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THE ROLE OF ELECTRON DONORS AND ACCEPTORS IN BASE STACKING IN DNA AND RNA

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The role of donor-acceptor interactions in base pair stacking in DNA and RNA has been minimized because of the perceived low or negative electron affinities of the purines and pyrimidines. The use of the electron capture detector was among the first methods for measuring electron affinities in the gas phase. Recently, the experimental determination of electron affinities has been extended and improved. Now, there are data for similar compounds in the literature which enable us to estimate electron affinities for purines and pyrimidines. These values are significant, and positive, such that donor-acceptor interactions can, and indeed should play a role in the stacking of bases in nucleic acids.

It is generally stated that "hydrophobic base stacking results from interaction between the electron systems of the stacked base pairs." (1) We propose that part of the base stacking interaction is a donor-acceptor pair. Some of the bases have the ability to act as both donors and acceptors.

The Mulliken theory of charge-transfer complexes (2), later renamed donor-acceptor complexes (3), predicts that the stabilities are related to the ionization potential of the donor, and the electron affinity of the acceptor. A positive value indicates that the reaction: $AB + e^- \longrightarrow AB^-$ is exothermic. The role of donor-acceptor complexes was considered (4) as early as 1957, but was disregarded because it was thought the electron affinity of the purines and pyrimidines was "too low." (5) As recently as 1976, it was written, "no member of these classes of compounds should possess electron-acceptor characteristics." (6) However, no experimental electron affinities were available, and the theoretical estimates were inconsistent. Some investigators reported values as positive, while others gave the same values as negative. (5,7)

In 1967, Wentworth, Chen, and Lovelock (8) presented a method for measuring absolute electron affinities of molecules. Since then, the method has been verified by

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Abbreviations used: ECD, electron capture detector; EA, electron affinity; IP, ionization potential; TCT, thermal charge transfer; ST, single temperature.

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measurements in other laboratories with different techniques. (9) We have recently made significant improvements in this procedure, and began to search for appropriate molecules to study. Lovelock (10) had previously noted that electron acceptors are very significant in biological processes. Thus, we turned our thoughts to such molecules. Based on the data in the literature, we felt that purines and pyrimidines should have positive electron affinities, and could act as acceptors in donor-acceptor interactions in both DNA, and RNA base stacking.

Absolute electron affinities can be determined from the temperature dependence of the ECD response. (11) Relative electron affities can be estimated from the ECD_1 response at one temperature (12) in some cases. For example, the electron affinity of acridine can be estimated from ECD data for acridine and anthracene at 523K from the equation $EA_2(\text{acridine}) = EA(\text{anthracene}) + 1.987*(523)\ \text{Ln}(K_{\text{acridine}}/K_{\text{anthracene}})$. The K values are the molar responses of acridine and anthracene in the ECD. The electron

Table I

Electron Affinities of Aromatic and Heterocyclic Compounds

Molecule	Absolute EA(eV)	Method	Reference
Benzene C_6H_6	−0.8 ± 0.2	$E_{1/2}$[a]	13
Pyridine C_5H_5N	0.1 ± 0.15	ECD-ST[b]$_5$	10
	−0.1 ± 0.2	$E_{1/2}$	13
Nitrobenzene $C_6H_5NO_2$	1.0 ± 0.10	TCT_4	15
Nitroaniline $C_6H_4NO_2NH_2$	0.95 ± 0.10	TCT	15
Benzonitrile C_7H_5N	0.24 ± 0.05	ECD	9
Cyanopyridine $C_6H_5N_2$	1.05 ± 0.15	$E_{1/2}$	20
Tetracyanobenzene $C_{10}H_2N_4$	2.15 ± 0.22	Magnetron	14
Tetracyanopyridine C_9HN_5	2.12 ± 0.17	Magnetron	14
Pentafluorobenzene C_6F_5H	0.73 ± 0.1	ECD	21
Pentafluoropyridine C_5F_5N	0.75 ± 0.1	TCT	16
	0.68 ± 0.1	TCT	
Naphthalene C_8H_{10}	0.15 ± 0.1	ECD	8
Quinoline C_7H_9N	0.55 ± 0.15	$E_{1/2}$	13
Hydroxyquinoline C_7H_8NOH	0.85 ± 0.15	$E_{1/2}$	22
Anthracene $C_{14}H_{10}$	0.60 ± 0.05	ECD/TCT	8,15
Acridine $C_{13}H_9N$	0.75 ± 0.15	ECD-ST	23
Carbazole $C_{12}H_9N$	0.60 ± 0.15	ECD-ST	23
Phenanthrene $C_{14}H_{10}$	0.30 ± 0.05	ECD	8
Benzoquinoline $C_{13}H_9N$	0.40 ± 0.15	ECD-ST	23
Pyridazine $C_4H_4N_2$	0.55 ± 0.15	$E_{1/2}$	13
Pyrimidine $C_4H_4N_2$	0.35 ± 0.15	$E_{1/2}$	13
Pyrazine $C_4H_4N_2$	0.60 ± 0.15	$E_{1/2}$	13
s-Triazine C_3H_3N	0.70 ± 0.15	$E_{1/2}$	13
Acetophenone C_8H_8O	0.35 ± 0.10	ECD	9
Hydroxyacetophenone $C_8H_8O_2$	0.86 ± 0.15	TCT	15

a) $EA(R) - EA(S) = E_{1/2}(R) - E_{1/2}(S)$

b) $EA(R) - EA(S) = RT\ \text{Ln}\ (K_S/K_R)$

where K_S and K_R are the molar responses of the sample, and of the reference compound, respectively. The values for EA from $E_{1/2}$, and ECD-ST are calculated in this work.

