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The Experimental Hardness and Electronegativity of the Purines and Pyrimidines in DNA and RNA Supported by the AM1 Calculation of the Electron Affinities and Ionization Potentials

Qi Zhang and E. C. M. Chen[a]

School of Natural and Applied Science, University of Houston, Clear Lake, Houston, Texas 77058

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Summary The ionization potential and electron affinities of the purines and pyrimidines in DNA and RNA were calculated with the AM1 semiempirical method. The values support the experimental values. The electron affinities are significant, and positive, such that donor-acceptor interactions can, and indeed should play a role in the stacking of bases in nucleic acids. Based on the confirmation of the experimental values by the theoretical calculations, reliable values of the experimental hardness and electronegativity were calculated.

The electron affinity (EA) is the fundamental property which measures the electron acceptor ability. The EA of a neutral atom or molecule A is given by the negative of the energy change in the reaction, $A + e^- \rightarrow A^-$. A positive EA indicates that the anion is stable while a negative value means that anion is unstable with respect to electron loss. (1,2) When the ionization potential (IP) and the EA of a molecule have been measured experimentally, then the hardness, $\eta\left(\eta = 1/2(IP - EA)\right)$ and electronegativity, $\chi\ \left(\chi = 1/2(IP + EA)\right)$ can be calculated. Accurate experimental values for the ionization potentials of the purines and pyrimidines (3) have been known since 1983 but the electron affinities have only recently been reported (1,2). These two fundamental quantities are important in determining the energy of base pair stacking. In 1990, we estimated the EA values of the purines and pyrimidines by using substitution and replacement rules for the hydroxyl, amino, and methyl groups and estimating the electron affinities of pyrimidine and purine. (1) We later determined these quantities experimentally by measuring the reversible half wave reduction potentials for these compounds along with other compounds with known electron affinities and calibrating the scale on the basis of the known values. (2,4)

As early as 1957, it was thought the electron affinity of the purines and pyrimidines was "too low." It was written, "no member of these classes of compounds should possess electron-

[a]To whom correspondence should be addressed.

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acceptor characteristics." (5,6) In 1966, for the first time a semi-empirical self-consistent field calculation was carried out for the purines and pyrimidines after an appropriate optimization of the integral values using reference compounds. (7) The energies of the lowest empty orbitals, in the four nucleic bases, were reported as a positive as opposed to the negative sign obtained by previous authors.

Recently Sevilla, Besler and Colson performed *Ab initio* molecular orbital calculations of the EAs and IPs of the DNA bases. (8) They estimated the adiabatic electron affinities of the bases to be -0.7, -0.3, 0.2, 0.3 and 0.4 eV based on the calculated vertical electron affinities of -1.23, -0.74, -0.4, -0.32, and -0.19 eV for guanine, adenine, cytosine, thymine and respectively. These values differ from the experimental values which we have reported from half wave reduction potentials, especially for the purines.

Nenner and Schulz (9) measured the electron transmission spectra for benzene, pyridine, s-triazine, and the three diazines. On the basis of this data, vertical EAs of the latter were estimated by correlating half wave reduction potentials with known vertical EAs of other molecules. This is similar to what we have done. The following values were estimated for pyridazine (0.25 eV), pyrimidine (0 eV), pyrazine (0.40 eV) and s-triazine (0.45 eV). Since these values would be lower limits to the adiabatic electron affinities, the good agreement between these values and ours support the validity of the values. The free negative ion of thymine has been observed in the gas phase. This supports the positive value of the electron affinity of thymine.

Recently, the use of the semi-empirical methods such as MINDO3, PM3 and AM1 have become of serious interest due to the development of software packages which can be run on desktop computers. One such commercially available package is HYPERCHEM. To our best knowledge, this is the first time that HYPERCHEM has been used to calculate the electron affinities of the purines and pyrimidines in DNA and RNA. The electron affinities of the purines and pyrimidines were calculated by semi-empirical calculation. By comparing the results to the experimental data the most appropriate set of parameters can be established and be used to calculate EA and IP for other molecules.

