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Nitrosative Adenine Deamination: Facile Pyrimidine Ring-Opening in the Dediazoniation of Adeninediazonium Ion†

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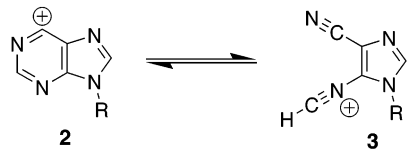
ABSTRACT



Dediazoniation of adeninediazonium ion, 1, forms the heteroaromatic cation, 2. Ab initio studies at the CCSD(fc)/6-31G//MP2(full)/6-31G** level now reveal that the cyclic cation 2 is kinetically and thermodynamically unstable with respect to the pyrimidine ring-opened cation, 3. The results suggest that 4-cyano-5-isocyano-imidazole, 4, and 4,5-dicyanoimidazole, 5, might be formed to some extent in nitrosative deaminations of adenine.**

The nitrosative deamination of adenine to hypoxanthine has been known since the discovery of adenine by Kossel in 1885.[1] A variety of disorders in people are likely to result from DNA base deamination and interstrand cross-linking due to reactions with HNO_2[2] or NO.[3] Nitric oxide is a bioregulatory agent[4] produced in the body, and certain nitrites are used in the process of curing meat products.[5] Because of the considerable exposure of the human body to oxides of nitrogen, there has been a wide interest in studying these deamination-related processes. The deamination of the nucleobases has long been thought to occur through the formation of diazonium ions that undergo nucleophilic substitution by water or other nucleophiles.[6]

In a theoretical study of the unimolecular dediazoniations of the DNA base diazonium ions of guanine, adenine, and cytosine, we found that the dediazoniation of guaninediazonium ion proceeds with the concomitant opening of the pyrimidine ring.[7−9] This discovery provided a straightforward

† Part 6 in the series titled DNA Base Deamination.

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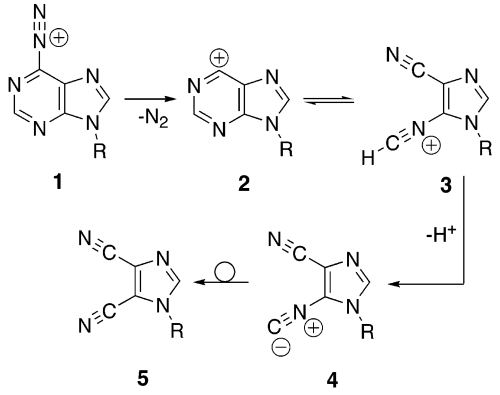
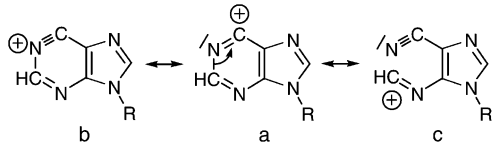
explanation for the formation of oxanosine in the nitrosative deamination of guanine. Whether xanthine is also formed from the ring-opened intermediate or via an S_N2-type mechanism without pyrimidine ring-opening is currently under investigation. In that same paper, we reported that the unimolecular dissociations of adenine- and cytosinediazonium ions lead to heteroaromatic phenyl cation analogues with intact pyrimidine rings.[7] We now report the results of a higher level ab initio molecular orbital study of the possibility for pyrimidine ring-opening of the cation **2** formed by dediazoniation of adeninediazonium ion, **1** (Scheme 1).

Scheme 1. Dediazoniation of Adeninediazonium Ion



The cation **2** does exist. On the basis of structural analysis, we recognized earlier that **2** stabilizes itself via hyperconjugation by the β,γ-N(1)−C(2) σ-bond (Scheme 2). We have

Scheme 2. Hyperconjugation in Cation **2**



now generated isodensity surface diagrams of the two most relevant occupied molecular orbitals[10] (MOs) of **2** (Figure 1). MO 25 largely represents the lone pair at N(1), and this

