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A QUANTUM CHEMICAL STUDY OF THE EFFECT OF Na^+ ON THE HYDROGEN BONDS IN THE ADENINE-THYMINE BASE-PAIR

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It is shown, by quantum chemical calculations, that an Na^+ located in the neighborhood of the adenine thymine base-pair can dissociate the hydrogen bonds in it. However, a water molecule placed between Na^+ and the base-pair would provide perfect protection for the hydrogen bonds. The suggestion is put forward that a hydrophobic carcinogen (for example) could perturb sufficiently the water structure around DNA to allow Na^+ to penetrate to molecular distance from the base-pair. This could result in the 'breaking' of hydrogen bonds and, eventually, irregular cell division.

1. Introduction

It is known that hydrogen bonds (H-bonds) play an important role in determining the structure of biomolecules. Perturbation or severance of H-bonds should therefore manifest itself in changes in the structure of biomolecules and in biological processes. In the past we have demonstrated through experimental [1] and theoretical [2a,2b] model studies the role of perturbation of H-bond equilibria in the mechanism of anesthetic action. Thus, it is tempting to examine the possibility of perturbing H-bonds in the nucleic acid base-pairs in DNA, the biological consequences of which could be very important. It was shown recently [3] that an excess of $CHCl_3$ is able to perturb the H-bond equilibrium in the adenine (A)-thymine (T) base-pair. We have decided to investigate theoretically the possibility of influencing the H-bonds in the A-T pair by Na^+. Recently, it was shown by Clementi and Corongiu [4] that Na^+ forms two additional helices along the DNA double helix: the ions are located not only in the vicinity of phosphate groups but could also be found over the H-bonds of the base-pairs.

Considering that ab initio calculations on the A-T pair would require very large amounts of computer time, and since we are interested not in A and T themselves but rather in the H-bonds

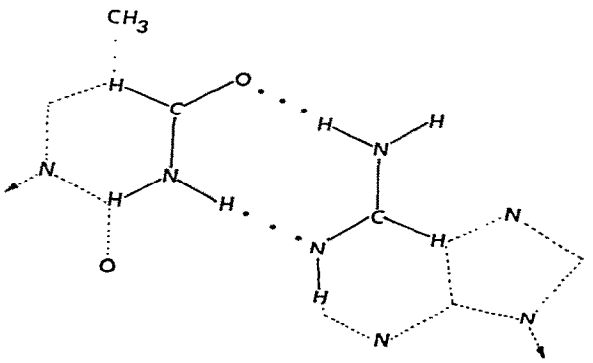

Fig. 1. The formamidine-formamide (FA-FI) complex (———), modeling the adenine-thymine base-pair (- - - - -).

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connecting them, we have chosen to treat a model system. This is derived by simply cutting the rings of both molecules and including only the atoms directly involved in the H-bonds. The model is shown in fig. 1, where formamide (FA) represents thymine and formamidine (FI) adenine. The H-bonds within the FA-FI complex are the same as those in the A-T pair and for our purposes the most important are the relative changes that are produced in the target (FA-FI) by a perturbing positive ion.

Our aim is to investigate the possible changes in the properties of the A-T pair in DNA under the action of an Na^+. Our model, however, corresponds to the action of the isolated (gaseous) Na^+ on the isolated (gaseous) FA-FI complex. It is clear that a given structure of the gaseous trimer, e.g., Na^+-Fa-FI, while energetically more stable than the others could, for steric reasons, not be realized in DNA. This has been taken into account in the selection of the systems which were studied.

2. Outline of the work

First we investigated whether Na^+ is able to break or weaken the H-bonds in the FA-FI complex by forming one of the competitive complexes on the right-hand side of equilibrium 1

$$\text{FA-FI} + Na^+ \rightleftharpoons Na^+\text{-FA} + \text{FI} \quad (1a)$$
$$\rightleftharpoons Na^+\text{-FI} + \text{FA} \quad (1b)$$
$$\rightleftharpoons Na^+\text{-FA-FI} \quad (1c)$$
$$\rightleftharpoons Na^+\text{-FI-FA} \quad (1d)$$

As a second step we attempted to explain the role of water molecules in this process. To do this the following equilibrium was studied:

$$\text{FA-FI} + Na^+\text{-}OH_2 \rightleftharpoons H_2O\text{-}Na^+\text{-FA-FI} \quad (2a)$$
$$\rightleftharpoons Na^+\text{-}OH_2\text{-FA-FI} \quad (2b)$$

In process 2a the Na^+ is hydrated from the 'outside', whereas in the second process the Na^+ is hydrated from 'inside' (the water molecule is located between the H-bonds of the target and the Na^+).

