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AB INITIO STUDIES OF THE REACTION BETWEEN DIAZONIUM IONS AND WATER

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Ab initio **calculations, using the 6–31G* basis set, were performed in order to study the energetics of the electrophilic attack on water by such diazonium ions as methyl-, ethyl- and fluoroethyldiazonium. For the first case, an indication of a transition state appears at the Hartree–Fock level, whereas for the other two, the energy is continuously decreasing from reactants to products. When correlation energy was taken into account via single-point MP2/6–31G* calculations, a deep ion–dipole energy minimum was observed for the methyldiazonium ion followed by a low transition state, whereas the other two did not change their energy pattern. On performing the MP2/6–31G* optimization for the methyl species, the Hartree–Fock results were confirmed, with a slight displacement of the transition state toward a shorter CO distance.**

INTRODUCTION

It has been established that nitrosoureas, which show mutagenic, carcinogenic and anti-tumor activity, decompose spontaneously under physiological conditions, producing electrophiles which alkylate the DNA bases, leading eventually to interstrand cross-linking, which is a lethal event for the cell.[1] It has been shown[1,2] that nucleophilic sites alkylated by nitrosoureas include the O-6 site on guanine, in addition to the N-7 site. Apparently, the O-6 alkylation leads to interstrand cross-linking, whereas the N-7 alkylation is less cytotoxic.[3] Since the ability to repair the alkylation at O-6 before cross-linking can occur seems to be lacking in tumor cell lines, the nitrosoureas are expected to show selective toxicity and, therefore, the determination of the site of attack by their products of decomposition becomes a crucial issue with respect to their anti-tumor activity. These products of decomposition are believed to be the highly reactive diazonium ions or their kinetically equivalent diazohydroxides.

The methyl- and ethyldiazonium ions attack both the N-7 and the O-6 sites on guanine, but experiments have shown that the latter reacts more extensively with the O-6 relative to N-7 than the former.[4]

Many studies have been carried out in order to try to explain this fact. Sapse *et al.*[5] attempted an interpretation of the observed base selectivity via the utilization of hard and soft acid–base theory. That study used *ab initio* calculations to obtain information about frontier orbitals and it was concluded that O-6 is a softer nucleophilic site than N-7. It was also found that the ethyl species are more prone to attack via a soft mechanism than their methyl counterpart.

Ford and Scribner[6a] performed MNDO calculations in which guanine was modeled by a series of small molecules, including water. They reported the presence of transition states and ion–dipole energy minima for these reactions. This work was followed by an MNDO study of the alkylation of the DNA bases by alkanediazonium ions.[6b] The goal of that study was to gather information about hard versus soft electrophilicity of the diazonium ions by measuring the energies of the transition states in their attack on nucleophiles such as water.

In this work, *ab initio* calculations were used in order to follow the energetics of the alkylation reaction of water by methyl-, ethyl- and fluoroethyldiazonium ions and to compare the results with those obtained by Ford and Scribner via MNDO calculations and the with the *ab initio* calculations of Raghavachari *et al.*[7] for a similar reaction. The fluoro species was included because haloethylnitrosoureas are known to exhibit strong anti-tumor activity.[8] This was done in order to

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establish whether transition-state calculations can indeed provide information about the hard versus soft electrophilic character of these species.

METHOD AND RESULTS

The geometries of the $CH_3N_2^+$, $C_2H_5N_2^+$ and $FC_2H_4N_2^+$ molecules were optimized using the 6–31G* Gaussian basis set, as implemented by the Gaussian-86 computer program.[9] The structures thus obtained are shown in Figures 1(a) (b) and (c).

One water molecule approaches the ions at C1. The path of the reaction is followed by assigning different values of the CO distance, keeping it fixed and optimizing all the other parameters of the complex, for each CO distance. Figures 2(a), (b) and (c) show the complexes thus defined. Figures 3(a), (b) and (c) show the products formed by the departure of the neutral N_2 molecule and the bonding of the oxygen of water to the carbon. The calculations performed at the 6–31G* level were augmented by MP2/6–31G* calculations, in order to examine the effects of the correlation energy on the energetics of the reaction. Since the reaction proceeds via the transfer of an electron pair and not by bond breaking, only the singlets were considered.