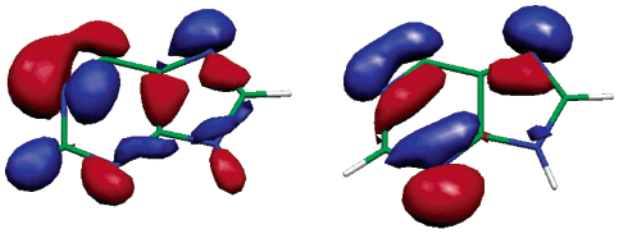


Figure 1. Occupied molecular orbitals 25 (left) and 27 (right) of **2**.

lone pair is not involved in dative bonding to C(2). MO 27 is most revealing as it already shows all the features of an in-plane π-MO; the C(6)≡N(1) bond clearly is preformed in **2**, and the dative bond to C(2) is due mostly to this MO. The shape of MO 27 suggests a high weight for the C(2)−N(1) nonconnected resonance form **c** of **2**.

The NPA analysis[11] of **2** (Figure 2) reveals that about half of the charge is associated with C(6) indicative of resonance

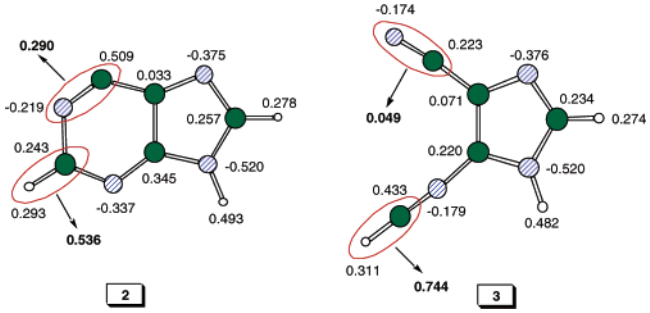


Figure 2. NPA charges of cations **2** and **3**.

form **a**. However, resonance form **a** is unable to explain the short C(6)−N(1) bond (1.207 Å) in **2**. The negative N(1) charge indicates that resonance form **b** also is not important. About a third of the charge is localized on the CN fragment, while more than half of the charge (0.536) is on the C(2)−H fragment. The C(2)-atom carries an H-atom, and hydrogens are known to play an important role in stabilizing carbocations.[12] Clearly, a large amount of charge is localized on the C(2) side of N(1). Hence, the NPA analysis fully supports the thesis that **2** is stabilized by β,γ-N(1)−C(2) σ-bond hyperconjugation.

If the β,γ-N(1)−C(2) σ-bond is weakened significantly by this mode of hyperconjugation, then this bond should be easy to break and a pyrimidine ring-opened cation **3** might exist. This is in fact the case.

Structures were optimized, and vibrational analyses were performed using second-order Møller−Plesset perturbation theory, MP2(full), with the 6-31G** basis set. We then performed single-point calculations on the optimized structures with coupled cluster theory and variational consideration of single and double excitations, CCSD. The frozen core approximation and the 6-31G** basis set were employed in the CCSD calculations; CCSD(fc)/6-31G**/MP2(full)/6-31G**. Models of the optimized structures are shown in Figure 3; energy data are listed in Table 1, and the least-energy path connecting **2** and **3** is shown in Figure 4.[13,14]

