Theor Chem Acc (2007) 117: 323–332
DOI 10.1007/s00214-006-0154-9

REGULAR ARTICLE

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Natural resonance structures and aromaticity of the nucleobases

Received: 1 February 2006 / Accepted: 31 May 2006 / Published online: 2 August 2006

Abstract Natural resonance theory (NRT) and nucleus-independent chemical shift (NICS) analyses have been applied to the standard nucleobases adenine, guanine, cytosine, uracil, and thymine. The molecular electron densities were obtained from density functional theory calculations at the B3LYP level and ab initio calculations at the HF, MP2, and CCD levels. Compared with the dominance of the two Kekulé structures in benzene, the structural modifications in the forms of endocyclic heteroatoms and exocyclic substituents introduce various degrees of charge separation in nucleobases. As a result, the leading resonance structures for cytosine, uracil, and thymine are found to be covalent structures, but their weightings decrease to ∼30% in the NRT expansion. For adenine and guanine, the covalent structures have weightings of ∼20%, and the leading ionic resonance structures have weightings of as high as about 8%. Methods that include electron correlation effects, B3LYP, MP2, and CCD, give smaller weightings for the covalent structures than HF. However, MP2 and CCD results often include "strange" resonance structures with connections between unbonded vicinal atoms, making DFT at the B3LYP level the better choice for calculating these molecules' electron density. The NICS at the ring center shows that the six-membered rings in cytosine, uracil, thymine, and guanine are nonaromatic with NICS within −3 to −1 ppm, while it is −7.3 ppm for the six-membered ring in adenine. The NICS of the five-membered rings of adenine and guanine is around −12 ppm, a slight decrease from the value of −15.0 ppm for pyrrole.

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Keywords Nucleobase · DFT · Natural bond orbital · Natural resonance theory · Quantum chemical calculations · Aromaticity · Nucleus-independent chemical shift (NICS)

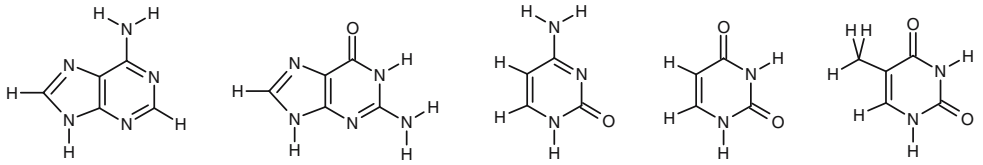
1 Introduction

The five standard nucleobases, adenine, guanine, cytosine, uracil, and thymine (Scheme 1), are the central building blocks of DNA and RNA, essential to all life forms. The structures and properties of these nucleobases determine to a large degree the structures and functions of specific DNA and RNA sequences [1], since they form the critical H-bonds within the duplex DNA/RNA structures.

All five nucleobases are heterocyclic compounds. Cytosine, uracil, and thymine can be viewed as analogues of benzene with endocyclic heteroatoms and exocyclic substitutions. The more complex molecules adenine and guanine can be viewed as analogues of benzene further fused with analogues of pyrrole. One goal of this study was to investigate how the structural modifications affect the π-electron distribution as compared with that in benzene and pyrrole, and how the aromaticity of these molecules compares with that of benzene. This can be done by computing and analyzing the natural bond orbitals (NBO).

The NBOs [2] are localized orbitals that are complete and orthonormal. Computable from the wavefunction or electron density obtained at any level of theory, they provide a unique representation of the molecular electronic configuration that is closely related to the chemical bonding concept. The natural resonance theory (NRT) [3–5], which is based on NBO, calculates the weighting of a particular resonance structure that represents a particular bonding pattern. The weighting of each resonance structure thus indicates the contribution from this resonance structure to the entire electron density and to certain properties of a molecular system such as reactivity.

For conjugated cyclic compounds, aromaticity is an important descriptor as it correlates well with many structural features and physical properties. The nucleus-independent chemical shift (NICS) [6,7] calculated at the



Scheme 1 The five standard nucleobases

ring center is a good criterion for aromaticity in such molecules. As demonstrated by Schleyer et al. [6], the NICS of benzene is −9.7 ppm, while it is −3.2 ppm for cyclopentadiene, thus the more negative the NICS, the more aromatic molecules with similar structures are.