The MP2 calculations for the ethylated and fluoroethylated species were performed using the MP2/6–31G*//6–31G* method. For the methylated species, geometry optimization using the MP2/6–31G* term was performed. The transition state for the methylated species attack on water was characterized by a transition state optimization using the 6–31G* basis set, optimizing all parameters of the system. It was also calculated at the MP2/6–31G* level via geometry optimization.

Table 1 shows the energies of the reactions and those of the products. Table 2 shows the energies of the complexes for different CO distances between 4 and 1.8 Å.

Table 3 shows the CO and CN distances and the energies for the transition state and for the optimized complex of the methylated species.

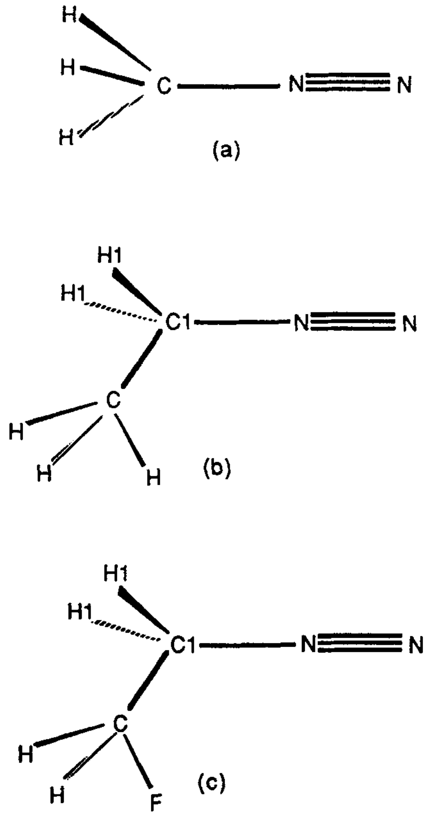

Figure 1. Methyl-, ethyl- and fluoroethyldiazonium ions

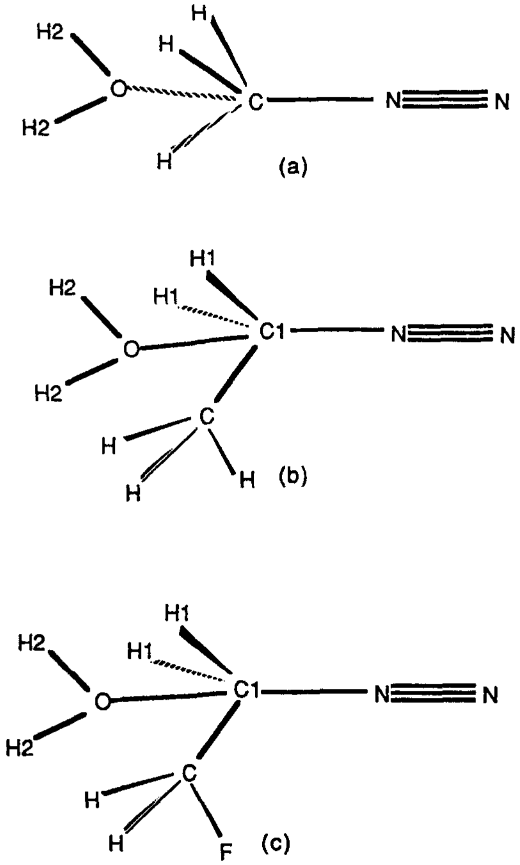

Figure 2. Complexes formed by the diazonium ions with a water molecule

Figures 4(a), (b) and (c) show the profile of the energy dependence on the CO distance, including the reactants and the products. The optimized geometry of the reactants and products at the HF/6–31G* calculation level is shown in Table 4.

Table 5 shows the differences in energies between the reactants, ion–dipole energy minima (for the methyl species), transition state (also for the methyl species) and the products.

In order to examine the superposition approximation error, the optimum energies of $CH_3N_2^+$, H_2O and $CH_3N_2^+ \cdots H_2O$ were also calculated using the 6–311G** basis set, which is a triple zeta set with d-polarization functions on non-hydrogen atoms and p-polarization functions on hydrogen atoms.

