Two adenine rings, related by a center of symmetry, overlap considerably in the crystal of the 9-ethyladenine-1-methyl-5-fluorouracil complex.[43] In that case, however, the C(6)–NH$_2$ group lies outside the plane of the other ring, and the main overlap was between the respective five- and six-membered rings. In the structure of α-D-2′-amino-2′-deoxyadenosine monohydrate,[44] there was overlap of the C(6)–NH$_2$ group with the pyrimidine ring of a molecule related by a screw axis. In the structure of adenosine triphosphate,[45] there was interleaving of adenine rings with extensive overlap of the two six-membered rings. In Ade–C$_3$–Nic$^+$, the interplanar spacing between the adenine rings is 3.35 Å, while the shortest interatomic contact between the parallel adenine groups is 3.38 Å between N(6) and N(9) (Table IV). The plane of the adenine moiety at x, y, $1 + z$ is also 3.35 Å on the same side of plane of the basic adenine residue as the ring at $1 - x$, $1 - y$, $1 - z$ (Figure 6). The shortest interatomic contact (excluding hydrogen) is 3.60 Å between N(3) and N(7) in the cation at x, y, $1 + z$. The other side of the adenine ring is not overlapped by any parallel planar group (Figure 1). The closest approaches are 2.88 Å between N(3) and H(16) in the molecule at $1 - x$, $-y$, $1 - z$ and 3.34 Å between C(4) and H(20b) in the same molecule.

There is also a slight overlap of pyridinium rings related by the center of symmetry at $^1/_2$, 0, $^1/_2$. The projections of atoms C(14) and C(15) in the symmetry-related ring onto the plane defined by the six ring atoms in the initial molecule lie within the ring. The interplanar distance, however, is 4.14 Å. The N(13)···O(21) distance between these two molecules is 3.92 Å.

A comparison of the conformation in Ade-C$_3$-Nic$^+$ with those found in AdeH$^+$-C$_3$-Nic$^+$ and in solution will be given in the following paper.[11]

Acknowledgment. We wish to thank Professor Nelson J. Leonard for bringing this problem to our attention and giving us the benefit of his advice during the study. Dr. T. Gordon Scott provided us with the sample. The stereo drawings were made with ORTEP (C. K. Johnson, Oak Ridge National Laboratory) with the assistance of Mrs. Nina Thayer. Computations were carried out on the IBM 1800 and 360-75 at the University of Illinois and were partly supported by a grant from the Research Board at the University of Illinois.

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Structures of Analogs of Nicotinamide–Adenine Dinucleotide. II. Crystal Structure of *N*-(3-(Aden-9-yl) propyl)-3-carbamoylpyridinium Bromide Hydrobromide Dihydrate, (AdeH$^+$-C$_3$-Nic$^+$)2Br$^-$·2H$_2$O[1]

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Abstract: The crystal structure of *N*-(3-(aden-9-yl)propyl)-3-carbamoylpyridinium bromide hydrobromide dihydrate, (AdeH$^+$-C$_3$-Nic$^+$)2Br$^-$·2H$_2$O, a dicationic species containing the bases found in NAD$^+$ linked by a trimethylene bridge, has been determined. The crystals are monoclinic with $a = 9.468$ (1), $b = 19.318$ (2), $c = 13.845$ (2) Å, and $\beta = 131°32'$ (2′), and there are four molecules of (C$_{14}$H$_{17}$N$_7$O)$^{2+}$2Br$^-$·2H$_2$O in the unit cell; the space group is $P2_1/c$. The structure has been refined to an R factor of 0.059 on 3062 nonzero reflections collected on an automatic diffractometer (Cu Kα radiation). The anion sites are occupied by chloride ions 33% of the time. The orientation of the trimethylene chain is such that the adenine and nicotinamide rings are close to being parallel (dihedral angle 4°58′) and the distances of atoms in the nicotinamide moiety from the best plane of the adenine ring range from 2.77 to 3.22 Å. While there is no intramolecular overlap of nonhydrogen atoms between the two rings, there is a close approach of C(2) and N(3) in the adenine ring to C(14) and O(21) in the nicotinamide moiety. The shortest interatomic contact is between N(3)···C(14) at 3.06 (1) Å. The amide group is rotated by 3°54′ out of the plane of the pyridine ring. The adenine ring is linked to another centrosymmetrically related adenine ring by two N(6)–H···N(7) hydrogen bonds. There is possible C–H···O hydrogen bonding between two pairs of centrosymmetrically related C(14) and O(21) atoms. The water molecules are involved in hydrogen bonding to the halide anions. In addition to the close intramolecular approach of an adenine ring to the nicotinamide group, there are some close approaches between the adenine ring and nicotinamide groups from other molecules. The dramatic differences in the conformations found for Ade-C$_3$-Nic$^+$ and AdeH$^+$-C$_3$-Nic$^+$ in the solid and in solution are discussed.

In the course of the preparation of the *N*-(3-(aden-9-yl)propyl)-3-carbamoylpyridinium bromide, (Ade-C$_3$-Nic$^+$)Br$^-$·3H$_2$O (I), samples,[3] crystals that were initially considered to be a different crystalline modification of I were obtained. These crystals are monoclinic

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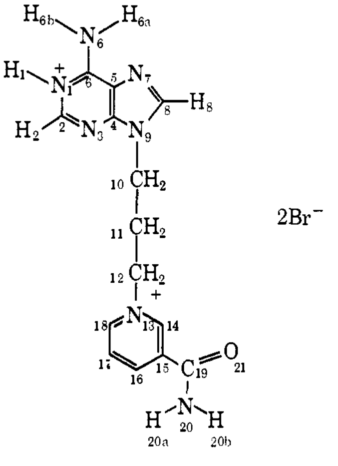
(1) This work was supported by USPH Grants GM 12470 and GM 19336 and Training Grant GM 722.

(2) Alfred P. Sloan Research Fellow.

(3) P. L. Johnson, C. A. Maier, and I. C. Paul, *J. Amer. Chem. Soc.*, **95**, 5370 (1973).

compared to the triclinic ones described in the previous paper.[3] As the enthusiasm of the crystallographers could not be contained until a complete chemical characterization of the material was carried out, the content of the crystals was established only after the crystallographic investigation was at an advanced stage. The crystals contain a dication, *N*-(3-(aden-9-yl)propyl)-3-carbamoylpyridinium bromide hydrobromide dihydrate, (AdeH$^+$-C$_3$-Nic$^+$)2Br$^-$·2H$_2$O (II), with two anionic sites that are mainly occupied by bromide anions but sometimes contain chloride anions. This mixture arose from the method of preparation which involved replacement of chloride by bromide on an ion exchange column. The present paper describes the crystal structure of this dicationic analog of NAD$^+$.



II

Experimental Section

The transparent, needle-like crystals[4] of this second "modification" of Ade-C$_3$-Nic$^+$ were sealed in a thin-walled glass capillary in the presence of mother liquor. As in the previous structure analysis,[3] the crystal instability and the limited number of crystals precluded a density measurement. As all the crystals were employed for the X-ray study, no elemental analysis on the sample used in the X-ray work was obtained. However, the results of the X-ray study indicate that there are two molecules of water of crystallization per molecule of II.

