Interaction of DNA fragments with counterions in aqueous solution

A. V. Teplukhin

*Institute of Mathematical Problems of Biology, Russian Academy of Sciences,
142292 Pushchino, Moscow Region, Russian Federation.
Fax: +7 (27) 73 2408. E-mail: tepl@impb.serpukhov.su*

Monte Carlo simulation of the hydration of metal ion—DMP$^-$ and metal ion—9-methylguanine complexes was performed. A comparative analysis of the results for Na$^+$ and K$^+$ ions was carried out. The main stages of dissociation were revealed. The energy effects of dissociation were evaluated.

Key words: computer simulation, DNA, ions, solutions, hydration, dissociation, Monte Carlo method.

The interaction of DNA with ions is one of the most important factors determining the local structure and general conformation of the DNA double helix both in solution and *in vivo*.[1,2] Detailed information on the distribution of the ions surrounding polynucleotides is required to understand the mechanisms of this interaction. However, neither experimental nor theoretical methods allow one to carry out systematic studies in this field. Thus, the major part of experimental data on complexation of nucleic acids in solutions is related to the ions of transition and alkaline-earth metals[1−3], leaving in the shadow Na$^+$ and K$^+$ ions, which are the most abundant in living organisms. Despite a certain progress in studying the models ignoring the molecular discreteness of aqueous medium (the polyelectrolyte theory[4]), the problem of simulation of large ion-molecular systems still persists. Therefore, various approaches using effective "potentials of mean force"[5] to take into account the interactions of solvent molecules are often employed in the computer simulation of macromolecules. However, calculations of realistic "potentials of mean force" describing the dissociation of a pair of ions, one of which has an angular potential component, require precise knowledge of the dissociation trajectory.

A cation—dimethyl phosphate (DMP$^-$) pair is a convenient model for studying the interactions between counterions and the sugar-phosphate backbone of nucleic acids. The "potential of mean force" of such a system (for Na$^+$ ion) was calculated[6,7] for two idealized trajectories: along the bisectrix of the O(1)$^-$—P—O(2)$^-$ angle and along the line prolonging the PO$^-$ bond. Therefore it is necessary to know the real dissociation mechanism of this ionic pair. The aim of this work was to find a possible trajectory of the motion of Na$^+$ or K$^+$ ions in the vicinity of DMP$^-$ or nitrogen base (9-methylguanine) and evaluate the energy effects of dissociation.

Procedure for Calculations

The molecular geometry, atomic charges, and potential function coefficients (PFC) were described in Ref. 8. The

Monte Carlo simulation of the hydration was performed at 300 K using the standard procedure described previously[9] (using the Metropolis algorithm in the NVT ensemble). To ensure the observed density of each system, the unit cell volume was calculated as the sum of the partial volumes of all its components at a given temperature and at a pressure of 1 atm. The values of partial volumes for water molecule, Na$^+$ and K$^+$ ions, and DMP$^-$ anion used in the calculations were 30 Å^3, −11 Å^3, 5 Å^3, and 100 Å^3, respectively.[8]

A system containing the DMP$^-$ anion, a counterion, and 400 water molecules was simulated using a cubic unit cell with an edge of 22.95 Å (22.96 Å) for Na$^+$ (K$^+$) (see Fig. 2 in Ref. 9). The DMP$^-$ anion was located at the cube center, so that the O(1)$^-$PO(2)$^-$ plane is parallel to the opposite faces of the cube. The maximum change in any ion coordinate per step of the Monte Carlo procedure of 0.065 Å corresponded to a probability to jump to a new position of 48% (for comparison, we will point out that the maximum displacement of water molecule is 0.122 Å).

A system containing the base (9-methylguanine), a counterion, and 400 water molecules was simulated using a cubic unit cell with an edge of 23.015 Å (23.017 Å) for Na$^+$ (K$^+$). The base molecule was located at the cube center so that its plane is parallel to the opposite faces of the cube. The Z axis was perpendicular to the plane of the base molecule and the X axis was parallel to the long axis of the base molecule (the C(8)—N(1) direction for purines).

Periodic boundary conditions were imposed on the systems; the minimum image prescription was used for energy calculations. Ion—ion interactions between neighboring cells were ignored.