The ability of the Na^+ (Na^+-OH_2) to perturb the H-bonds in the target, at temperature T, was deduced from the value of the equilibrium constant K_T, or according to eq. 3, by the corresponding change of the Gibbs free energy, ΔG^0.

$$\Delta G^0_T = -RT \ln K_T \quad (3)$$

In order to determine ΔG^0 it was necessary to determine the geometries, total energies and the frequencies of the normal vibrational modes for all the systems involved with the respective equilibrium. Geometries and total energies for all the systems in equilibria 1 and 2 were evaluated quantum chemically (using the nonempirical ab initio SCF method) (sections 4 and 5), vibrational frequencies for some systems in those equilibria were determined by a Wilson FG analysis (section 6). The thermodynamic treatment is discussed in section 7, and, finally, the biological aspects of the processes investigated are discussed briefly in section 8.

The selection of the basis set presents a rather serious problem. We have accumulated an extensive amount of evidence [5,6] that the 4-31G basis set [7] is able to give reasonable values of SCF interaction energies (ΔE^{SCF}), the basis set superposition corrections (BSSC) and geometries for complexes formed by neutral systems. In the present study, however, ions and ionic complexes are also considered. The following computational strategy was therefore selected: for all the atoms of FA and FI the 4-31G basis was used. For Na^+ the modified STO-3G basis set was applied [8] (reoptimized exponents for the inner shell with retention of p-orbitals in the valence shell). It was shown recently [9] that BSSC for ionic complexes Na^+-M (M = ethane, 2-methylpropene, and benzene) is only a small percentage of ΔE^{SCF} if the modified STO-3G basis set is used for Na^+ and 4-31G for molecule M. Finally, for O and H of H_2O the standard STO-3G basis set [10] was applied.

For the complexes investigated we did not take into account either the BSSC or the dispersion energy. The values of δE^{SCF} are indeed so negative (both for neutral and ionic complexes) that the respective corrections would play only a minor role; furthermore, it is known that the two contributions tend to compensate for one another.

Table 1

Theoretical characteristics of FA-FI, FA-Na^+ and FI-Na^+ complexes

Bond distances are given in Å, angles in degrees, and ΔE^{SCF} values in kJ/mol.

Complex	Geometrical parameter[a]									ΔE^{SCF}
FA-FI	R	α	β	ϕ	ω_1	ω_2	N_1-H_5	C_9-O_8	$N_{10}-H_{12}$	−66.02
	2.981	117.1	120.1	0	0	0	1.001	1.226	1.012	
FA-Na^+	R	α	β	C_2-O_3	$\sphericalangle N_1-C_2-O_3$	$\sphericalangle C_2-N_1-H_4$	$\sphericalangle N_1-C_2-H_6$			−181.04
	2.076	187.3	0	1.235	124.4	120.4	114.7			
FI-Na^+	R	α	β	N_3-H_4	C_2-N_3	$\sphericalangle C_2N_3-H_4$	$\sphericalangle N_3-C_2-N_2$	$\sphericalangle C_2-N_3-H_5$		−171.50
	2.236	139.1	0	1.002	1.277	142.6	123.9	120.8		

[a] cf. fig. 2.