Crystal data: (C$_{14}$H$_{17}$N$_7$O)Br$_2$·2H$_2$O, $M = 495.2$, monoclinic, $a = 9.468$ (1), $b = 19.318$ (2), and $c = 13.845$ (2) Å, $\beta = 131°32'$ (2′), $V = 1895.6 \times 10^{-24}$ cm^3, $Z = 4$, $\rho_{\text{calcd}} = 1.73$ g cm^{-3}; $F(000) = 992$, $\mu = 62.9$ cm^{-1} (Cu Kα). Systematic absences, $h0l$, when $l = 2n + 1$, and $0k0$, when $k = 2n + 1$, establish the space group as $P2_1/c$.

The procedures for determination of cell parameters and data collection were as described previously.[3] The cell for which dimensions were determined and which formed the basis for the data collection corresponded to the $P2_1/n$ setting with $a = 9.468$ (1), $b = 19.318$ (2), and $c = 10.367$ (1) Å, and $\beta = 91°35'$ (1′) To transform the data to the $P2_1/c$ setting, the relationships $h = -h$, $k = -k$, $l = h + l$, were used. The crystal, mounted about the a axis, had dimensions 0.6 × 0.2 × 0.3 mm along the three crystallographic axes. The scan rate was 1°/min. In terms of the transformed cell parameters, the octants of data $h\bar{k}l$ and $h\bar{k}\bar{l}$ were measured. The criteria used to determine if a reflection was sufficiently above background were that the net count be 0.05 × the total background count, or 50 counts, whichever is greater. After averaging symmetry-equivalent reflections, the set of unique data consisted of 3226 reflections, of which 3062 had intensities considered significantly above zero. Lorentz and polarization corrections were applied to the data but no correction was made for absorption.

The structure was solved by the symbolic addition method[5] using the programs FAME-MAGIC-LINK-SYMPL.[6] Signs for 392 of 396 reflections with normalized structure amplitude[5] $(E) > 1.5$ were determined with a 97.9% internal consistency on the basis of a particular set of signs given to six reflections that had been given letter symbols. An E map, calculated with the 392 reflections, contained two peaks of almost equal height and several smaller peaks from which the atoms comprising the adenine and pyridinium ring systems and the trimethylene bridge could be identified. Initially, as the complex was thought to be (C$_{14}$H$_{16}$N$_7$O)$^+$Br$^-$·nH$_2$O, the two large peaks were assumed to represent two sites for one bromide anion, with these sites being occupied on a statistical or near-statistical basis. Fourier refinement revealed positions for two water molecules in the crystal asymmetric unit. Full-matrix least-squares refinement of this model, varying positional and isotropic thermal parameters (0.5 occupancy for each bromide site), employing unit weights for all reflections, and minimizing $\Sigma w||F_o| - |F_c||^2$ gave an R factor of 0.207 and R_2 of 0.261 on all observed data.[7] Introduction of anisotropic temperature parameters into the model, followed by least-squares refinement, gave an R factor of 0.134 and R_2 of 0.172. It was necessary to divide the atoms in the structure into two groups to refine the anisotropic temperature factors. The two largest *positive* peaks on a difference map calculated at this stage in the analysis were at the positions occupied by the bromide anions.

A second interpretation of the initial E map would be that a dipositive organic species was present and that the two anionic sites were fully occupied by bromide anions. Unfortunately, there was no longer a sufficient supply of sample to perform an elemental analysis to distinguish between these models. Full-matrix least-squares refinement of the two-bromine model employing isotropic temperature factors gave R of 0.126 and R_2 of 0.122. When anisotropic temperature factors were employed in the refinement, an R of 0.089 and R_2 of 0.095 were obtained. A difference map calculated at this point, however, revealed two large *negative* peaks at the bromide sites.

These results can be explained by assuming the presence of a dication and two fully occupied halide sites. The bromide salt was prepared by displacement of chloride by bromide on an ion exchange column.[8] If, however, this exchange were incomplete and some of the chloride ions were still present in the crystal, then a difference map calculated from a model with full bromide occupancy would show negative regions at the anionic sites. Supporting evidence for a dication is given by the size of the C(6)–N(1)–C(2) angle. Several authors[9,10] have pointed out that this angle is very sensitive to protonation of N(1) (the first site of protonation in adenine). In a compilation of dimensions for unprotonated adenine rings, Donohue[11] gives an average value of 118.4 (1.3) for this angle, whereas values of 123.3 (3) and 122.8 (8)° were found in the structures of adenosine 3′-phosphate dihydrate[12] and adenosine 5′-phosphate,[13] respectively. In the present structure, the values found for the C(6)–N(1)–C(2) angle at the conclusion of the refinement of the two models were 123.4° (half-bromine occupancy) and 122.8° (full-bromine occupancy). Virtually conclusive evidence for the dication was obtained by the subsequent preparation[14] of crystals of an analytically pure dibromide. A photographic examination of these crystals demonstrated that they were isostructural with the material used in the X-ray study. The X-ray analysis was therefore continued assuming an organic dication and two halide anionic sites, occupied partially by chloride and bromide anions.

Least-squares refinement of the occupancy of the anionic sites was begun at this point in order to obtain an approximate assessment of the percentage of bromide ions present. Three cycles of full-matrix refinement, varying the positional, occupancy, and anisotropic thermal parameters for the bromine atoms, followed by two full cycles in which, in addition, the positional and aniso-

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(4) The crystals of II were generously provided by Dr. T. G. Scott of this department.

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(14) We thank Dr. John H. Craig for the preparation of these crystals.

Table I. Final Atomic Coordinates in Fractions of the Unit Cell Edge[a]