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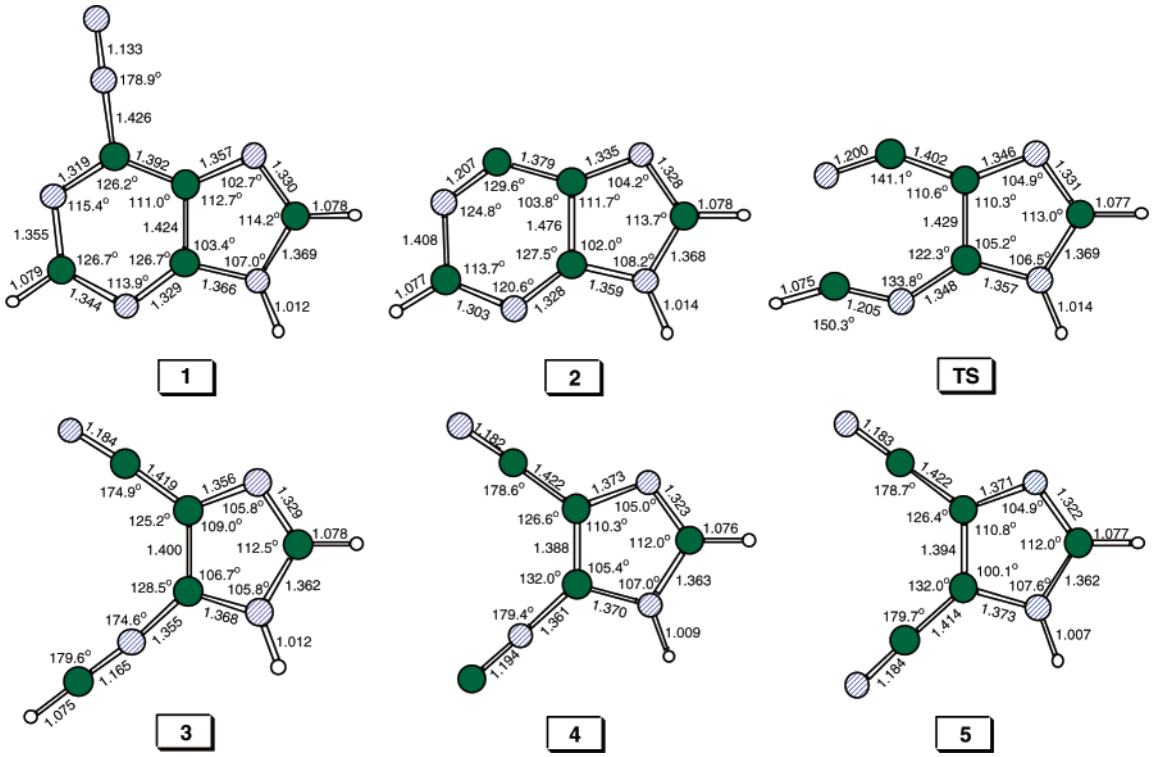

Figure 3. Molecular models of the MP2(full)/6-31G** optimized structures. Distances are in Å and angles in degrees.

Ⓦ Three-dimensional rotatable molecular models of the MP2(full)/6-31G**-optimized structures of Ⓦ **1**, Ⓦ **2**, Ⓦ **TS(2,3)**, Ⓦ **3**, Ⓦ **4**, and Ⓦ **5** and experimental molecular (Ⓦ ZORTAB, Ⓦ ZORTAB01) and crystal (Ⓦ ZORTAB, Ⓦ ZORTAB01) structures of the 4,5-dicyanoimidazole **5** are available in PDB format.

Figure 4 shows in a compelling fashion that the dative bond in **2** is very weak indeed and the ring-opening of **2** is thermodynamically favored and kinetically hardly hindered. At the level of optimization, MP2(full)/6-31G**, the acyclic structure **3** is 0.81 kcal/mol *more* stable than the cyclic structure **2** and the activation barrier for ring-opening is only 12 kcal/mol. The more correlated levels show essentially the same activation barrier, while the stability of the pyrimidine ring-opened cation **3** over cyclic **2** is increased to almost 5 kcal/mol at the highest level (Table 2). Ring-opening allows for more internal motion, and entropy thus favors the process. The Gibbs free energies of activation and of reaction are 10.2 and 9.0 kcal/mol, respectively (Table 3).

The dediazoniation of **1** is a facile process with an activation barrier of less than 10 kcal/mol, and the entropy causes dediazoniation to become a spontaneous process. Hence, **2** is created essentially as a free cation. Cation **2** may then capture a nucleophile, and the well-known formation of hypoxanthine by water addition exemplifies this possibility. On the other hand, the results presented here suggest that **2** also might have the option to follow the reaction channel involving pyrimidine ring-opening to **3** and subse-

Table 1. Total Energies (E_{tot}, Hartrees), Vibrational Zero-Point Energies (VZPE, kcal/mol), Thermal Energies (TE, kcal/mol), Entropies (S, cal mol^{-1} K^{-1}), and Character of the Stationary Structure (NI, number of imaginary modes)