We calculated the electron affinity and ionization potential of the purines and pyrimidines in DNA and RNA using the AM1, PM3 and MINDO3 procedures. Comparisons of these results with experimental data indicate that the AM1 method is much better than either MINDO3 or PM3. These calculations bring the scientific process to a complete cycle since substitution and replacement rules and the experimental determinations of the electron affinities was prompted by the calculated negative values. These values conflicted with the idea that the replacement of a CH by a more electronegative nitrogen atom in an aromatic system should increase the electron affinity of the molecule not decrease it. Now the experimental results and the theoretical

calculations support each other and the simple intuitive concepts. It is now possible to calculate reliable experimental values of electronegativity and hardness of these compounds. Typical values of hardness for donor-acceptor pairs range from 3-4 eV which is comparable to the calculated values in Table 2.

Procedure and Discussion

The calculations were performed using HYPERCHEM version 3 and 4 running on a 486 personal computer at the University of Houston-Clear Lake and on a personal 586 computer. The calculations were carried out by the standard AM1, PM3 and MINDO3 programs based on the Unrestricted Hartree-Fock (UHF) methods. Geometries were optimized in internal coordinates. All optimizations were terminated when the change in energy on successive iterations was less than 0.01 Kcal/mole. All calculations were geometry optimized and converged. In some cases, local minima were reached. In these cases, Molecular Mechanics calculations were carried out to "anneal" the system by raising the temperature to 1000K and then geometry optimizing. The resultant energies were reproducible and are to the best of our knowledge global minima.

In the calculations for guanine, thymine, cytosine and uracil, two conformations were considered: one is the keto-form and the other is enol-form. (See Fig. 2) By our calculation, for cytosine, uracil, and thymine, the values for the enol form are closer to the experimental values. It indicated that they take enol-form. However, for guanine, the value of keto-form is closer to the experimental data. Note that in every case, the keto-form has a higher electron affinity than the enol-form.

The AM1 parameters give more accurate values than the PM3 or MINDO3 parameters. The PM3 parameters give positive values which are consistently higher than the AM1 values. The MINDO3 parameters give negative values for some compounds. Table 1 lists the calculated EA values obtained by using AM1 parameters. Also shown are the recent calculated values of the adiabatic electron affinities from Sevilla, Besler and Colson and the vertical electron affinities reported by Nenner and Schulz. (9) It is clear that the electron affinities calculated by AM1 agree with experimental data very well for the purines and pyrimidines (average deviation +0.11 eV). All of the deviations are positive. The greatest deviation is for cytosine (0.26 eV). The average deviation for the ionization potentials is 0.01 eV with some values high and some low. The greatest deviation is 0.24 eV for adenine.

The agreement of the AM1 calculated electron affinities of the other compounds is not as good as for the bases but the order is the same for both the experimental values obtained from reduction potentials (2) and from electron transmission data. (9) This is better investigated by considering the correlation between the experimental and calculated electron affinities. It is not

Table 1

Experimental and Calculated Electron Affinities and Ionization Potentials (eV)

Molecule	EA (Calculated)	EA (Experimental)	EA (Literature)	IP (Calculated)	IP (Experimental)
Pyridine	0.24	-0.21			
Pyridazine	0.75	0.31	0.25[a]		
Pyrazine	0.71	0.36	0.40[a]		
s-Triazine	1.04	0.47	0.45[a]		
as-Triazine	1.17	0.91			
s-Tetrazine	1.73	1.67			
Pyrimidine	0.62	0.19	0.00[a]		
Cytosine-1[c]	1.19				
Cytosine-2	0.82	0.56	0.2 [b]	8.46	8.45
Uracil-1	1.14				
Uracil-2	0.87	0.80	0.4 [b]	9.12	9.20
Thymine-1	1.16				
Thymine-2	0.90	0.79	0.3 [b]	8.78	8.80
Purine	1.26	1.02			
Adenine	1.06	0.96	-0.3[b]	8.04	7.80
Guanine-1	1.48	1.51	-0.7[b]	7.70	7.85
Guanine-2	1.23				

a. Reference 9.
b. Reference 8.
c. 1 is keto-form, 2 is enol-form.

bad for the purines and pyrimidines and related compounds. (See Fig. 1) However, the slope is not unity. Indeed, considering the experimental values of electron affinities which are less than 0.7 eV, the average deviation is 0.4 eV while for those values above 0.79 eV, the average deviation is only 0.13 eV. This indicates that an adjustment of some of the parameters might improve the agreement between the experimental and theoretical results.