Results and Discussion

Counterion-DMP$^-$ pair. The initial position of counterion corresponded to the global minimum for the ion—DMP$^-$ pair in vacuum.[8] The first 50 thousand of Monte Carlo trials (calculated per one water molecule) were performed for a system with fixed geometry of the ion—DMP$^-$ pair and then excluded from the averaging. Thereafter, the motion of the ion was allowed. The generation of the Markovian chain was terminated when the distance between the phosphorus atom and the counterion reached 10.5 Å. For K$^+$, such a "dissocia-

tion' occurs relatively "fast" (150—200 thousand trials for one water molecule or one ion). At the same time, a 3 to 4 times larger number of trials is required for Na^+. To make sure that the results obtained are reliable, this procedure was repeated several times (each time new initial configuration of water molecules was used).

To trace the pathway of the ion dissociation, the space of the unit cell was divided into cells of volume $0.5 \times 0.5 \times 1.5$ Å³ (the Z axis is orthogonal to the $O(1)^-PO(2)^-$ plane and the X axis coincides with the bisectrix of the $O(1)^- - P - O(2)^-$ angle) using a three-dimensional network. In this case the PO_2^- group is centrally located in the central Z-layer. The probability of finding the ion in a cell was calculated as the ratio N_i/N, where N_i is the number of Monte Carlo configurations in which the ion is in the given cell i and N is the total number of configurations in the given Markovian chain. As follows from comparative analysis of probability distribution maps, the pathways of ion dissociation have many common characteristics. Thus, after the beginning of its motion from the initial position, the ion

gradually (after dozens of thousands of trials) deviates from the $O(1)^-PO(2)^-$ plane by 1.5 Å and shifts by about 1 Å along the Y axis breaking the van der Waals contact with one of the anionic O^- atoms. This is a rather stable configuration, since 100 or 150 thousand trials are required to either continue dissociation or to "jump" to another O^- atom (the latter is more probable for Na^+). The succeeding part of the dissociation pathway runs inside a slightly bent tube (1.5 Å and up to 2.5 Å in diameter for Na^+ and K^+, respectively) passing parallel to the bisectrix of the $O(1)^- - P - O(2)^-$ angle. It is possible to reveal two trap areas in the vicinity of each anionic oxygen atom where the ion spends the most time before being dissociated. The first trap corresponds to the van der Waals contact with one of the anionic O^- atoms. The second trap, which is characterized by a larger volume and lower probability density to find the ion in a separate cell (for Na^+, it is nearly halved as compared to that of K^+), is at a distance of 4.5 Å from anionic O^- atom, which can be interpreted as contact of the ion with the O^- atom mediated by a water molecule
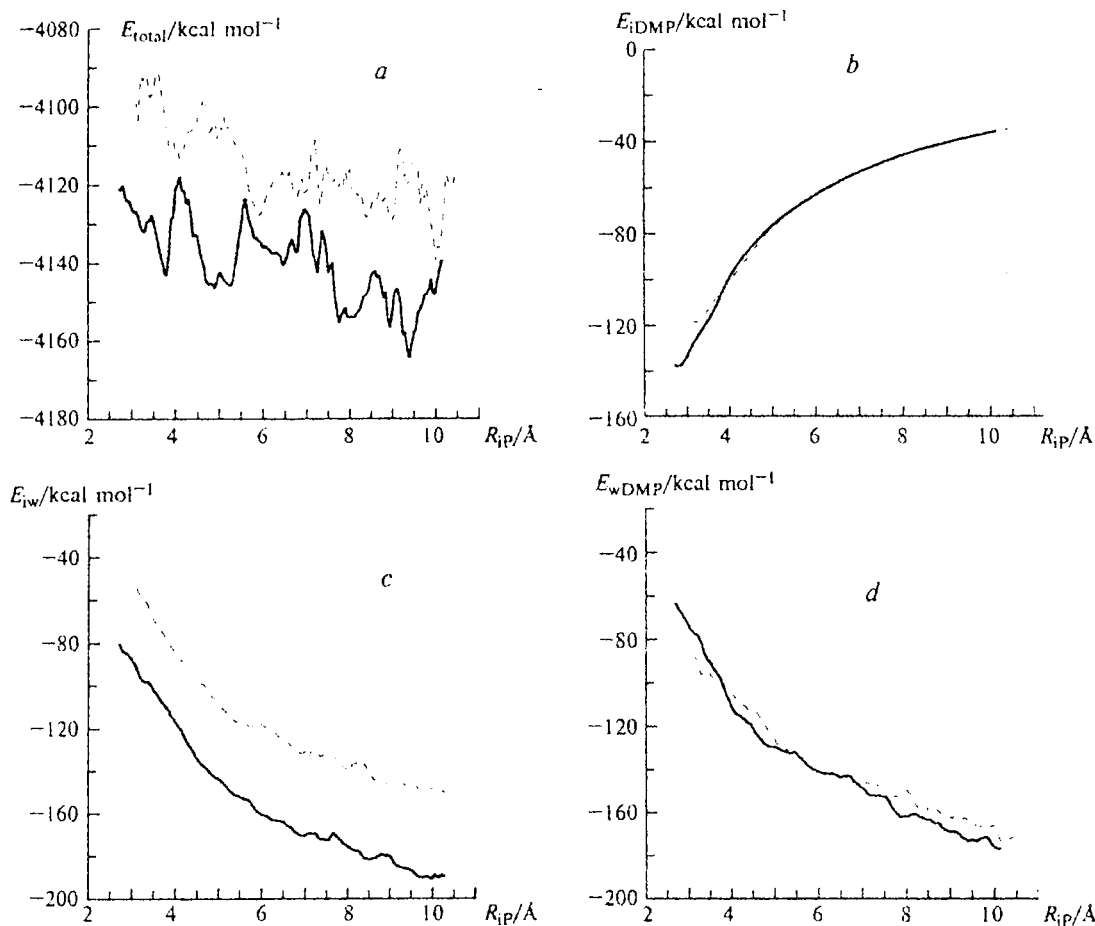

