−90	134.4	−58.1	68.8	−97.5	−16.37	8	A′
150	−60	60	90	139.9	−63.4	69.0	80.9	−16.35	9	B
−150	60	−60	−90	−145.6	61.2	−76.4	−82.9	−16.09	10	B′
				−61.2	−70.0	−62.3	103.6	−11.04	Crystal	

which correspond to the conformer observed in the crystal structure,[6] were minimized to folded forms without direct stacking of the aromatic rings (their energies range from −11 to −14 kcal/mol). The conformers listed in Table III, as in the IC3A molecule, could be divided into four kinds of stacking groups, designated by the letters A, A′, B, and B′, based on the differences in stacking mode between the aromatic rings. The most energetically stable conformations are shown in Fig. 5. The stacking modes are quite similar to those in IC3A shown in Fig. 3. It is noteworthy that the conformer A is significantly favored for the IC3MA molecule. This implies that there is a site-specificity in the stacking interaction between the indole and adeninium rings. This is in sharp contrast with the stacking specificity of the indole and adenine rings in the IC3A molecule.

3. Ring Orientation in Indole–Adenine and Indole–Adeninium Stacking Interactions

It appears important for modeling of the tryptophan residue of protein, stacked with natural or methylated adenine bases of nucleic acid, to elucidate what factors influence the indole–adenine or indole–adeninium stacking formations obtained by the present energy calculations.

Figure 6 and Table IV summarize some parameters concerning the stacking orientations of the four kinds of conformers observed in the IC3A and IC3MA molecules, in which the values of the permanent dipole moments and the atomic orbital coefficients in the HOMO and LUMO were calculated by the CNDO/2 method for 3-methylindole, 9-methyladenine and 1,9-dimethyladeninium molecules. Stabilization energy (ΔE_{st}) was obtained by the following equation: $\Delta E_{st} = E$ (stacked pair) − [E(3-methylindole) + (E(9-methyladenine or 1,9-dimethyladeninium)], where E value, the total energy of each molecule or pair, was calculated by the CNDO/2 method. The term ΔE_{st} represents the stabilization energy caused only by the stacking association of both rings, and is therefore not comparable with the energy calculated by the PPF method. The vectors of the permanent dipole moments for the molecules are indicated by arrows above the stacked structures.

As already stated, the four kinds of stacking modes, A, A′, B, and B′, of IC3A are very similar to those of IC3MA. Therefore the factors determining the stacking orientations may be the same in both molecules, irrespective of the structural difference between the adenine and adeninium rings. Compared with the A and A′ stacking forms of the two molecules, the B and B′ forms are substantially stabilized by the strongly coupled dipole–dipole interaction