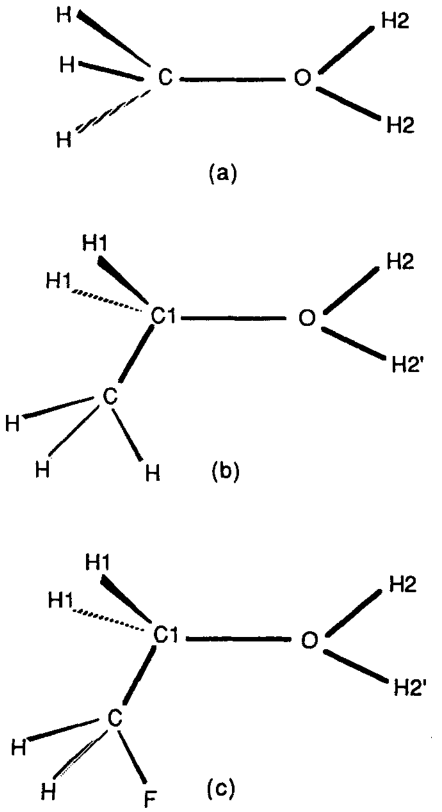

Figure 3. Hydrated CH_3^+, $C_2H_5^+$ and $FC_2H_4^+$ groups: the products of reaction

Table 1. Energies (au) of reactants and products

Species	HF/6–31G*	MP2/6–31G*
H_2O	−76·0108	−76·1992
$CH_3N_2^+$	−148·2160	−148·6661
$C_2H_5N_2^+$	−187·2638	−187·8484
$FC_2H_4N_2^+$	−286·0914	−286·8519
N_2	−108·9439	−109·2616
$CH_3H_2O^+$	−115·3390	−115·6530
$C_2H_5H_2O^+$	−154·3866	−154·8358
$FC_2H_4H_2O^+$	−253·2207	−253·8318

DISCUSSION

The reaction

$$RN_2^+ + H_2O \rightarrow RH_2O^+ + N_2$$

is exothermic, as shown from the energies reported in Table 1.

The geometries of the reactants, as seen from Table 4, feature a very short NH bond, as previously observed by Vincent and Radom,[10] and in agreement with the results of Ford,[6] who has previously studied the geometries of the $CH_3N_2^+$ and $C_2H_5N_2^+$ ions, using large basis sets such as 6–31G** and including the correlation energy via MP3/6–31G** calculations. That study also reported dissociation energies for these ions in good agreement with the experimental results.

The products feature a CO bond in the vicinity of 1·5 Å and an OCH angle of 107° for the methylated species and smaller for the others. In the methyldiazonium–H_2O complex the water molecule is tilted, the hydrogen forming angles of 66° and −66° with the OCH plane, showing that the two hydrogens of water, the oxygen and carbon are not coplanar. It is observed that twisting and bending the HOH plane around the CO bond does not change significantly the energy for some points. For instance, when the angles of 66° and −66° are replaced by angles of 54° and −172°, the energy is higher by only 10^{-5} au.

As seen from Table 2 and Figure 4, the attack of the ethyldiazonium and fluoroethyldiazonium ions on water proceeds without a transition state or an ion–dipole interaction minimum, both at the Hartree–Fock level and when the correlation energy is taken into account via the MP2/6–31G* single-point calculations. The reaction of the methyldiazonium ion is described at the Hartree–Fock level as proceeding via a shallow ion–dipole well, followed by a slight rise on the energy curve, the maximum being located at a CO distance of 2·4 Å and lower in energy than the sum of the energies of reactants by 12 kcal mol^{-1} (1 kcal = 4·184 kJ). The optimization of a complex to a transition state, varying all the parameters, leads to an energy of −224·2463 au for a CO bond length of 2·350 Å and a CN-1 bond length of 1·823 Å. There is a negative eigenvalue whose main components are CO and CN-1. When MP2/6–31G* calculations are performed, the well deepens and apparently the transition state is present, although staying lower in energy than the sum of the energies of the reactants by 7.1 kcal mol^{-1}. This result is similar to the calculations of Raghavachari *et al.*[7] on the $CH_3OH_2^+ + H_2O$ system, where the transition state is also lower in energy than the sum of the energy of the reactants for the methyl species. At the MP2/6–31G* calculational level, using complete geometry optimization of the methyl complexes to the transition state, the transition state moves from a CO bond length of 2·4 Å to 2·08 Å and features an energy of −224·8766 au and a CN-1 bond length of 1·764 Å. This point features, as expected, a negative eigenvalue whose main components are CO and CN-1. After the transition state, that is, toward the product, there is a small minimum of 3 kcal mol^{-1} at both the HF and MP2 calculational levels. This is explained by the fact that the non-polar N_2 molecule and the $CH_3H_2O^+$ species exhibit a small ion–dipole interaction, much weaker than the ion–dipole interaction of the diazonium ion and the polar water molecule.