	MP2(full)/6-31G**							
structure	E_{tot}	TE	VZPE	S	NI	MP3 E_{tot}	MP4SDQ E_{tot}	CCSD E_{tot}
1	−519.145289	63.34	58.50	87.59	0	−519.082686	−519.107610	−519.103768
N_2	−109.261574	4.60	3.12	45.87	0	−109.246062	−109.257076	−109.255080
2	−409.870650	55.72	52.09	77.20	0	−409.816461	−409.837525	−409.835259
TS(2,3)	−409.851529	53.72	49.78	79.31	1	−409.794605	−409.818370	−409.814798
3	−409.871939	54.18	49.38	86.38	0	−409.822435	−409.846416	−409.842769
4	−409.550502	47.22	42.61	85.23	0	−409.506889	−409.530359	−409.526135
5	−409.596657	47.32	42.77	85.01	0	−409.543538	−409.568312	−409.563657

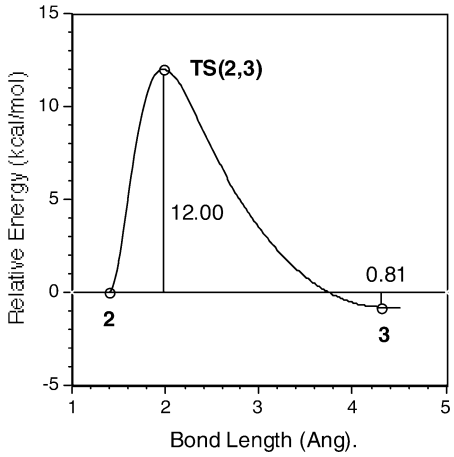

Figure 4. Pyrimidine ring-opening of **2** at MP2/6-31G**.

Ⓦ Molecular models of the MP2(full)/6-31G**-optimized structures along the ring-opening path from **2** to **3** are available in PDB format. The N(1)−C(2) distance in pm: Ⓦ 150, Ⓦ 160, Ⓦ 170, Ⓦ 180, Ⓦ 198 (TS), Ⓦ 200, Ⓦ 210, Ⓦ 220, Ⓦ 230, Ⓦ 240, Ⓦ 250.

Table 2. Relative Energies for Processes Involving the Dediazoniation of the Adeninediazonium Ion (kcal/mol)

process	MP2	MP3	MP4	CCSD
dediazoniation	8.20	12.75	8.16	8.43
ring-opening	−0.81	−3.75	−5.58	−4.71
ΔE_A	12.00	13.71	12.02	12.84
proton affinity	201.70	198.01	198.33	198.69
isomerization energy	−28.96	−23.00	−23.82	−23.55

[a] Dediazoniation energy: reaction energy for **1** → **2** + N_2. Ring-opening energy: reaction energy for **2** → **3**. Activation energy ΔE_A: energy difference between **2** and **TS(2,3)**. Proton affinity: negative reaction energy for process **4** + H^+ → **3**. Isomerization energy: reaction energy for **4** → **5**.

quent deprotonation to **4** or nucleophile addition. Isonitriles are known to undergo isomerization to the more stable nitriles.[15] Hence, **4** is likely to isomerize to the dicyanoimidazole **5** and this isomerization is greatly exothermic and exergonic (Tables 2 and 3). Compound **5** is known, and its crystal structure[16] agrees well with the computed structure.

Table 3. Gibbs Free Energy for Processes Involving the Dediazoniation of the Adeninediazonium Ion (kcal/mol)

process	MP2	MP3	MP4	CCSD
dediazoniation	−4.81	−0.35	−4.84	−4.58
ring-opening	−5.09	−8.03	−9.86	−8.99
ΔG_A	9.37	11.09	9.39	10.21
proton affinity	195.09	191.39	191.71	192.07
isomerization energy	−28.80	−22.83	−23.65	−23.38

[a] See Table 2 for definition of terms.

EI-MS spectra of adenine show several HCN losses during fragmentation.[17] In contrast, the ESI-MS/MS spectrum of adenine[18] also shows NH_3 loss from $[M + H]^+$ to form a cation with $m/z = 119$, **2** and/or **3**. In our own work,[19] we have detected a peak with $m/z = 92$ that provides evidence for HCN loss from **3**. The spectrum shows further details of fragmentation that all are consistent with the initial formation of **3**.

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Supporting Information Available: Cartesian coordinates of the optimized structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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