	x	y	z
Br(1)[b]	0.2955 (1)	0.23855 (4)	1.17399 (8)
Br(2)[b]	0.6704 (1)	0.34019 (4)	1.13305 (8)
N(1)	0.1535 (6)	0.1226 (2)	0.8434 (5)
C(2)	0.1415 (8)	0.1043 (3)	0.7430 (6)
N(3)	0.0754 (7)	0.0452 (2)	0.6805 (5)
C(4)	0.0215 (8)	0.0029 (3)	0.7295 (6)
C(5)	0.0226 (8)	0.0170 (3)	0.8272 (6)
C(6)	0.0936 (8)	0.0807 (3)	0.8899 (5)
N(6)	0.1104 (8)	0.1016 (3)	0.9873 (5)
N(7)	−0.0430 (7)	−0.0391 (2)	0.8495 (5)
C(8)	−0.0819 (9)	−0.0856 (3)	0.7656 (6)
N(9)	−0.0435 (7)	−0.0635 (2)	0.6907 (5)
C(10)	−0.0603 (10)	−0.1042 (3)	0.5929 (6)
C(11)	0.0714 (9)	−0.1656 (3)	0.6487 (6)
C(12)	0.2795 (9)	−0.1529 (3)	0.7635 (6)
N(13)	0.3587 (6)	−0.0966 (2)	0.7380 (4)
C(14)	0.4346 (8)	−0.0405 (3)	0.8143 (5)
C(15)	0.5108 (8)	0.0124 (3)	0.7949 (5)
C(16)	0.5094 (9)	0.0071 (4)	0.6940 (6)
C(17)	0.4329 (10)	−0.0516 (3)	0.6168 (6)
C(18)	0.3589 (9)	−0.1033 (3)	0.6402 (6)
C(19)	0.5885 (8)	0.0732 (3)	0.8851 (5)
N(20)	0.6537 (8)	0.1268 (3)	0.8663 (5)
O(21)	0.5902 (6)	0.0703 (2)	0.9752 (4)
W(22)	0.3004 (9)	0.2512 (3)	0.9111 (6)
W(23)	0.8470 (8)	0.2421 (3)	1.0450 (6)
H(1)[c]	0.233 (10)	0.179 (4)	0.898 (7)
H(2)	0.191 (11)	0.143 (4)	0.719 (8)
H(6a)	0.059 (11)	0.068 (4)	1.011 (8)
H(6b)	0.156 (9)	0.149 (4)	1.030 (6)
H(8)	−0.108 (11)	−0.139 (4)	0.765 (8)
H(10a)	−0.212 (9)	−0.117 (3)	0.521 (6)
H(10b)	−0.033 (6)	−0.067 (2)	0.555 (4)
H(11a)	0.036 (8)	−0.199 (3)	0.680 (6)
H(11b)	0.054 (10)	−0.189 (4)	0.574 (7)
H(12a)	0.299 (10)	−0.131 (4)	0.840 (7)
H(12b)	0.346 (7)	−0.197 (3)	0.774 (5)
H(14)	0.453 (6)	−0.042 (2)	0.891 (5)
H(16)	0.561 (8)	0.042 (3)	0.678 (6)
H(17)	0.436 (9)	−0.058 (3)	0.542 (6)
H(18)	0.311 (9)	−0.148 (3)	0.594 (6)
H(20a)	0.650 (13)	0.130 (5)	0.806 (9)
H(20b)	0.710 (11)	0.178 (4)	0.928 (8)
H(22a)	0.352 (16)	0.263 (6)	0.891 (11)
H(22b)	0.443 (14)	0.265 (5)	1.018 (10)
H(23a)	0.986 (11)	0.248 (4)	1.103 (7)
H(23b)	0.825 (15)	0.269 (6)	1.083 (10)

[a] Standard deviations in parentheses. [b] In the final calculations the form factor for this atom was 66.3% Br^- and 33.7% Cl^-. [c] Hydrogen atoms are given the number of the atoms to which they are attached.

tropic thermal parameters of all the other nonhydrogen atoms were varied, were then carried out. For the latter cycles, the refinement was done in two parts. The first partial cycle consisted of the atoms N(1), C(2), N(3), C(4), C(5), C(6), N(6), N(7), C(8), N(9), C(10), and C(11), while the other consisted of C(12), N(13), C(14), C(15), C(16), C(17), C(18), C(19), N(20), and O(21); the atoms Br(1), Br(2), W(22), and W(23) were common to both partial cycles. After this refinement, R was 0.075 and R_2 was 0.076, while the occupancy factors for Br(1) and Br(2) were 0.837 (4) and 0.809 (4), respectively. These latter figures correspond to approximately 67% bromide and 33% chloride occupancy of the anionic sites.

A difference map was then calculated and no areas of large positive or negative density around the anionic sites were found. All of the hydrogen atoms of the cation, including the one on N(1), and the two hydrogen atoms of one of the water molecules, W(23), were located from this map. However, no reasonable positions for the hydrogen atoms of W(22) could be determined. Consequently, positions based on hydrogen bonding to two anions were proposed. The positional and isotropic thermal parameters of the hydrogen atoms were refined in the same partial cycle as the positional and thermal parameters of the atoms to which they are bonded. After three full cycles, R was 0.060 and R_2 was 0.062, while the occupancy factors were 0.849 (3) and 0.814 (3) for Br(1) and Br(2), respectively.

For the final series of refinements, a scattering curve composed of a 66.3% contribution from the Br^- curve, and a 33.7% contribution from the Cl^- curve in "International Tables for X-Ray Crystallography"[15] was used for the halide sites. Both curves were corrected for the effects of anomalous dispersion.[16] Two full cycles of refinement varying positional and anisotropic thermal parameters for the heavy atoms and positional and isotropic thermal parameters for the hydrogen atoms, but holding the temperature parameters of the two hydrogen atoms attached to W(22) constant, gave a final R value of 0.059 and R_2 of 0.061 on the 3062 nonzero reflections. In the last cycle of refinement, none of the parameters of a nonhydrogen atom shifted by as much as one half of its estimated standard deviation. The scattering curves for neutral C, N, and O were taken from ref 15, while the curve for H was that calculated by Stewart, *et al.*[17]

The final positional parameters are given in Table I. The final thermal parameters and the list of the final values of h, k, l, $|F_o|$, and F_c have been deposited in the microfilm edition of the journal.[18]

Results and Discussion

Stereoscopic views of the cation, AdeH$^+$-C$_3$-Nic$^+$(II), are shown in Figure 1a and b. Bond lengths and angles in the adenine moiety are given in Figure 2. The other bond lengths and angles are given in Table II.

Table II. Bond Lengths (Å)[a,b] and Bond Angles (deg)[c]

Bond Lengths		Bond Angles	
C(10)–C(11)	1.510 (10)	N(9)–C(10)–C(11)	113.4 (4)
C(11)–C(12)	1.521 (12)	C(10)–C(11)–C(12)	117.8 (6)
C(12)–N(13)	1.491 (9)	C(11)–C(12)–N(13)	112.1 (5)
N(13)–C(14)	1.341 (8)	C(12)–N(13)–C(14)	119.6 (4)
N(13)–C(18)	1.361 (10)	C(12)–N(13)–C(18)	119.9 (5)
C(14)–C(15)	1.377 (9)	C(14)–N(13)–C(18)	120.5 (5)
C(15)–C(16)	1.391 (11)	N(13)–C(14)–C(15)	121.5 (6)
C(16)–C(17)	1.389 (10)	C(14)–C(15)–C(16)	119.0 (4)
C(17)–C(18)	1.377 (11)	C(14)–C(15)–C(19)	116.7 (6)
C(15)–C(19)	1.503 (9)	C(16)–C(15)–C(19)	124.4 (5)
C(19)–N(20)	1.316 (9)	C(15)–C(16)–C(17)	119.0 (4)
C(19)–O(21)	1.239 (9)	C(16)–C(17)–C(18)	119.9 (5)
		N(13)–C(18)–C(17)	120.1 (5)
		C(15)–C(19)–N(20)	119.0 (4)
		C(15)–C(19)–O(21)	118.3 (4)
		N(20)–C(19)–O(21)	122.6 (7)

[a] Other bond lengths are shown in Figure 2. [b] The C–H lengths range from 0.94 (6) to 1.11 (12) Å; the N–H lengths range from 0.81 (12) to 1.26 (10) Å. [c] The C–C–H angles external to the pyridinium ring range from 116 (5) to 124 (5)°, and the C–C–H angles in the trimethylene chain range from 100 (5) to 115 (4)°.

Molecular Dimensions in the Cation. As discussed in the Experimental Section, N(1) is the site of protonation in the adenine residue.

The bond lengths and angles in the adenine rings in AdeH$^+$-C$_3$-Nic$^+$(II) and Ade-C$_3$-Nic$^+$(I)[3] are compared in Figure 2. There are significant differences in the dimensions of the C(5)–C(6)–(N(6))–N(1)–C(2) portion of the ring. The endocyclic angle at N(1) has increased by almost 4° upon protonation

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(15) "International Tables for X-Ray Crystallography," Vol. III, Kynoch Press, Birmingham, England, 1962, pp 201-209.