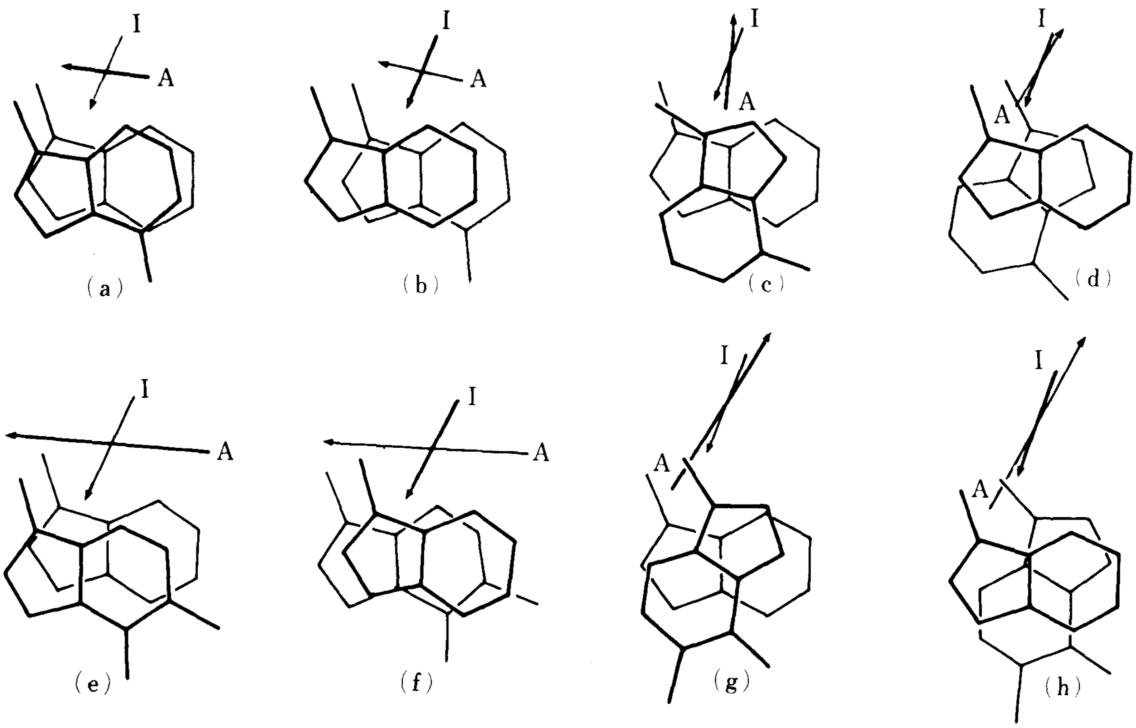


Fig. 6. The Stacking Orientation of Indole–Adenine or Adeninium Rings, Viewed Perpendicular to the Indole Ring

The vectors of the permanent dipole moments are represented by arrows, which were calculated using 3-methylindole [I = 2.10 debye (D)] and 9-methyladenine (A = 2.48 D) or 1,9-dimethyladeninium (A = 5.11 D). The letters in parentheses, a – h, correspond to the overlapping modes in Table IV.

Table IV. Stacking Parameters of Indole–Adenine and Indole–Adeninium Rings in IC3A and IC3MA

Compound	Type	Stacking mode	Spacing in Å	Dihedral angle (°)	Stabilization energy (kcal/mol)	Electronic energy (kcal/mol)[a]
IC3A	A	Fig. 6(a)	3.116	12.9	100.084	−4.038
	A′	Fig. 6(b)	3.096	16.0	118.972	−3.313
	B	Fig. 6(c)	2.983	7.5	142.753	−4.129
	B′	Fig. 6(d)	3.145	18.4	108.555	−4.579
IC3MA	A	Fig. 6(e)	3.095	15.0	−75.581	16.698
	A′	Fig. 6(f)	3.066	10.4	−79.032	16.081
	B	Fig. 6(g)	2.979	9.9	−79.503	14.525
	B′	Fig. 6(h)	3.105	16.1	−79.314	14.848

a) This value was calculated by using the coordinates of 3-methylindole and 9-methyladenine or 1,9-dimethyladeninium, and Eq. (3) in the PPF energy calculation.

forces. The electrostatic interactions are also favorable in these forms; the positive values in the IC3MA molecule result from the formation of the adeninium ring by the *N*(1)-methylation of adenine. On the other hand, the A and A′ stacking modes, which are energetically more stable than the B and B′ modes, are significantly stabilized by the HOMO–LUMO interactions; the atomic orbital coefficients, in the short contact pairs of less than 3.4 Å, between the HOMO of 3-methylindole and the LUMO of 9-methyladenine or 1,9-dimethyladeninium are listed in Table V. Of the atomic coefficients in the short contact pairs, more than two-thirds have the same signs, implying that their atomic orbitals can interact

Table V. Atomic Orbital Interaction between the HOMO of Indole and the LUMO of Adenine or Adeninium