3. Geometry optimization

The geometrical parameters for FA and FI were determined by the gradient optimization method and are summarized in fig. 2. The geometrical characteristics for the FA-FI complex (fig. 3) determined by step-by-step optimization of six intermolecular parameters are summarized in table 1. The geometries of the subsystems were kept fixed during optimization (and taken from optimized FA and FI) with the exception of the N_1–H_5 bond in FI, and the C_9–O_8 and N_{10}–H_{12} bonds in FA. The respective optimized values are given in table 1. It is worthwhile to point out here that there is a reasonable agreement between the theoretical geometry of the Fa-FI complex and the experimental geometry of the A-T pair [11] in DNA: the N_1–O_8 and N_3–N_{10} distances in FA-FI amount to 2.981 and 2.980 Å; the same distances in the A-T base pair are 2.82 and 2.91 Å, respectively. Geometrical characteristics of the FA-Na^+ and FI-Na^+ complexes (cf. fig. 3) are summarized in table 1, where the optimized values of the intramolecular parameters are also given (the remaining geometrical characteristics were taken from optimized FA and FI).

For complexes formed by the three subsystems (FI, FA, Na^+) more geometrical structures are encountered; without any calculation it seems obvious that the *trans* structures (cf. fig. 4) of both complexes (Na^+-FA-FI, Na^+-FI-FA) are more stable than the respective *cis* structures (pilot calculations confirmed the assumption, see later). As mentioned previously, however, our goal is to mimic the situation of the A-T pair in DNA and we can hardly expect that such pronounced changes of geometry (corresponding to the formation of a *trans* structure) can take place. For this reason we have limited ourselves to *cis* forms only. The respective geometrical characteristics are summarized in table 2. From the entries of this table and fig. 4 it appears clearly that the perturbation of the FA-FI complex by an Na^+ at the N_3–H_{12}-N_{10} H-bond (cf. fig. 3) results in far more significant changes of the skeleton geometry than in the case of a perturbation of the N_1-H_5–O_8 H-bond. The N_3–N_{10} distance in FA-FI equals 2.98 Å, the same distance in Na^+-FI-FA is 5.45 Å. The N_1–O_8 distance in FA-FI equals 2.98 Å, and the same distance in the Na^+-FA-FI complex is 4.13 Å. From the latter it is evident that, on the one hand, the N–H–O H-bond vanishes and, on the other, that the geometry changes are not too profound and can probably be accommodated within DNA. From this point of view only the Na^+-FA-FI structure was studied further, and, consequently, only the Na^+-OH_2-FA-FI and H_2O-Na^+-FA-FI structures of the most extended complex were investigated (cf. fig. 5 and table 3). For these two complexes the geometry of the Na^+-OH_2 part was kept fixed; it was taken from the optimization of the Na^+-OH_2 complex with the same basis sets as used for the whole complex. (C_{2v}, R(O–Na^+) = 2.004 Å; the geometry of H_2O was kept fixed at the STO-3G optimized values: R(O–H) = 0.989 Å, H–O–H = 100°. The positions of Na^+-OH_2 and

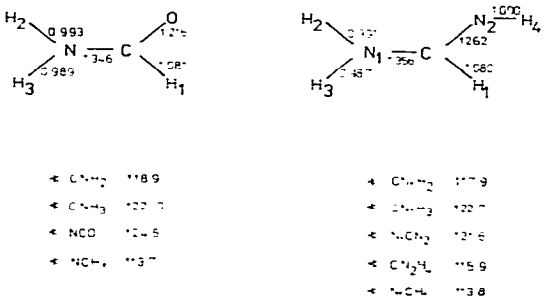

Fig. 2. Optimized geometries for formamide (left) and formamidine (right).

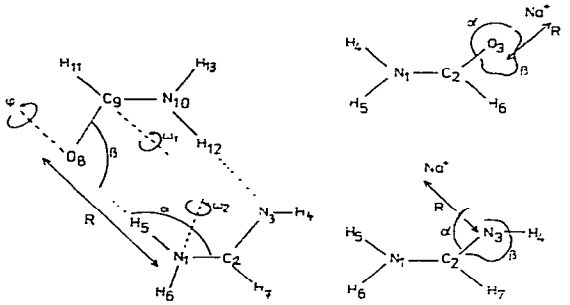

Fig. 3. The geometrical characteristics of the formamide-formamidine complex. See table 1.