(16) Reference 15, pp 213-216.

(17) R. F. Stewart, E. R. Davidson, and W. T. Simpson, *J. Chem. Phys.*, 42, 3175 (1965).

(18) The final thermal parameters, the list of h, k, l, $|F_o|$, and F_c, and some details of the best plane calculations will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JACS-73-5377.

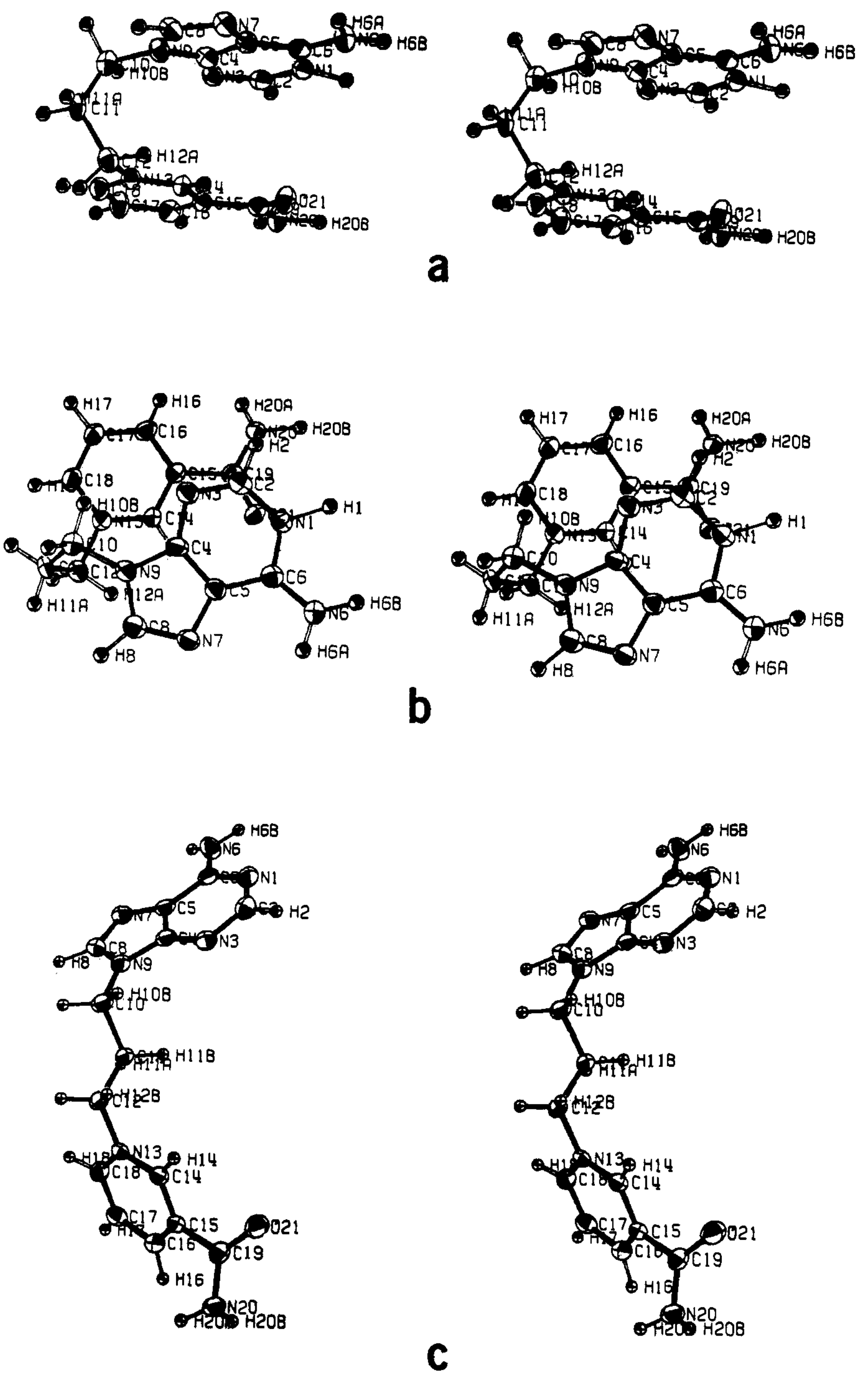
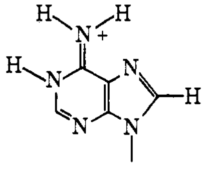


Figure 1. (a) Stereoscopic view of the AdeH$^+$-C$_3$-Nic$^+$dication, showing the near parallel arrangement of the two rings. (b) Another stereoscopic view of the AdeH$^+$-C$_3$-Nic$^+$ dication looking almost along the perpendicular to the planes of the two rings. (c) A stereoscopic view of the Ade-C$_3$Nic$^+$ monocation.[3] The probability level of the thermal ellipsoids is 36%.

with concomitant and comparably large decreases in the N(1)C(6)C(5) and N(1)C(2)N(3) angles; smaller (~2°) increases are also seen in the C(4)C(5)C(6) and N(3)C(4)C(5) angles. The N(1)–C(2) and N(1)–C(6) lengths increase significantly (~0.03 Å) upon protonation with accompanying decreases in the lengths of the C(6)–N(6), C(5)–C(6), and C(4)–C(5) bonds; the C(4)–C(5) bond was, however, rather longer in the Ade-C$_3$-Nic$^+$ (I) structure than is usually found in neutral adenine derivatives.[3] Some of these changes can be explained by an increase in the importance of structures of type III in the resonance hybrid. There is also a very considerable difference in the exocyclic angles at C(6) with C(5)C(6)N(6) being 6.6° greater than N(1)C(6)N(6); these angles were more nearly equal in the unprotonated compound I. Some aspects



III

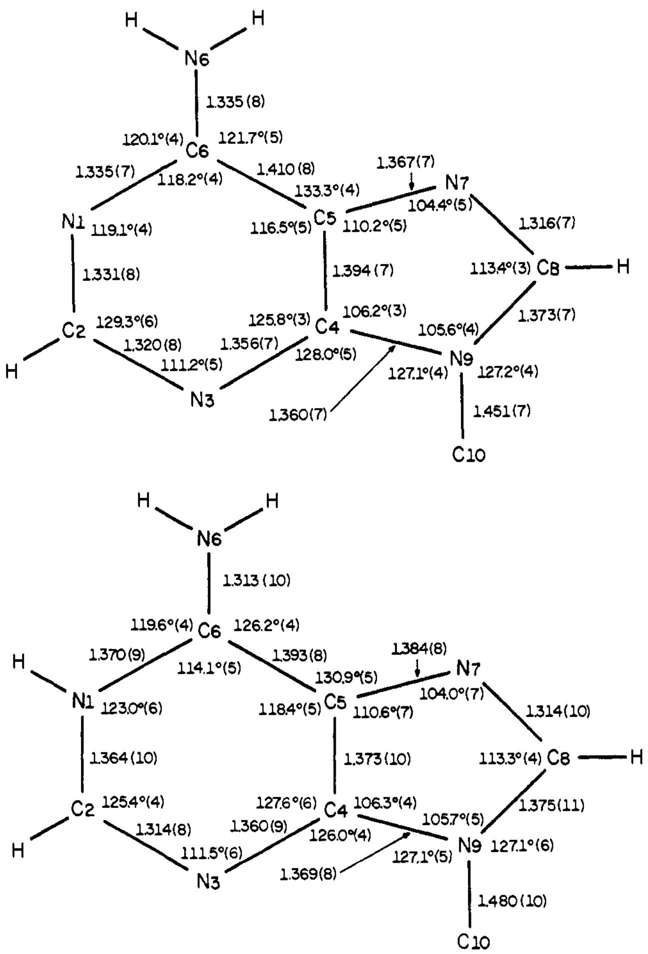


Figure 2. Molecular dimensions in (a) Ade-C_3-Nic$^+$ (I) monocation and (b) AdeH$^+$-C_3-Nic$^+$ (II) dication.