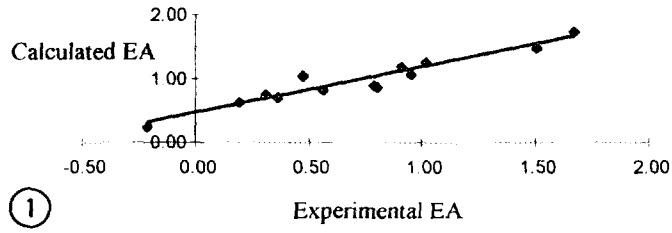
In summary, the values calculated with the AM1 semi-empirical method support the experimental values for the ionization potentials and electron affinities of the purines and

Table 2

Electron Affinities, Ionization Potentials, Electronegativities and Hardness(eV)

Molecular	EA[a]	IP[b]	Hardness	Electronegativity
Cytosine	0.56	8.45	3.90	4.51
Uracil	0.90	9.20	4.20	5.00
Thymine	0.89	8.80	4.01	4.80
Adenine	0.96	7.80	3.43	4.38
Guanine	1.51	7.85	3.17	4.68

a. Reference 2.
b. Reference 3.



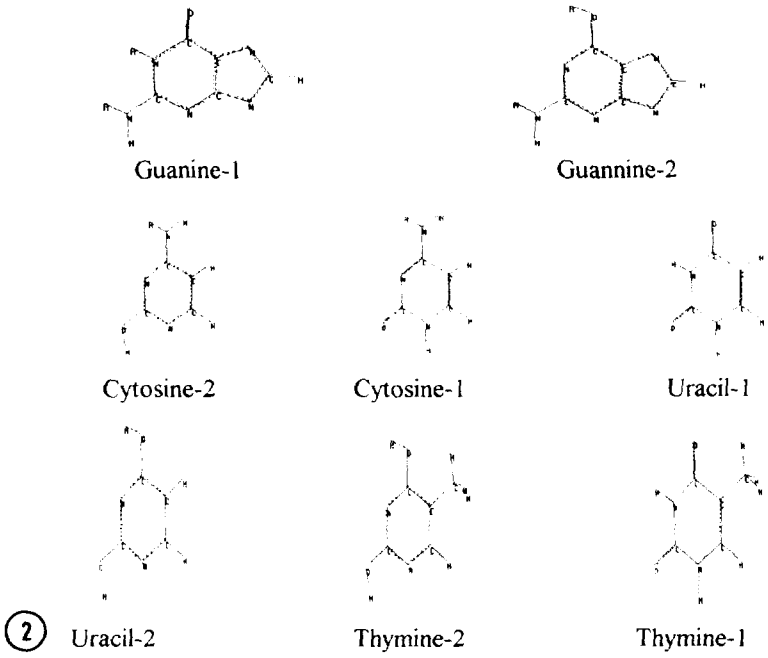


Figure 1. Fit of the calculated electron affinities of the various molecules presented in Table 1 to the experimental electron affinities. Assuming the linear relationship EA(theory)=a+b(EA, experimental), the fit gives a=0.4622, b=0.7119, and R^2=0.923.

Figure 2. The structures used in the calculation of guanine, cytosine, uracil, and thymine.

pyrimidines. With this support, the values of the hardness and electronegativity of these compounds can be calculated. On the basis of the magnitude of the hardness, it is clear that donor-acceptor interactions can, and indeed should play a role in the stacking of bases in DNA and RNA.

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