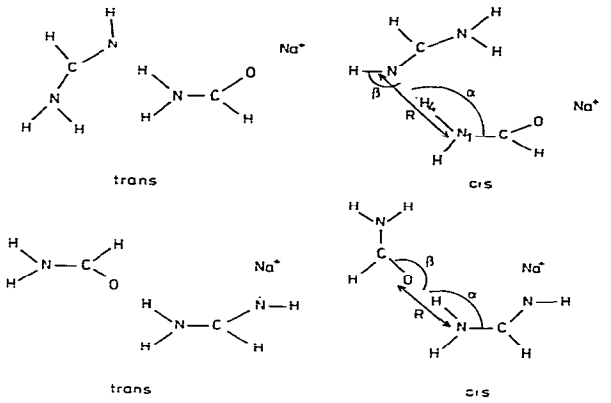

Fig. 4. Possible *cis* and *trans* structures for the sodium-formamidine-formamide complex.

H_2O-Na^+ with respect to the rest of the complexes were taken from the FA-Na^+-OH_2 and FA-H_2O-Na^+ complexes and are given in table 3.

Table 2

Theoretical characteristics of Na^+-FA-FI and Na^+-FI-FA complexes

Bond distances are given in Å, angles in degrees, and ΔE^{SCF} values in kJ/mol.

Complex	Geometrical parameter [a]				ΔE^{SCF}
	R	α	β	N_1–H_4	
Na^+-FA-FI	2.932	130.9	106.8	1.017	−239.49
Na^+-FI-FA	2.931	103.4	240.2		−285.18

[a] cf. fig. 3.

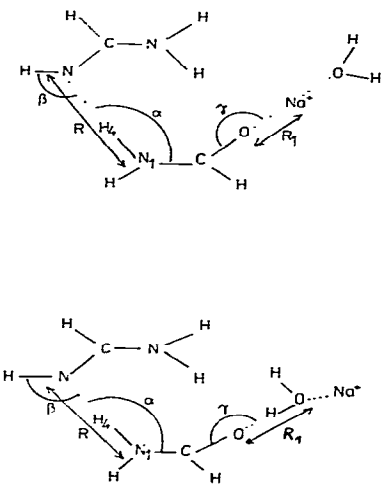

Fig. 5. The models adopted for the sodium-formamidine-formamide complex. See table 3.

4. SCF interaction energy

Let us first investigate the reliability of the basis set used. It is known [5] that the stabilization energies obtained with the 4-31G basis set for neutral complexes (containing one H-bond) are too negative. For FA-FI, which contains two H-bonds, we do not know of any SCF calculation performed with an extended basis set which we could use for comparison. The quality of ΔE^{SCF}(4-31G) for this complex (−66.02 kJ/mol, cf. table 1) can be judged only indirectly by using the known experimental value of ΔH for the A-T

Table 3

Theoretical characteristics of H_2O-Na^+-FA-FI and Na^+-OH_2-FA-FI complexes

Bond distances are given in Å, angles in degrees, and ΔE^{SCF} values in kJ/mol.

Complex	Geometrical parameter [a]							ΔE^{SCF}
	R	α	β	N_1–H_4	R_1	γ [b]	C–O [b]	
H_2O-Na^+-FA-FI	2.933	123.5	116.2	1.015	2.103	187.5	1.234	−218.19
Na^+-OH_2-FA-FI	2.929	132.7	101.3	1.014	3.948	178.2	1.227	−64.46

[a] cf. fig. 4.

[b] Taken from the H_2O-Na^+-FA and Na^+-OH_2-FA complexes, respectively.