of the changes in the molecular dimensions of adenine upon protonation were first pointed out by Hoogsteen,[9] and have since been commented upon by several authors.[10,11,19–21]

The nine atoms comprising the adenine ring system depart significantly from coplanarity; deviations from the best plane range from −0.032 (N(9)) to 0.031 Å (C(5)). Full details of these calculations will appear in the microfilm edition.[18] In contrast to the Ade-C_3-Nic$^+$ structure, the five-membered ring is planar, whereas the deviations from the plane of the six-membered ring are marginal. The dihedral angle between the five- and six-membered rings in AdeH$^+$-C_3-Nic$^+$ (2°46′) is much greater than that in Ade-C_3-Nic$^+$ (0°43′). The pattern of deviations from the best plane through the nine atoms in II is very similar to those found in the 3′-deoxy-3′-(dihydroxyphosphinylmethyl)adenosine[22] and 5′-methyleneadenosine 3′,5′-cyclic monophosphate[23] molecules. In all three structures large deviations (>0.020 Å) on one side of the plane are found for N(1) and N(9), while comparable deviations on the other side of the plane occur in the cases of N(3), C(5), and N(7).

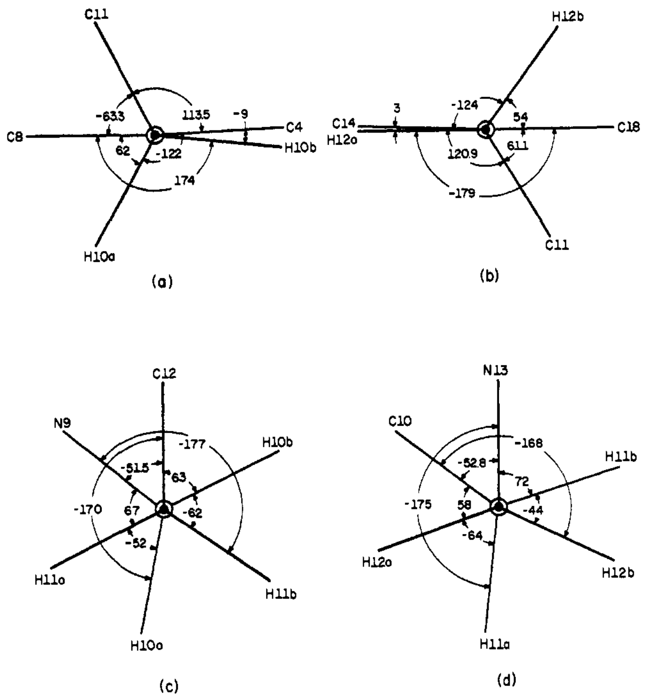


Figure 3. Torsion angles about (a) the C(10)–N(9) bond, (b) the C(12)–N(13) bond, (c) the C(11)–C(10) bond, and (d) the C(12)–C(11) bond. Angles (ABCD) are considered positive if, when looking along the B–C bond, atom A has to be rotated clockwise to eclipse atom D.

In general, there seem to be larger deviations from the plane through the nine atoms of the ring system in protonated adenine derivatives,[13,22,23] than in non-protonated ones,[3,21] but exceptions to this statement can be found.[24] The exocyclic atoms, N(6) and C(10), lie 0.032 and 0.142 Å (on the same side as the deviation for the atom N(1)) from the best plane through the adenine moiety. Correspondingly large deviations for these atoms have been found in the case of 3′-deoxy-3′-(dihydroxyphosphinylmethyl)adenosine,[22] while distances ranging from 0.03 to 0.24 Å have been found in the case of C(10).[25]

In contrast to the results obtained for I, the pyridinium ring in II is planar within the accuracy of the analysis and the amide group is nearly coplanar (dihedral angle 3°54′) with the ring. The two substituent atoms, C(12) and C(19), lie only −0.010 and 0.010 Å out of the plane of the ring. The greatest difference in the dimensions of the amide group between I and II is found in the angles C(15)–C(19)–N(20) and N(20)–C(19)–O(21); in I, these angles are 114.1 (4) and 125.4 (3)° and in II, they are 119.0 (4) and 122.6 (7)°. In fact, all the dimensions of the amide group support a greater amount of conjugation with the pyridinium ring in the case of the AdeH$^+$-C_3-Nic$^+$, where the group is almost coplanar with that ring.

Conformation of the Cation. The trimethylene chain adopts a conformation that allows the adenine and nicotinamide ring systems to approach an overlapping position. This is achieved by H(10b) almost eclipsing C(4) along the C(10)–N(9) bond, H(12a) almost eclipsing C(14) along the C(12)–N(13) bond, N(9) and C(12)

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Table III. Molecular Dimensions Relevant to the Hydrogen Bonding Scheme[a,b]