Fig. 1. Dependences of the total potential energy E_{total} of the water—counterion—DMP⁻ system (a) and contributions of ion—DMP⁻ E_{iDMP} (b), water—ion E_{iw} (c), and water—DMP⁻ E_{wDMP} interactions (d) on the distance R_{ip} between the phosphorus atom and the ion. Solid and dotted line correspond to the data for Na^+ and K^+, respectively.

(actually, there are several water molecules distributed along the line linking the ion and the O^- atom). Nevertheless no specific features of the dependences of energy characteristics of the system on the ion—phosphorus distance were found (see Fig. 1 and Ref. 7).

The dependences of the total potential energy of the system in question E_{total} (as well as those of its contributions E_{iDMP}, E_{wDMP}, and E_{iw}) on the ion—phosphorus distance are shown in Fig. 1. It is noteworthy that at an ion—phosphorus distance of 9.5 Å the contributions from water—DMP^- (E_{wDMP}) and water—ion (E_{iw}) interactions reach values corresponding to hydration of an individual DMP^- ion or cation (see Ref. 8) and remain constant at longer distances. The standard deviation of instantaneous E_{total} values (the energy of one molecular configuration) is 32—35 kcal mol^{-1} and can be directly associated with thermal fluctuations, so the corresponding heat capacity C_v is 20—23 cal (mol deg)$^{-1}$ (the experimental value for bulk water is 21 cal (mol deg)$^{-1}$).[10] Nevertheless, the standard deviation of E_{total} values obtained by averaging over microintervals R_{ip} (0.05 Å) and shown in Fig. 1 is only 10 kcal mol^{-1}. This makes it possible to establish that the total energy of aqueous system with dissociated complex E_{total} is nearly 25 kcal mol^{-1} lower than that of associated pair.

Ion—base pairs in aqueous solution. The molecule of 9-methylguanine was chosen for studying the ion—base pair dissociation, since it forms the most stable complex with the ion in vacuum (the more favorable positions for binding with 1-methylcytosine are inaccessible in the DNA double helix). The initial position of the ion corresponded to the global minimum for the 9-methylguanine—ion pair in vacuum[8] (the "bridge" between the N(7) and O(6) atoms) (see Fig. 5 in Ref. 8). The first 50 thousand Monte Carlo trials (calculated per one water molecule) were performed for a system with fixed geometry of the ion—base pair and then excluded from the averaging. Thereafter, the motion of the ion was allowed. The generation of the Markovian chain was terminated when the distance between the N(7) atom and the counterion reached 10.5 Å.

The pathway of ion dissociation was found using the same approach as that used in the case of the ion—DMP^- complex. The base molecule was centrally located in the central Z-layer. After beginning the motion from the initial position, the ion gradually deviates from the plane of the base molecules by 1.5 Å, breaking the van der Waals contact with the O(6) atom (a peak of the radial distribution function is observed; the distances between the ion and the O(6) atom reach 3.6 Å). The duration of contact with the N(7) atom is, on the average, 100 (for Na^+) or 50 (for K^+) thousand trials for the ion and each water molecule. After breaking the contact with the N(7) atom, the ion usually moves toward the O(6) atom and comes into contact with this atom. The mean "lifetime" of this state corresponds to 10 to 20 thousand trials. After two or three such jumps the ion moves away to the second, blurred area of

relative stability at a distance of 4.5 Å from the N(7) and O(6) atoms within the limits from 2 to 4 Å out of the plane of the base molecule. Here the ion moves randomly along the C(8)—N(1) edge of 9-methylguanine. To leave this area, 100 000 (for K^+) or 200 000 (for Na^+) trials are required for ion and each water molecule.