complex [12], which is −54.4 kJ/mol. (ΔH is smaller [5] in absolute value than the respective ΔE, i.e., the experimental ΔE should be more negative.) Further evidence for the 'soundness' of ΔE^{SCF}(4-31G) for complexes with two H-bonds could be gained from the $(HCOOH)_2$ dimer. ΔE^{SCF}(4-31G) equals [13] −84.5 kJ/mol, whereas the experimental [14] ΔH amounts approximately to −59 kJ/mol (the experimental ΔE should again be more negative). We may therefore state that the 4-31G calculation gives a rather good estimate of the interaction energy for FA-FI. (One should keep in mind that with complexes with one H-bond ΔE^{SCF}(4-31G) is sometimes overestimated by a factor of 2.) Pullman et al. [8] obtained −138.5 kJ/mol for δE^{SCF} for the Na^+-OH_2 complex with the modified STO-3G and 4-31G basis sets for Na^+ and H_2O, respectively, while we obtained −105.4 kJ/mol with the extended basis set of Kistenmacher et al. [15]. Let us mention finally that the BSSC for Na^+-ethane (calculated with the same basis sets as in the present paper) amounts [9] to only −4.5 kJ/mol, whereas the respective ΔE^{SCF} is −48.5 kJ/mol. On the basis of the data presented here we may expect reasonable values for the SCF interaction energy for all the complexes investigated. It is further necessary to stress that for our purposes the most important quantities are the relative values of stabilization energies for all the complexes taking part in equilibria 1 and 2.

ΔE^{SCF} is, for all the complexes investigated, defined in the usual way (eq. 4):

$$\Delta E^{SCF} = E^{SCF}(\text{complex}) - \Sigma E^{SCF}(\text{subsystem}) \qquad (4)$$

Only for complexes containing the Na^+-OH_2 part is ΔE^{SCF} determined by taking into account the total energy of this part and not the energies of Na^+ and H_2O separately. In other words we are taking Na^+-OH_2 as one pseudosystem making the tedious optimization of the most extended complexes easier.

SCF interaction energies for FA-FI, FA-Na^+ and FI-Na^+ are given in table 1. Those for Na^+-FA-FI and Na^+-FI-FA are presented in table 2. From the entries of table 2 it is evident that the Na^+-FI-FA complex is more stable than Na^+-FA-FI, but the geometry cnanges within the former are much more severe (see above) than with the latter. As mentioned earlier the *trans* forms of Na^+-Fa-FI and Na^+-FI-FA are expected to be more stable than the respective *cis* forms. ΔE^{SCF} for the *cis* and *trans* structures of Na^+-FA-FI equal −239.5 and −247.7 kJ/mol, respectively. However, owing to more pronounced changes in the geometry, the *trans* structures were not taken into consideration. SCF stabilization energies for H_2O-Na^+-FA-FI and Na^+-OH_2-FA-FI are summarized in table 3. These values should be compared with the SCF stabilization energy of Na^+-FA-FI (−239.49 kJ/mol). It becomes evident that if water hydrates the Na^+ from outside ΔE^{SCF} decreases only slightly; on the other hand, if water is placed between the target and the Na^+ ΔE^{SCF} decreases considerably. Let us finally compare ΔE^{SCF} for the complexes on the left- and right-hand sides of equilibria 1 and 2. We have to conclude that ionic complexes formed by two or three systems are more stable than the FA-FI complex, which is especially true for trimers. This means that from the energetical point of view equilibrium 1 is strongly shifted to the right. The same is true for the first reaction of equilibrium 2, while with the second one the stabilizations of FA-FI and Na^+-OH_2-FA-FI complexes are approximatively equal. It is known [2,6] however, that entropy influences the equilibrium between van der Waals molecules, sometimes quite dramatically. (See below.)

5. Wilson FG analysis

Force constants were evaluated with the 4-31G basis for FA-FI and with 4-31G and modified STO-3G for FA-Na^+. Besides the intermolecular force constants, the N–H stretching force constants for both FA and FI were evaluated for the FA-FI complex as well. The respective inter- and intramolecular vibrational frequencies are presented in table 4. The most significant contribution to the vibration entropy comes from low frequencies ($\lesssim 100$ cm^{-1}). However, owing to the character of the complex (two strong H-bonds) as well as the motion corresponding to the respective coordinates (perturbation of one or both H-bonds) we do not expect that these frequencies possess

such low values. On the other hand, high frequencies ($\geq 2000\ cm^{-1}$) make important contributions to the zero-point energy but, again, we do not expect that the frequencies could reach such values.