We used density functional theory (DFT) to obtain the electron density at optimized structures. Starting from benzene and pyrrole, we investigated the gradual change in the resonance structures and aromaticity after one or two structural modifications. The properties of the nucleobases were then compared with benzene and pyrrole, and other intermediate molecules.

2 Computational methods

The structures of the five nucleobases and many intermediate structures (see Fig. 1) starting from benzene and pyrrole were optimized with DFT. We used the hybrid B3LYP functional [8,9] and the medium-size basis set 6-31G* [10]. Numerous applications indicate that this level of theory provides the best compromise between accuracy and CPU time requirement, as it provides a computationally affordable method of dealing with electron correlation effects. To obtain the electron density required for the NRT analysis, we used four commonly employed methods in order to study the effect of different levels of theory: the Hartree–Fock (HF) approximation [11], the second order Møller–Plesset (MP2) perturbation theory [12], the coupled-cluster method with double substitutions (CCD) [13], and the hybrid DFT B3LYP functional approach [8,9]. We used the 6-31G* basis set for all molecules. In addition, basis sets ranging from STO-3G to 6-311++G(3df, 2pd) were used for specific analyses. We performed the NRT analysis [3–5] using the NBO5.0 program [14].

One important parameter in the NBO algorithm that influences the weightings of the resonance structures is the energy threshold, NRTTHR, used to determine whether to include a particular delocalization from a filled donor orbital to an empty acceptor orbital. Although large values (5 or 10 kcal/mol) are commonly used to eliminate the numerous minor resonance structures, we used the relatively small default of 1.0 kcal/mol in this work to specifically study them. Another issue that influences the NRT expansion is the determination of reference structures. For the molecules with one six-membered ring, the NBO algorithm is able to select the covalent structures as the chemically reasonable reference structures. For the molecules with one five-membered ring and the more complicated two-ring systems, we explicitly specified the covalent structures as the reference structures to assure that a consistent set of reference structures are used for similar molecules. The reference structures are denoted by asterisks in all schemes of the NRT expansions, whether automatically selected by the NBO algorithm or specified by the user.

To study the aromaticity of the nucleobases, the NICS at the center of all rings was calculated using the gauge-independent atomic orbital (GIAO) method [15] at the HF/6-31+G* level of theory as defined by Schleyer et al. [6,7]. All calculations were performed using the Gaussian 98 program package [16].

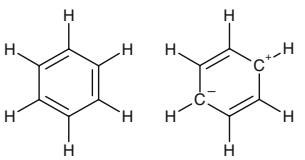
3 Results and discussion

We first present the NRT expansions for benzene, pyrrole, and some representative intermediate molecules. This is followed by the NRT expansions of the nucleobases. In the NRT expansions, we omit the resonance structures that have very small weightings. As a result, the total of the weightings listed may be less than 100%. Only the DFT results are presented, but in cases where significant discrepancies exist between the different methods we comment on the results from the other methods. Finally, we present the calculated NICS values for all molecules and discuss the change in their aromaticity associated with the structural modifications.

3.1 Benzene and derivatives

3.1.1 Benzene

The two Kekulé structures of benzene have very large NRT weightings and dominate the NRT expansion. The DFT calculated weighting (38.84% × 2) is smaller than the HF value (45.80% × 2) reported by Weinhold and co-workers [5]. This discrepancy is mostly due to the inclusion of a large number of minor resonance structures, as our HF calculations give very good agreement with the earlier data. The weightings (2.14% × 6) in the DFT results for the singly ionic structure with charge transferred from C1 to C4 are much larger than in the corresponding HF results (<0.01%) [5]. (We are using the nomenclature "ionic" coined by Weinhold [2] for the charge-separated resonance structures.)