The profile of the energy versus the reaction coordinate, calculated via point-by-point optimization of the parameters of the complex for different frozen

Table 2. Energies (au) of complexes

Species	CO(Å)	CN(Å)(HF)	HF/6–31G*	MP2/6–31G*	MP2 optimized
$CH_3N_2^+ \cdots H_2O$	1·517	3·173	−224·2862		−224·9196[a]
	1·8	2·91	−224·2730		−224·9047
	2·0	2·70	−224·2612		−224·8885
	2·1	2·58	−224·2564		−224·8816
	2·2	2·47	−224·2523		−224·8820
	2·3	2·34	−224·2489		−224·8855
	2·4	1·62	−224·2472		−224·8878
	2·5	1·57	−224·2483		−224·8890
	2·6	1·55	−224·2488		−224·8895
	2·7	1·54	−224·2488		−224·8893
	2·8	1·53	−224·2484		−224·8884
	3·0	1·52	−224·2470		−224·8871
	4·0	1·50	−224·2465		−224·8775
$C_2H_5N_2^+ \cdots H_2O$	1·8	3·21	−263·3252	−264·0631	
	2·0	3·04	−263·3172	−264·0485	
	2·2	2·92	−263·3119	−264·0398	
	2·3	2·87	−263·3096	−264·0362	
	2·4	2·83	−263·3073	−264·0329	
	2·5	2·80	−263·3050	−264·0300	
	2·6	2·77	−263·3029	−264·0272	
	2·7	2·75	−263·3008	−264·0247	
	3·0	2·70	−263·2953	−264·0182	
	3·5	2·55	−263·2922		
	4·0	2·56	−263·2903		
	4·5	2·52	−263·2878		
	5·0	1·57	−263·2847		
$FC_2H_4N_2^+ \cdots H_2O$	1·8	3·19	−362·1561	−363·0594	
	2·0	2·99	−362·1476	−363·0442	
	2·3	2·81	−362·1365	−363·0280	
	2·6	2·70	−362·1280	−363·0168	
	3·0	2·63	−362·1190	−363·0064	

[a] At the MP2 level, CO = 1·527 Å and CN = 2·985 Å.

Table 3. Minimum and transition-state calculations of $CH_3N_2^+ \cdots H_2O$

	Energy (au)		CO (Å)		CN (Å)	
Calculation	HF	MP2	HF	MP2	HF	MP2
Minimum	−224·2862	−224·9196	1·517	1·523	3·173	2·985
Transition-state	−224·2463	−224·8766	2·349	2·082	1·823	1·764