Atomic name		Distance (Å)	Atomic coefficients		Orbital interaction[a]
Indole	Adenine or adeninium		HOMO	LUMO	
IC3A Type A					
C(4)	C(2)	3.168	0.3289	0.3341	+
C(5)	C(2)	3.298	0.1057	0.3341	+
C(9)	C(2)	3.343	0.0839	0.3341	+
C(3)	N(3)	3.239	−0.5069	0.0456	−
C(4)	N(3)	3.007	0.3289	0.0456	+
C(9)	N(3)	2.908	0.0839	0.0456	+
C(2)	C(4)	3.198	−0.4131	−0.4930	+
C(3)	C(4)	2.966	−0.5069	−0.4930	+
C(8)	C(4)	3.348	0.1973	−0.4930	−
C(9)	C(4)	3.027	0.0839	−0.4930	−
N(1)	C(5)	3.236	0.4206	0.1015	+
C(8)	C(5)	3.361	0.1973	0.1015	+
C(2)	C(8)	3.018	−0.4131	−0.0861	+
C(2)	N(7)	3.399	−0.4131	−0.1834	+
C(2)	N(9)	2.903	−0.4131	0.2137	−
C(3)	N(9)	2.824	−0.5069	0.2137	−
C(3)	C(9)	3.053	−0.5069	−0.0196	+
IC3A Type A′					
C(4)	C(2)	2.949	−0.3289	−0.3341	+
C(5)	C(2)	3.289	−0.1057	−0.3341	+
C(9)	C(2)	3.250	−0.0839	−0.3341	+
C(3)	N(3)	3.192	0.5069	−0.0456	−
C(4)	N(3)	3.089	−0.3289	−0.0456	+
C(9)	N(3)	3.046	−0.0839	−0.0456	+
C(2)	C(4)	3.235	0.4131	0.4930	+
C(3)	C(4)	2.869	0.5069	0.4930	+
C(9)	C(4)	3.050	−0.0839	0.4930	−
N(1)	C(5)	3.254	−0.4206	−0.1015	+
C(2)	C(5)	3.357	0.4131	−0.1015	−
C(8)	C(5)	3.239	−0.1973	−0.1015	+
C(9)	C(5)	3.393	−0.0839	−0.1015	+
C(8)	C(6)	3.302	−0.1973	−0.5419	+
N(1)	N(7)	3.198	−0.4206	0.1834	−
C(2)	N(7)	3.216	0.4131	0.1834	+
C(2)	C(8)	2.965	0.4131	0.0861	+
C(2)	N(9)	2.985	0.4131	−0.2137	−
C(3)	N(9)	2.849	0.5069	−0.2137	−
IC3MA Type A					
C(4)	C(2)	3.025	0.3289	0.3718	+
C(5)	C(2)	3.219	0.1057	0.3718	+
C(3)	N(3)	3.331	−0.5069	−0.4180	+
C(9)	N(3)	3.077	0.0839	−0.4180	−
C(4)	N(3)	2.996	0.3289	−0.4180	−
C(3)	C(4)	2.930	−0.5069	0.1423	−
C(9)	C(4)	2.978	0.0839	0.1423	+
N(1)	C(5)	3.354	0.4206	0.1787	+
C(9)	C(5)	3.378	0.0839	0.1787	+
C(8)	C(5)	3.255	0.1973	0.1787	+
N(1)	N(7)	3.251	0.4206	0.2756	+
C(2)	C(8)	2.946	−0.4131	−0.4115	+

TABLE V. (continued)

Atomic name		Distance (Å)	Atomic coefficients		Orbital interaction[a]
Indole	Adenine or adeninium		HOMO	LUMO	
C(3)	C(8)	3.331	−0.5069	−0.4115	+
C(2)	N(9)	2.995	−0.4131	0.1153	−
C(3)	N(9)	2.792	−0.5069	0.1153	−
C(3)	C(9)	3.117	−0.5069	−0.0227	+
IC3MA Type A′					
C(5)	C(2)	3.199	−0.1057	−0.3718	+
C(4)	N(3)	2.915	−0.3289	0.4180	−
C(5)	N(3)	3.194	−0.1057	0.4180	−
C(9)	C(4)	3.043	−0.0839	−0.1423	+
C(4)	C(4)	2.909	−0.3289	−0.1423	+
C(9)	C(5)	3.338	−0.0839	−0.1787	+
C(8)	C(5)	3.370	−0.1973	−0.1787	+
N(1)	N(7)	3.359	−0.4206	−0.2756	+
C(8)	N(7)	3.326	−0.1973	−0.2756	+
C(2)	C(8)	3.075	0.4131	0.4115	+
C(3)	C(8)	2.908	0.5069	0.4115	+
C(9)	C(8)	3.164	−0.0839	0.4115	−
C(3)	N(9)	2.853	0.5069	−0.1153	−
C(9)	N(9)	2.913	−0.0839	−0.1153	+
C(4)	N(9)	3.197	−0.3289	−0.1153	+
C(3)	C(9)	3.031	0.5069	0.0227	+

a) The coupling or uncoupling of orbital interaction is designated by + or −, respectively.

with each other. Some short contact pairs exhibiting orbital uncoupling can be attributed to the rigidity of the respective aromatic rings. Such HOMO–LUMO interaction also exists in the ring orientations of the B and B′ stacking modes: the same signs are observed in more than one-half of the atomic coefficients of the short contact pairs.

The stabilization energy may explain why the stacking interaction is not observed in IC3A crystals,[9] but is in IC3MA crystals.[6] Judging from only the ΔE_{st} for the respective stacked pairs, the stacking formation of the indole ring with the adenine ring becomes energetically unstable ($\Delta E_{st} = 100$—142 kcal/mol). Conversely, an energy of $-75 \sim -79$ kcal/mol is obtained by stacking formation between the indole and adeninium rings. These results would, in part, result from the difference in the LUMO energy between the adenine and adeninium rings: the LUMO energy value of adenine [0.1367 atomic unit (a.u.)] is significantly lowered by the protonation, *e.g.*, −0.1182 a.u. for 1-protonated adenine. Thus, protonation saves an energy of 0.2549 a.u. (*ca.* 160 kcal/mol) in the stacking interaction with the HOMO of the indole ring (its energy = −0.3996 a.u.).

References and Notes

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