6. Thermodynamic treatment

Thermodynamic characteristics of equilibria 1 and 2 were obtained by means of partition functions computed from SCF (4-31G) and SCF (modified STO-3G) molecular constants. The rigid rotor, harmonic oscillator, and ideal gas approximations were adopted (see, e.g., ref. 16).

The evaluation of the translational and rotational partition functions for all the complexes (as well as isolated systems) investigated is trivial if their mass and geometry are known; for the evaluation of vibrational partition functions all the vibrational frequencies must be known. For FA-FI these frequencies were calculated directly (see above). For the Na^+-FA-FI trimer the calculation is too tedious. We have therefore taken these frequencies from the two dimers forming the trimer, namely, from Na^+-FA and FA-FI. This assumes that in Na^+-FA-FI there are two sets of independent frequencies corresponding to the Na^+-FA and FA-FI parts (see, e.g., ref. 17). The vibrational frequencies for the Na^+-FA part were taken from the optimized Na^+-FA complex (table 4), that for the FA-FI part (open structure with one H-bond) were identified with the intermolecular frequencies of the formamide dimer [2] (open structure with the same H-bond as the FA-FI part).

From the preceding part it becomes evident that the energetical balance of equilibria 1c and 1d are much more negative than those of equilibria 1a and 1b. Without making any calculation it is obvious that entropy disfavours formation of the trimer; i.e., the interaction entropy is acting in the opposite direction to the interaction enthalpy (interaction energy). In view of the very negative values of ΔE for the process we may expect that $T\Delta S^0$ does not reach its absolute value. The other reason why we do not expect too large values for the $T\Delta S^0$ term is the fact that there are complexes on both sides of equilibrium 1. The formation of A-B from A and B is naturally chararacterized by a rather large entropy loss [5] arising from the loss of three translational and three rotational degrees of freedom which is not compensated by the gain of six vibrations. The most important contribution to $T\Delta S^0$ in our process comes, however, from the loss of translational entropy of Na^+ which is not compensated by the gain of vibrational entropy of the trimer. It is likely that the vibrational and rotational entropies on either side of equilibrium [1] will not be too different: hence, they will contribute negligibly to $T\Delta S^0$. For a rough estimate of $T\Delta S^0$ for equilibrium 1c we can therefore use the experimental value [18] of $T\Delta S_{298}$ for the formation of Na^+-OH_2, which is -28.56 kJ/mol. The calculated thermodynamic characteristics for equilibrium 1c are summarized in table 5. From this table it is clear that the $T\Delta S^0$ term is much

Table 4

Calculated harmonic normal frequencies (cm^{-1}) for FA-FI, FA-Na^+, and FI-Na^+ complexes [a]

Complex	Intermolecular				Intramolecular [b]
	1	2	3	N_1–H_5 [c]	N_{10}–H_{12} [d]
FA-FI	384	397	936	3720	3491
FA-Na^+	196	219	453		

[a] cf. fig. 3.
[b] Change of C–O stretching upon complex formation is small and was therefore not considered.
[c] N–H stretching (harmonic) in isolated FI equal to 3905 cm^{-1}.
[d] N–H stretching in isolated FA equal to 3917 cm^{-1}.

Table 5

Thermodynamic characteristics of the FA-FI + Na^+ ⇌ Na^+-FA-FI process

All the molecular characteristics were calculated with the SCF method with 4-31G and modified STO-3G basis sets; for details see text. The standard state is the ideal gas phase at 101 325 Pa.

T(K)	ΔE (kJ/mol)	ΔH^0 (kJ/mol)	$T\Delta S^0$ (kJ/mol)	ΔG^0 (kJ/mol)	log K [a]
100	−173.4	−178.3	−9.6	−168.7	88.1
298		−175.4	−24.0	−151.4	26.5

[a] K in (atm^{-1}): 1 atm = 101 325 Pa.

less important than the ΔH^0 term, and, further, that the rough estimate of the entropy term made above is rather close to the calculated value. The very negative value of ΔG^0 (for both temperatures investigated) confirms the fact that the Na^+ breaks the C-O–H-N bond in FA-FI.