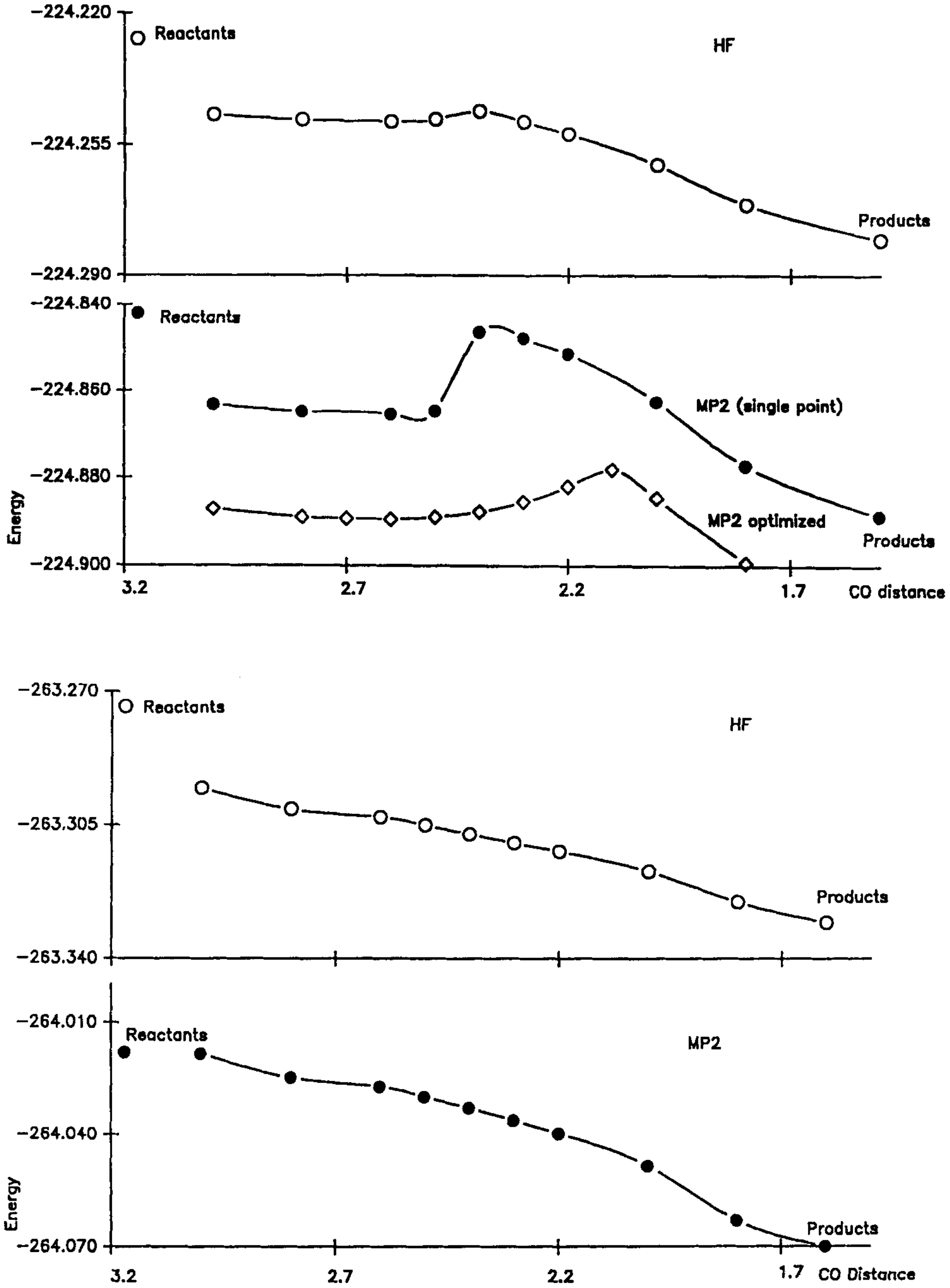

Figure 4. Profile of the energy dependence on the CO distance

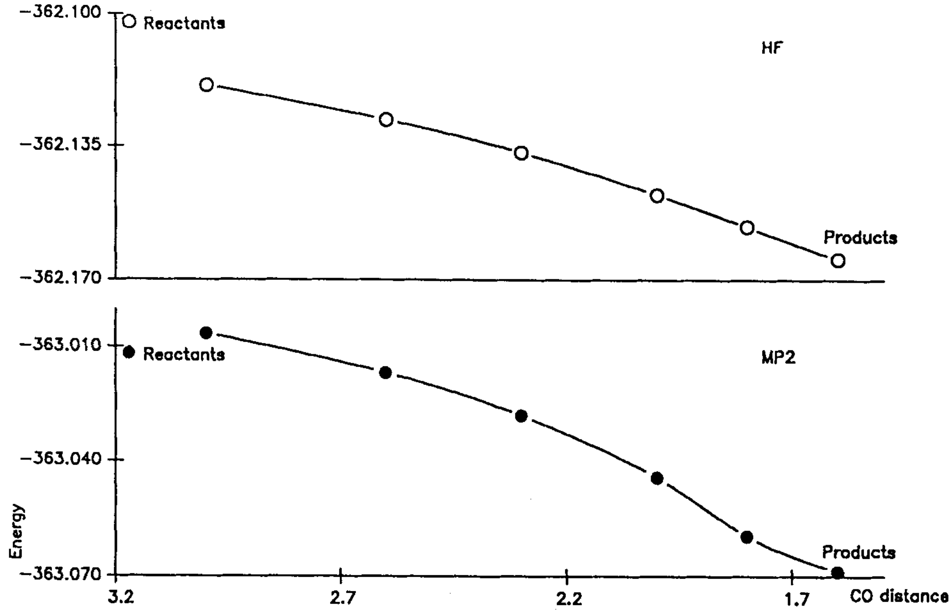

Figure 4. *Continued*

Table 4. Optimized parameters (bond lengths in ångstroms, angles in degrees)