Bond		Angle	
Hydrogen Atoms from AdeH$^+$-C$_3$-Nic$^+$			
N(6)···N($7^{\rm I}$)	2.980 (10)	C(6)–N(6)···N($7^{\rm I}$)	135.5 (5)
N(6)···Br$^-$(1)	3.278 (8)	C(6)–N(6)···Br$^-$(1)	134.1 (5)
H(6a)···N($7^{\rm I}$)	2.12 (10)	N(6)–H(6a)···N($7^{\rm I}$)	146 (6)
H(6b)···Br$^-$(1)	2.28 (11)	N(6)–H(6b)···Br$^-$(1)	165 (5)
N(1)···W(22)	2.692 (8)	C(6)–N(1)···W(22)	131.4 (4)
H(1)···W(22)	1.49 (8)	N(1)–H(1)···W(22)	159 (1)
C(2)···Br$^-$($1^{\rm II}$)	3.755 (6)	N(1)–C(2)···Br$^-$($1^{\rm II}$)	105.4 (4)
H(2)···Br$^-$($1^{\rm II}$)	2.72 (8)	C(2)–H(2)···Br$^-$($1^{\rm II}$)	169 (5)
C(8)···Br$^-$($1^{\rm I}$)	3.970 (7)	N(7)–C(8)···Br$^-$($1^{\rm I}$)	101.9 (4)
H(8)···Br$^-$($1^{\rm I}$)	3.09 (9)	C(8)–H(8)···Br$^-$($1^{\rm I}$)	141 (7)
N(20)···Br$^-$($2^{\rm II}$)	3.397 (7)	C(19)–N(20)···Br$^-$($2^{\rm II}$)	131.2 (4)
H(20a)···Br$^-$($2^{\rm II}$)	2.59 (12)	N(20)–H(20a)···Br$^-$($2^{\rm II}$)	170 (6)
N(20)···W(23)	2.903 (9)	C(19)–N(20)···W(23)	123.3 (5)
H(20b)···W(23)	1.75 (14)	N(20)–H(20b)···W(23)	166 (8)
C(14)···O($21^{\rm III}$)	3.128 (9)	N(13)–C(14)···O($21^{\rm III}$)	104.6 (4)
H(14)···O($21^{\rm III}$)	2.21 (6)	C(14)–H(14)···O($21^{\rm III}$)	160 (9)
Environment of W(22)			
W(22)···Br$^-$($1^{\rm II}$)	3.258 (9)	Br$^-$($1^{\rm II}$)···W(22)···Br$^-$(2)	102.0 (2)
W(22)···Br$^-$(2)	3.224 (12)	N(1)···W(22)···Br$^-$($1^{\rm II}$)	92.7 (2)
W(22)···N(1)	2.692 (8)	N(1)···W(22)...Br$^-$(2)	143.9 (2)
H(22a)···Br$^-$($1^{\rm II}$)	2.68 (18)	H(22a)–W(22)–H(22b)	85 (12)
H(22b)···Br$^-$(2)	2.18 (18)	W(22)–H(22a)···Br$^-$($1^{\rm II}$)	136 (12)
W(22)···H(1)	1.49 (8)	W(22)–H(22b)···Br$^-$(2)	144 (3)
		N(1)–H(1)···W(22)	157 (1)
Environment of W(23)			
W(23)···Br$^-$($1^{\rm IV}$)	3.342 (10)	Br$^-$($1^{\rm IV}$)···W(23)···Br$^-$(2)	126.8 (1)
W(23)···Br$^-$(2)	3.252 (6)	N(20)···W(23)···Br$^-$($1^{\rm IV}$)	107.4 (2)
W(23)···N(20)	2.903 (9)	N(20)···W(23)···Br$^-$(2)	125.2 (2)
H(23a)···Br$^-$($1^{\rm IV}$)	2.40 (13)	H(23a)–W(23)–H(23b)	99 (10)
H(23b)···Br$^-$(2)	2.42 (11)	W(23)–H(23a)···Br$^-$($1^{\rm IV}$)	157 (3)
W(23)···H(20b)	1.75 (14)	W(23)–H(23b)···Br$^-$(2)	163 (6)
		N(20)–H(20b)···W(23)	166 (8)

[a] Lengths in Å; angles in degrees. [b] I refers to $-x, -y, 2 - z$; II, $x, {}^1/_2 - y, -{}^1/_2 + z$; III, $1 - x, -y, 2 - z$; IV, $1 + x, y, z$; V, $1 + x, {}^1/_2 - y, {}^1/_2 + z$.

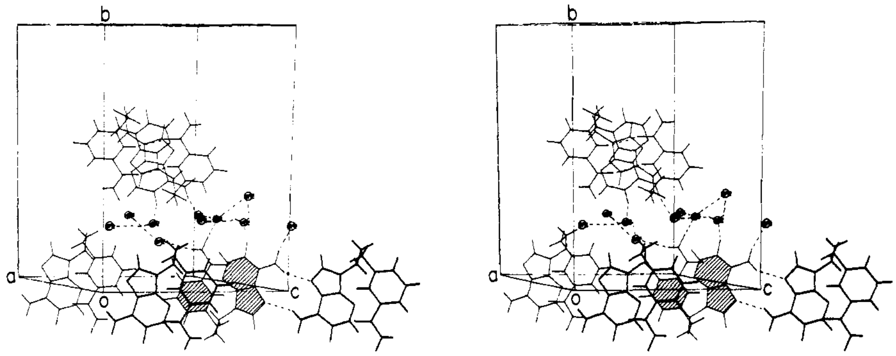


Figure 4. Stereoscopic drawing of the packing of the AdeH$^+$-C$_3$-Nic$^+$ structure. Hydrogen bonds are shown by discontinuous lines. The basic molecule (*i.e.*, that whose coordinates are listed in Table I) is shaded; molecules closer than that are drawn in heavy lines.

being adjacent, although staggered along the C(10)–C(11) bond, and N(13) and C(10) being similarly arranged along the C(12)–C(11) bond (Figure 3). In this way, the conformation of the chain resembles that in 1,1′-trimethylenebisthymine (Thy-C$_3$-Thy) where considerable overlap of the two bases was found.[26] The C(12)–C(11)–C(10)–N(9) and N(13)–C(12)–C(11)–C(10) torsion angles are −51.5 and −52.8°. In contrast to the monocation (I), C(12) lies almost in the plane of the pyridine ring while C(10) deviates substantially from the plane of the adenine ring. This arrangement for the trimethylene bridge allows the adenine and nicotinamide groups to be almost parallel (dihedral angle 4°58′) (Figure 1). The centers of mass of the two rings are 4.568 Å apart. The intramolecular N(1)$^+$···N(13)$^+$ distance is 5.254 (7) Å.

Hydrogen Bonding and Ionic Contacts. A stereoscopic view of the contents of the unit cell is shown in Figure 4. In the following discussion, we refer to the anions as bromide ions although, of course, the sites are occupied partially by chloride ions. The adenine rings associate as centrosymmetrically related dimers by N(6)–N(6a)···N(7) hydrogen bonding as found in Ade-C$_3$-Nic$^+$ [3] and in several other adenine derivatives.[27] The N(6)···N($7^{\rm I}$) distance is 2.980 (10) Å (Table III). The other hydrogen atom on N(6) forms a hydrogen

[26] J. K. Frank and I. C. Paul, *J. Amer. Chem. Soc.*, **95**, 2324 (1973).

[27] See corresponding section and references cited in ref 3.

bond to Br^- (1) with an $N\cdots Br^-$ length of 3.278 (8) Å. The hydrogen atom on N(1) hydrogen bonds to W(22) with an $N(1)\cdots W(22)$ distance of 2.692 (8) Å. The possibility of $C\text{-}H\cdots Br^-$ hydrogen bonding was examined for the cases of C(2)–H(2) and C(8)–H(8), as these two hydrogen atoms often participate in $C\text{-}H\cdots O$ hydrogen bonding in adenine and particularly in protonated adenine derivatives.[12,23,28] While a somewhat more convincing case can be made in the case of the $C(2)\text{-}H(2)\cdots Br^-(1^{II})$ interaction, with the $C(2)\cdots Br^-(1^{II})$ and $H(2)\cdots Br^-(1^{II})$ distances being 3.755 (6) and 2.72 (8) Å and the $C(2)\text{-}H(2)\cdots Br^-(1^{II})$ angle being 169 (5)°, whereas the sum of the van der Waals radii of Br and H is 3.15 Å,[29] the stability gained by the association must be very small indeed and we hesitate to designate it as hydrogen bonding.