The weak point of this calculation is the determination of the vibrational frequencies for FA-FI, some of which turn out to be too high. Therefore, we have recalculated the equilibrium by replacing the intermolecular vibrations of FA-FI (table 4) by the experimentally known frequencies [19] of the formic acid dimer, which are 68, 164, 215, 248 and 519 cm^{-1}. These low-frequency modes of the $(HCOOH)_2$ dimer are expected to be similar to those of the nucleic base-pairs. With these frequencies $T\Delta S_{298}$ decreases from -23.2 (table 5) to -34.8 kJ/mol and ΔG_{298} increases from -160.9 to -149.3 kJ/mol. These changes do not affect our conclusions. It should be mentioned here that ΔE for process 1c is less negative than that for process 1d. This means that for the isolated (gaseous) FA-FI complex the N–H-N H-bond will be broken more easily than the C-O–H-N bond (the entropy contribution to both structures of the trimer will be similar).

For equilibrium 2 we did not calculate entropy contributions because (i) we expect that they will not be significantly different from those of equilibrium 1, and (ii) the calculation of force constants for the complexes on the right-hand side of equilibrium 2 would be too cumbersome.

7. Conclusions: Biological consequences

We have shown on the basis of calculated ΔG^0 values that the Na^+ breaks the H-bond of FA-FI; in the light of the previous arguments we expect that the same will be true for the A-T pair. What is the reason that this does not happen in DNA? It is known that water plays an important role in the determination of the structure and proper functioning of DNA. Following Clementi and Corongiu [20] each Na^+ is hydrated; in the relative humidity range from 400 to 240 water molecules (per B-DNA turn) the average hydration number amounts to 4.0. It is thus evident that it is water that (under normal conditions) protects the H-bonds in the DNA base-pairs. This was confirmed by our calculations: if water hydrates Na^+ from 'inside' (i.e., is located between the H-bonds of the FA-FI complex and Na^+) the ΔE of the process is positive and amounts to 1.6 kJ/mol. (A positive value indicates that the equilibrium is shifted in favour of the left-hand side.) On the basis of data presented in table 5 and similarities of equilibria 1 and 2 we expect that the ΔG^0 for the process investigated, at 298 K, amounts to approx. 24 kJ/mol. The calculations further indicate that if water hydrates Na^+ from 'outside' the ΔE of the process is still very negative and amounts to -152.2 kJ/mol. Estimating the ΔG_{298} of this process (similarly to the previous case) we obtain the large negative value of approx. -132 kJ/mol. The 'water protection' could be perturbed by increasing the concentration of Na^+ or decreasing the number of water molecules, or both. In either case the breaking of an 'unprotected' H-bond in A-T could ensue. It is noteworthy to mention here [4,20] that changes in the hydration number of Na^+ occur already on decrease of the number of water molecules from 400 to 220 or 180 (per B-DNA turn): the respective hydration number (4.0) is changed to 3.8 or even to 3.5, respectively (the latter value means that from 20 Na^+, 10 are hydrated by 4 water molecules and 10 by only 3).

The concentration of water in the close vicinity of DNA could be influenced, e.g., by insertion of a hydrophobic molecule. Let us only mention in this connection the action of polyaromatic hydrocarbons (PAH), some of which are known to be potent carcinogens. A PAH either binds covalently with nucleic acids (preferably with the amino group of the guanine residue) or intercalates non-covalently in the DNA helix. The molecular mechanisms involved in carcinogenesis are, however, not fully understood (see, e.g., ref. 21). The very first result of both processes mentioned should without doubt be the decrease in concentration of water molecules in the vicinity of nucleic acids as a consequence of the insertion of a hydrophobic PAH. The critical point of carcinogenic processes may be not the covalent or non-covalent binding of PAH, but the removal of water molecules screening the Na^+, followed by damage to the H-bonds in the A-T pair.

This could be the first step in the unfolding of the double helix.

The hypothesis proposed in this paper would help in understanding the role of cations and salts in carcinogenesis and the lack of a common chemical type among carcinogens. What is involved at the initial stage could be not the formation or breaking of covalent bonds but only a change in the pattern of molecular associations, among them H-bonds.

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