Information on the final part of dissociation pathway is less reliable since the process occurs at a rather high rate at this stage. To obtain a more reliable information, a series of numerical experiments should be performed. Each experiment requires several weeks of round-the-clock operation on a personal computer equipped with a Pentium®-150 processor. We have carried out three numerical experiments, one for Na^+ ion and two for K^+ ion. In two cases (in one, more than 1 million trials (for Na^+ ion and each water molecule), in the other 300 thousand trials (for K^+ ion)) the dissociation motion of the ion occurred toward the C(8) atom while in the third case (500 thousand of trials (for K^+ ion)) the ion moved toward the N(1) atom. In the latter case the deviation of the K^+ ion out of the plane of the base molecule was 6 Å (in the former two cases it was within the limits 2 to 4 Å). Finally, owing to periodic boundary conditions, all three "trajectories" terminated with an accuracy of ±2 Å in the middle of the segment (collinear to the long axis of Watson—Crick pair) linking the C(8) atoms of 9-methylguanine residues from adjacent cells. In this connection it should be noted that the final position of an ion can be strongly dependent on the choice of geometric parameters of the unit cell of simulating system and PFC.

The dependences of the total energy E_{total} (and those of the contributions from ion—9-methylguanine (E_{ig}), water—9-methylguanine (E_{wg}), and ion—water (E_{iw})) interactions on the distance $R_{iN(7)}$ between the ion and the N(7) atom of 9-methylguanine are shown in Fig. 2. The E_{ig} jump near 4.5 Å is due to the strengthening of the ion interactions with the O(6) atom when the ion moves toward the N(1) atom (this occurs when the ion "switches" the van der Waals contact from the N(7) atom to the O(6) atom). At an ion—N(7) distance of 8.5 Å, the contributions from water—9-methylguanine and water—ion interactions (E_{wg} and E_{iw}, respectively) reach the values corresponding to hydration of individual 9-methylguanine molecule or cation and remain constant at longer distances.

The total potential energy of the dissociated complex (E_{total}) is only 10 (for Na^+) or 5 (for K^+) kcal mol^{-1} lower than that of the associate (see Fig. 2). This gain is rather small compared to the standard deviation of E_{total} values averaged over microintervals $R_{iN(7)}$ of size 0.05 Å (about 10 kcal mol^{-1}). Nevertheless, this value can serve as an illustration of the dissociation tendences of an ion—base complex in water.