The two N–H hydrogen atoms of the nicotinamide group are involved in hydrogen bonding to a bromide anion, $Br^-(2^{II})$, and a water molecule, W(23). A plausible case for $C\text{-}H\cdots O$ hydrogen bonding can be made for the $C(14)\text{-}H(14)\cdots O(21^{III})$ association. There are two of these contacts related by a center of symmetry between effectively coplanar nicotinamide rings. The $C(14)\cdots O(21^{III})$ and $H(14)\cdots O(21^{III})$ distances are 3.128 (9) and 2.21 (6) Å and the $C(14)\text{-}H(14)\cdots O(21^{III})$ angle is 160 (9)°. It would be unusual for the O(21) atom not to be involved in hydrogen bonding, and the effective coplanarity of the amide group with the pyridinium ring and the consequent conjugation between these groups would lead to residual negative charge on the oxygen atom. It is of interest that a rather similar pairing of $C(14)\text{-}H\cdots O(21)$ intermolecular contacts was found in the structure of Ade-C_3-Nic^+.[3]

The two water molecules are involved in $Br^-\cdots H\text{-}O\text{-}H\cdots Br^-$ hydrogen bonding. The environment of the hydrogen bonds around the water molecules is shown in Figure 5 and the details of the distances are listed in Table III. In the case of W(22), the hydrogen atoms could not be located from the difference map and were positioned (although they were subsequently adjusted in the least-squares refinement) such that they were involved in $O\text{-}H\cdots Br^-$ hydrogen bonding. However, there can be no real doubt as to their general location. The arrangement of the three atoms involved in hydrogen bonding to each water molecule is approximately trigonal planar.

If one excludes the possible $C\text{-}H\cdots Br^-$ hydrogen bonding, each bromide ion acts as an acceptor for three hydrogen bonds, two from water molecules and one from an NH_2 group.

The shortest $N^+\cdots N^+$ distance is 4.43 Å between $N^+(1)$ (assuming the positive charge mainly resides on this atom) and $N^+(13^{III})$. The shortest $Br^-\cdots Br^-$ distance is 4.41 Å between $Br^-(1)$ and $Br^-(2)$. The shortest $N^+\cdots Br^-$ distances are 3.50 Å (between $N^+(1^V)$ and $Br^-(2)$) and 3.80 Å (between $N^+(13)^{III}$ and $Br^-(1)$).

Relationship of the Conformations of Ade-C_3-Nic^+ and $AdeH^+$-C_3-Nic^+ in Solution and in the Crystal to That of NAD^+. The conformations found (Figure 1) in the solid-state studies of Ade-C_3-Nic^+ [3] and $AdeH^+$-C_3-Nic^+ are quite different from the general types suggested from the hypochromism observed for these molecules in very dilute aqueous solution.[30] In neutral solution, there was an indication of the presence of folded conformations, while at low pH more open or extended conformations were proposed. The hypochromism results on I and II were supported by a similar series of experiments on the analog (IV), where the sugar ring was incorporated into the model.[31]

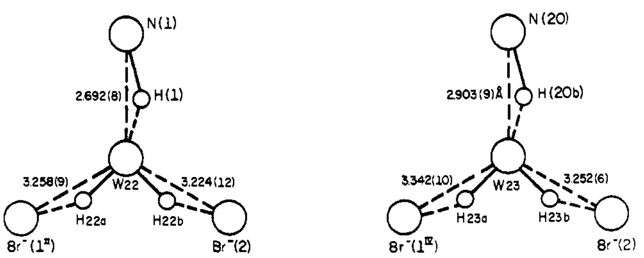
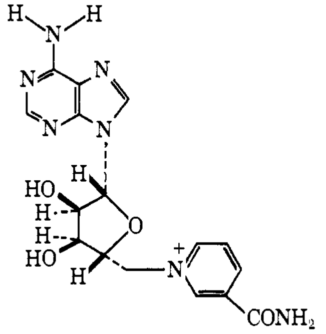
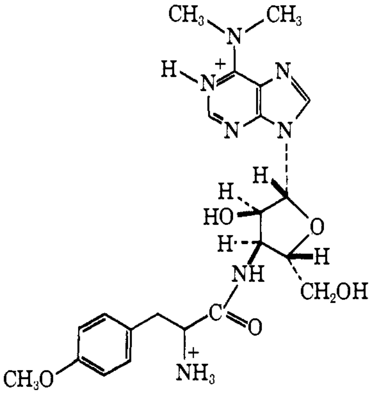


Figure 5. Schematic representation of the hydrogen bonding arrangement for the two water molecules. The Roman numerals refer to the equivalent positions listed in Table III.

There are relatively few dications, comparable to $AdeH^+$-C_3-Nic^+, for which the detailed conformation is known. One possible comparison could be with the structure of the antibiotic puromycin dihydrochloride pentahydrate,[32] which also contains a substituted adenine. In that case, the dication V adopts an extended conformation, with intermolecular overlap of the adenine residue with the *O*-methyl tyrosine ring; the oxygen atom of the tyrosine lies over C(5) and the two carbon atoms of tyrosine ortho to the methoxyl



IV



V

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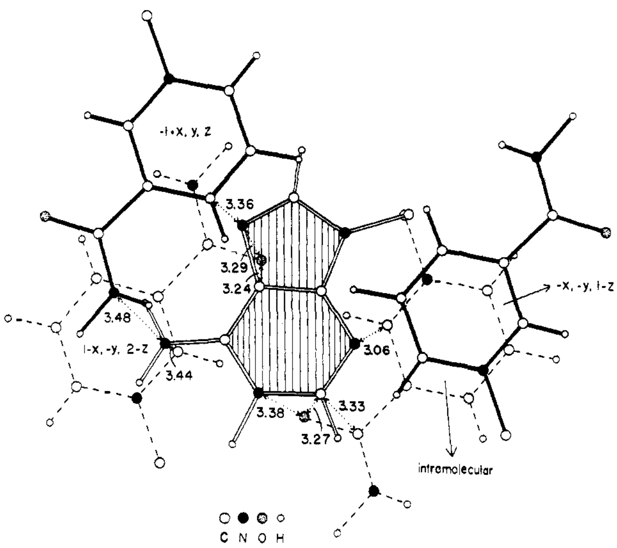

Figure 6. Projection of four adjacent nicotinamide rings (including the basic one) onto the best plane of the adenine ring. Some short atom–atom contacts are shown.

group lie over N(1) and N(3).[32] In V the intramolecular N(1+)$\cdots$NH$^+_3$ distance is 9.84 Å.[33]

Circular dichroism[34] and nuclear magnetic resonance studies[35,36] have been interpreted to support the presence of a folded form of the dinucleotide in both the oxidized (NAD$^+$) and reduced (NADH) forms. Some questions, however, have been raised regarding other possible interpretations of these results.[37] X-Ray analysis of the lactate dehydrogenase–NAD enzyme–coenzyme complex indicates that the coenzyme is in an extended conformation,[38] not inconsistent with that found for Ade-C$_3$-Nic$^+$ (Figure 1c) as described in the previous paper in this series.[3]