Parameter	$CH_3N_2^+$	$C_2H_5H_2^+$	$FC_2H_4N_2^+$
NN	1·0728	1·0732	1·0733
CN, C1N	1·5096	1·5571	1·5259
CC, CC1	1·5241	1·5403	
CH	1·0782	1·0821	1·0804
CF			1·3406
C1H1		1·0778	1·0789
CC1N		107·2	108·4
HCN, H1C1N	104·98	102·5	104·0
HCC1		110·0	111·1
FCC1			103·9
H1C1CH, H1C1CF		60·00	65·0
	$CH_3H_2O^+$	$C_2H_5H_2O^+$	$FC_2H_4H_2O^+$
CO, C1O	1·511	1·5446	1·5231
CC1		1·5058	1·5079
CH	1·075	1·0834	1·0824
CF			1·3507
C1H1		1·0763	1·0766
OH2	0·962	0·9613	0·9618
OCH, OCH1	107·7	103·4	104·5
CC1O		106·6	106·5
COH2, C1OH2	116·4	115·8	117·8
C1CH		110·3	110·0
C1CF1			108·3
CC1H1		115·0	113·8
H2OH2		110·4	111·4
CC1OH2		−52·0	−50·6
CC1OH2′		162·7	167·2
H1C1CH (H1C1CF)		55·5	55·5

Table 5. Energy differences (kcal mol^{-1})

	Methylated[a]		Ethylated[a]		Fluoroethylated[a]	
Species	(a)	(b)	(a)	(b)	(a)	(b)
Reactants	0	0	0	0	0	0
Ion–dipole energy minimum	−13·8	−15·2	—	—	—	—
Transition state	+12·1	−7·1	—	—	—	—
Products	−33·7	−30·9	−35·6	−31·1	−39·2	−26·5

[a] (a) HF/6–31G*; (b) MP2/6–31G*.

values of CO, agrees with the results obtained by transition-state optimization.

When the values of CN bond lengths are examined at different fixed CO distances, as seen from Table 1, it becomes clear that the N_2 molecule starts leaving the CH_3^+ entity between CO = 2·4 and 2·5 Å. However, the ethyl system exhibits a different behavior. As soon as the water approaches, namely between CO = 5·0 and 4·5 Å, the N_2 molecule starts to leave. The CN bond elongates until the products are formed. Therefore, this reaction does not proceed via an S_N2 mechanism but rather by an initial dissociation of $C_2H_5N_2^+$ into $C_2H_5^+$ and N_2. These facts might contribute to the presence of a transition state in the methylated species and the lack of it in the other two reactions.

Examining Table 5, one can see that the exothermicity of the reaction increases in the order

$$CH_3N_2^+ < C_2H_5N_2^+ < FC_2H_4H_2^+$$

at the HF level, whereas at the MP2/6–31G* level, the methyl and ethyl species are equal and the fluoroethyl species is less exothermic.

The binding energy of $CH_3N_2^+\cdots H_2O$, calculated as

$$E(CH_3N_2^+\cdots H_2O) - [E(CH_3N_2^+) + E(H_2O)]$$

was determined using both the 6–31G* and the larger 6–311G** basis sets. The two energies are within 0·005 au of each other, with the second larger than the first. It can thus be assumed that the superposition error introduced in the 6–31G* calculations is negligible. No conclusion about the hard versus soft electrophilicity of the species can be derived from the calculations, since, in addition to charge effects, there are steric effects, covalent effects and, even though water is a hard nucleophile, it is difficult to estimate the contribution of all these effects. It is clears though, that the ion–dipole energy minimum is present for $CH_3N_2^+$ and not for the others. The energy of the LUMO is the lowest for the fluoroethyldiazonium ion, followed by the methyldiazonium ion, and the ethyldiazonium ion has the highest energy LUMO. Therefore, it is difficult to estimate the hard versus soft nature of these electrophiles.

A clearer picture emerges, however, from the transition-state optimization; whereas the methyl species features a transition state, the ethyl and fluoroethyl species do not and, as such, it is difficult to draw conclusions about the hardness or softness of these species based on transition-state energies.

Given the fact that the methyl species attacks the N-7 site in guanine preferentially to the O-6 site while the ethyl species also attacks preferentially the N-7 site but at a lower N-7/O-6 ratio, and given the fact that the O-6 site is a softer nucleophile as compared with the N-7 site,[5] it might be inferred that the attacking agents are the diazohydroxides where it has been calculated that the ethyldiazohydroxide is a softer electrophile than the methyldiazohydroxide,[5] rather than the diazonium ions which do not present a clear difference in this respect.

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