The dissociation of metal ion—DMP^- and metal ion—9-methylguanine complexes is a multistage process and has some features common to all the systems con-
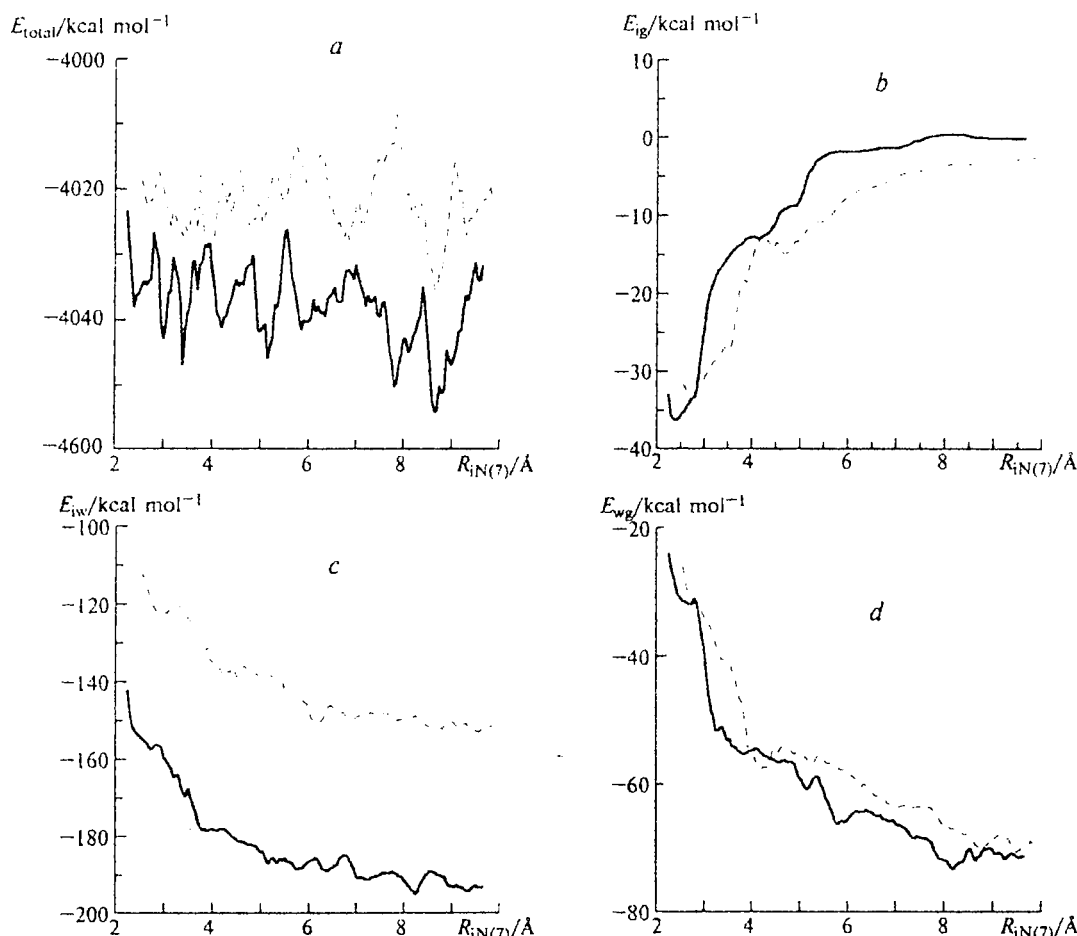
Fig. 2. Dependences of the total potential energy E_{total} of the 9-methylguanine—water—ion system (*a*) and contributions of ion—methylguanine E_{ig} (*b*), ion—water E_{iw} (*c*), and water—methylguanine E_{wg} interactions (*d*) on the distance $R_{iN(7)}$ between the N(7) atom and the ion. Solid and dashed line correspond to the data for Na^+ and K^+, respectively.

sidered. The evaluation of energy differences for the systems after and before dissociation showed that the energy effect for Na^+ ion is 1.5 to 2 times higher than that for K^+ ion. The simulation results show that random walks of Na^+ ion in the initial dissociation stage occur in a much smaller volume than those in the latter stages. The delocalization degree of K^+ ion on dissociation changes to a lesser extent. This points to a considerably larger entropy contribution in the case of Na^+ ion.

References

1. Yu. P. Blagoi, V. L. Galkin, G. O. Gladchenko, S. V. Kornilova, V. A. Sorokin, and A. G. Shkorbatov, *Metallokompleksy nukleinovykh kislot v rastvorakh* [*Metallocomplexes of Nucleic Acids in Solutions*], Naukova dumka, Kiev, 1991, 272 pp. (in Russian).
2. W. Saenger, *Principles of Nucleic Acid Structure*, Springer-Verlag, New York, 1984.
3. K. B. Yatsimirskii, E. E. Kriss, and V. L. Gvyazdovskaya, *Konstanty ustoichivosti kompleksov metallov s bioligandami* [*Stability Constants of Metallocomplexes with Bioligands*], Naukova dumka, Kiev, 1979, 228 pp. (in Russian).
4. M. D. Frank-Kamenetskii, V. V. Anshelevich, and A. V. Lukashin, *Usp. Fiz. Nauk*, 1987, **151**, 595 [*Sov. Phys.-Usp.*, 1998, **151** (Engl. Transl.)].
5. B. M. Pettitt, M. Karplus, and P. J. Rossky, *J. Phys. Chem.*, 1986, **90**, 6335.
6. S. E. Huston and P. J. Rossky, *J. Phys. Chem.*, 1989, **93**, 7888.
7. R. A. Friedman and M. Mezei, *J. Chem. Phys.*, 1995, **102**, 419.
8. A. V. Teplukhin, G. G. Malenkov, and V. I. Poltev, *Izv. Akad. Nauk, Ser. Khim.*, 1998, 2166 [*Russ. Chem. Bull.*, 1998, **47**, 2098 (Engl. Transl.)].
9. V. I. Poltev, T. I. Grokhlina, and G. G. Malenkov, *J. Biomol. Struct. Dyn.*, 1984, **2**, 413.
10. H. L. Friedman, and C. V. Krishnan, in *Water: A Comprehensive Treatise*, Ed. F. Franks, Plenum Press, New York, 1973, **3**, 1.