What then is the explanation for the diametrical differences in conformations of Ade-C$_3$-Nic$^+$ and AdeH$^+$-C$_3$-Nic$^+$ in dilute aqueous solution, as inferred from studies on hypochromism,[30,31] when compared to those determined in the crystal? Clearly, the situation pertaining in these crystals corresponds to extremely concentrated aqueous solutions (effectively 20 *M* in the case of Ade-C$_3$-Nic$^+$ and 30 *M* in the case of AdeH$^+$-C$_3$-Nic$^+$) and intermolecular effects are almost certainly responsible for the differences cited above. As we have seen in the discussion in the previous paper,[3] there are several structures containing overlapping adenine rings.[13,24,39–42] Two of these cases, adenosine 5′-phosphate[13] and adenosine triphosphate (ATP),[42] involve N(1) protonated adenine bases. Similarly, examples of N(1) protonated adenine derivatives involved in centrosymmetric N(6)-H$\cdots$N(7) hydrogen bonding are well established.[43,44] The Ade-C$_3$-Nic$^+$ monocation[3] appears to be the only adenine derivative that both participates in centrosymmetric N(6)–H$\cdots$N(7) hydrogen bonding and has base overlap of the adenine residues. The molecular packing of the hydrogen bonded dimers (through the N(6)–H$\cdots$N(7) atoms of adenine) of Ade-C$_3$-Nic$^+$ can be likened to a stacking of chairs with the seats (*i.e.*, the two coplanar hydrogen-bonded adenine rings) being stacked but displaced somewhat from each other.[45] This seems to be a particularly effective form of self-packing for a molecule shaped like the extended conformation of Ade-C$_3$-Nic$^+$. Furthermore, the nicotinamide groups in Ade-C$_3$-Nic$^+$ are able to participate in N(20)–H$\cdots$N(3) hydrogen bonding to an adenine of an adjacent stack. Folding and intramolecular overlap of the adenine and nicotinamide groups as found in the structure of the dicationic AdeH$^+$-C$_3$-Nic$^+$, however, would prevent the adenine rings from participating in the form of self-association found in the crystal of the monocation, Ade-C$_3$-Nic$^+$. Such a packing arrangement for AdeH$^+$-C$_3$-Nic$^+$ would bring a large number of positive charges into the stacked planar part of the crystal structure (*i.e.*, the seat of the chair). A packing arrangement is therefore sought whereby the positive charges on the adenine rings can be somewhat insulated from each other. The centrosymmetric hydrogen bonding arrangement is retained but the molecules are folded such that nicotinamide groups are placed above and below the adenine rings (Figure 6). The N(1) center of positive charge is placed near the polarizable oxygen atom of the nicotinamide ring in the same molecule. The folding brings the AdeH$^+$-C$_3$-Nic$^+$ dication to the near-overlapping conformation shown in Figure 1a,b.

The exact projection of the atoms of several nicotinamide moieties onto the best plane through the atoms of the adenine ring system is shown in Figure 6. The adenine ring is surrounded by four nicotinamide groups, two above and two below its mean plane. However, there is very little overlap of the groups, especially if hydrogen atoms are neglected. The plane of the nicotinamide group from the same molecule is closest to the adenine ring with the atoms C(2) and N(3) being approached quite closely by the C(14)–C(15)–C(19)–O(21) portion of the nicotinamide residue. The perpendicular distances of the atoms of the nicotinamide group from the best plane through the adenine ring range from 2.77 [C(18)] to 3.22 Å [O(21)]; the distances of N(13), C(14), C(15), C(19), and N(20) from this plane are 2.80, 2.92, 3.00, 3.11, and 3.11 Å, respectively. The shortest distances between atoms in the two ring systems are C(2)$\cdots$O(21), 3.27 (1) Å; C(2)$\cdots$C(19), 3.33 (1) Å; N(1)$\cdots$O(21), 3.38 (1) Å; N(3)$\cdots$C(14), 3.06 (1) Å; N(3)$\cdots$C(15), 3.35 (1) Å; and C(4)$\cdots$C(14), 3.36 (1) Å. Some of these constants are less than the sums of the appropriate van der Waals radii (3.40 for C$\cdots$C, 3.20 for C$\cdots$N, and

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(45) See Figure 1 in ref 3.

3.10 Å for C···O).[29] The slight dihedral angle between the planes through the two groups occurs so that the contacts between these atoms are slightly greater than they would otherwise be for a structure with exactly parallel rings and with the centers of mass unchanged.

Of the other nicotinamide rings shown in Figure 6, that at $-1 + x, y, z$ is closest to the plane of the adenine ring with distances ranging from 2.97 [O(21)] to 3.42 Å [C(18)]. The shortest interatomic contacts are N(7)···C(16), 3.36 Å, and N(6)···N(20), 3.48 Å. The ring at $1 - x, -y, 2 - z$ is slightly further away from the plane of the adenine ring, 3.16 [O(21)] to 3.61 Å [C(18)], although there are some short interatomic contacts; the C(5)···O(21), N(7)···O(21), N(7)···C(19), and N(6)···C(14) distances are 3.24, 3.29, 3.39, and 3.44 Å, respectively. The nicotinamide ring at $-x, -y, 1 - z$ is considerably further away. The distances of atoms from the plane of the adenine ring range from 3.40 to 3.85 Å and the shortest interatomic contact is N(3)···C(18) of 3.70 Å. Some of the stacking distances involving these nicotinamide rings are somewhat shorter than the normal stacking interactions between aromatic rings (3.40 Å).[29]

Significance of the Results. What then do our results say about the conformations of Ade-C_3-Nic$^+$, AdeH$^+$-C_3-Nic$^+$ in solution, and about the role of NAD$^+$ in biological activity? The investigations underline the fact that results obtained in the solid state can be dominated by interactions that will not be present in very dilute solution. They indicate that the conformation of Ade-C_3-Nic$^+$ and probably also of NAD$^+$ are very adaptable to their molecular environment. The disposition of the adenine and nicotinamide rings in the conformation of NAD$^+$ in the lactate dehydrogenase complex places them 12 Å apart.[38] In the crystal of Ade-C_3-Nic$^+$, the centers of mass of the rings are 7.31 Å apart. The demonstration of the folded conformation for AdeH$^+$-C_3-Nic$^+$ must indicate that it is a possible conformation for Ade-C_3-Nic$^+$ also. Indeed, in the isolated molecule this conformation must be more favored in the case of Ade-C_3-Nic$^+$ than in that of AdeH$^+$-C_3-Nic$^+$. One should note, however, that the relative order of conformational stability in an isolated molecule can readily be upset when there is a tendency toward self-association, or indeed, toward association with other molecules. The folded structure is not always found in crystals of dications separated by a trimethylene bridge, as Nic$^+$-C_3-Nic$^+$ has been shown to have an extended conformation in the solid.[46] There are, of course, several features to the structure of NAD$^+$ that are not present in this analog. In NAD$^+$, the ribose–phosphate backbone could have a very important influence on the resulting conformation.

It is also significant that there is very little hydrogen-bonded interaction between the adenine and nicotinamide rings in either the Ade-C_3-Nic$^+$ or the AdeH$^+$-C_3-Nic$^+$ crystal; the N(amide)–H···N(3) hydrogen bond in Ade-C_3-Nic$^+$ is the only such interaction in the two crystals. These findings would support the conclusion of Voet[47] that there is little complementarity between these rings and suggest that an intramolecular hydrogen-bonded structure for NAD$^+$ or NADH would be unlikely. The packing interactions in both crystal structures seem to be largely determined by the adenine moieties, and the role of the nicotinamide group in this regard appears to be less important. Even in the structure of Nic$^+$-C_3-Nic$^+$, there seem to be few specific interactions beyond the hydrogen bonding capacity of the amide nitrogen.[46] These results would add some credence to the view that in the coenzyme, the role of the adenine is concerned with binding to the enzyme while the nicotinamide is more directly involved in the oxidation–reduction process.

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