affinity of anthracene has been measured by several techniques. This is a general relationship if the two molecules form a molecular negative ion and detachment is the predominant mechanism for the loss of the negative ion. Values for other heterocyclic compounds are given in Table I along with the reference molecules.

Nenner and Schulz (13) have measured the electron transmission spectra for benzene, pyridine, s-triazine, and the three diazines. They estimated values of the vertical EA's of the latter by correlating half wave reduction potentials with known vertical EA's of other molecules. In this work, we have placed these on an absolute and adiabatic basis, using EA's determined in the ECD. Other EA's have been established from $E_{1/2}$ data ($EA_s - EA_R = E_{1/2,S} - E_{1/2,R}$). The values correspond to the sample and the reference compounds respectively. The EA of the reference compound must be known. These values are all given in Table I. Absolute EA's may be determined using the Magnetron method (14), and from relative thermal charge transfer energies, referenced to the absolute value of SO_2. (15,16)

Substituting a nitrogen for a -CH in an aromatic hydrocarbon may not increase the EA as in the case of pentafluorobenzene to pentafluoropyridine, or it may increase the EA at most 0.8 eV as in the change from benzene to pyridine. Substitution of an -OH for an -H on a molecule increases the EA. The increase from quinoline to hydroxyquinoline is 0.3 eV, and that from acetophenone to hydroxy acetophenone is 0.5 eV. To illustrate the effect of addition of an $-NH_2$ group, the EA's of nitrobenzene and nitroaniline show a difference of - 0.05 eV. These values, and the methods used to obtain them are summarized in Table I. No specific examples are given for the addition of a methyl group, but this is known to slightly decrease the electron affinity of the molecule. (9)

On the basis of the substitution and replacement rules given above, empirical estimates of the EA's can be postulated. Cytosine, uracil, and thymine are all simply substituted pyrimidines. The EA of pyrimidine is 0.35 ± 0.15 eV. Cytosine is a hydroxy, and amino substituted pyrimidine. Thus, EA(cytosine) is 0.60 eV. Thymine and uracil are dihydroxy substituted pyrimidines. The effect of a second substituent is less than that of the first substituent. Thus, EA(uracil) is 0.75 eV, and EA(thymine) is 0.65 eV.

Table II

Ionization Potentials and Estimated Electron Affinities of the Common Purines and Pyrimidines

Molecule	Chemical Formula	Ionization[17] Potential (eV)	Estimated EA EA (eV)
Cytosine	$C_4H_5N_3O$	8.45	ca. 0.60
Uracil	$C_4H_4N_2O_2$	9.20	ca. 0.75
Thymine	$C_5H_6N_2O_2$	8.80	ca. 0.65
Adenine	$C_5H_5N_5$	7.80	ca. 0.75
Guanine	$C_5H_5N_5O$	7.85	ca. 1.05

The EA's of adenine and guanine can be estimated from the EA of purine. We know purine is similar to carbazole with three nitrogens substituted for -CH's. The EA of purine is greater than 0.60 eV, the EA of carbazole, and we approximate it to be 0.80 eV. Adenine is purine with an amino group. EA(adenine) is 0.75 eV. Guanine is a hydroxy and amino substituted purine. Therefore, EA(guanine) is 1.05 eV. These values, and the currently accepted experimental ionization potentials[3](17) are summarized in Table II.

It is crucial to remember that these values refer only to the free bases. When the bases are joined to either ribose, or deoxyribose, there should be a change in the electron affinity of the pyrimidines. The conjugation of the ring is disrupted in thymine and uracil, which should lower the EA. The conjugation of the cytosine ring is less affected, and the "extended conjugation" of the purines should not be affected. This "altered order" of stacking energies (G>A>C>U>T) (5) is identical to that previously reported for the nucleotides. It has been shown that for base stacking energy in DNA and RNA the order is: purine - purine > purine - pyrimidine > pyrimidine - pyrimidine. This is exactly the order that would be expected based upon the IP - EA values. In summary, we believe that a donor-acceptor interaction is important to base stacking in nucleic acids. Similar interactions have been observed for aromatic hydrocarbons complexed with methylbenzenes in solution. (19) The (IP - EA) values of compounds known to form donor-acceptor complexes are roughly comparable to those of the nitrogenous bases. The sugar-phosphate backbone of DNA and RNA forces the bases to be only a few Angstroms apart. This should definitely lead to some donor-acceptor interactions.

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