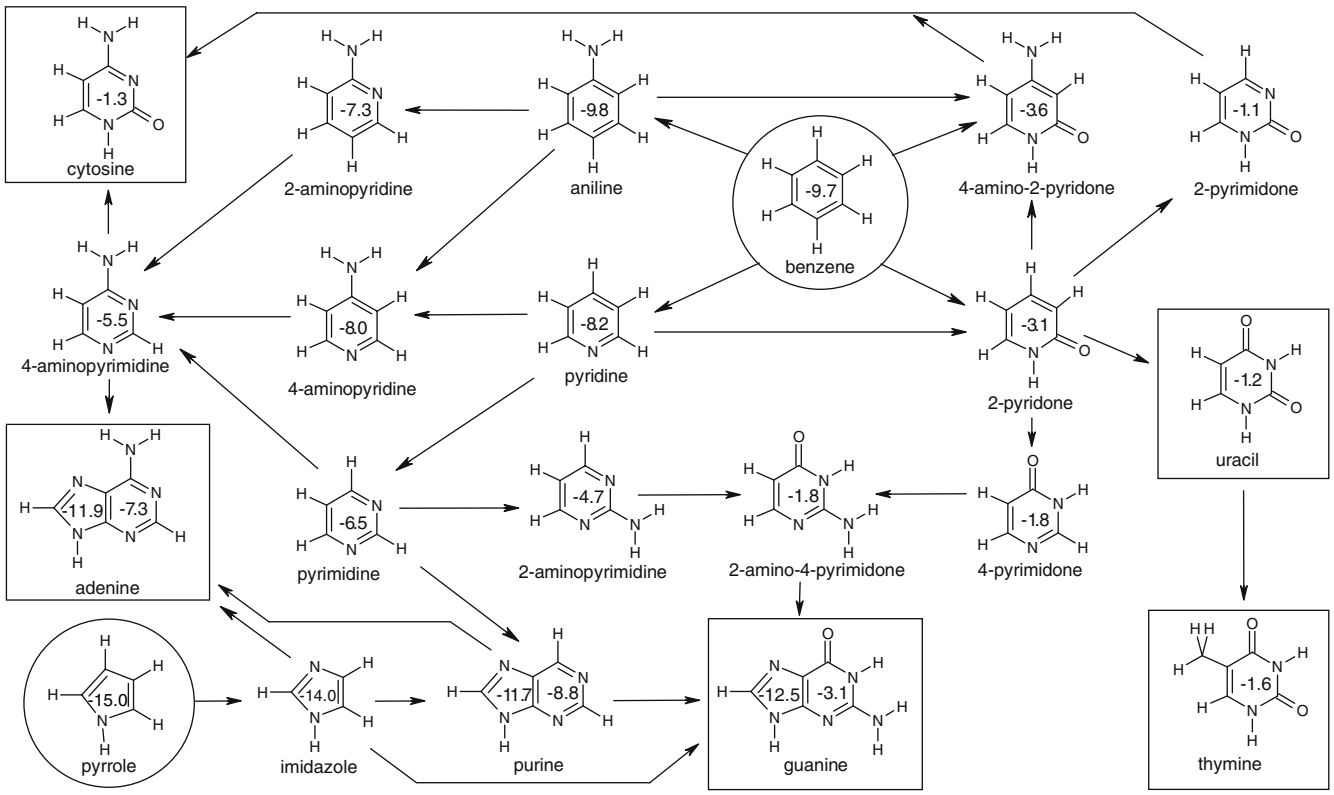


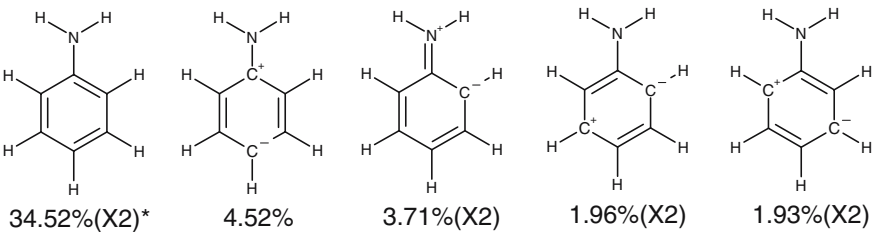
Fig. 1 The calculated NICS at the center of all rings for the nucleobases, benzene, pyrrole, and many intermediate structures

The two post-HF methods, MP2 and CCD, give very similar weightings (∼38% × 2) for the covalent structure, which is very close to the results obtained using the B3LYP functional. However, the ionic structure has much smaller weighting: we find the resonance structures with one of the single bonds broken to form the minor resonance structures in the post-HF methods.

3.1.2 Aniline

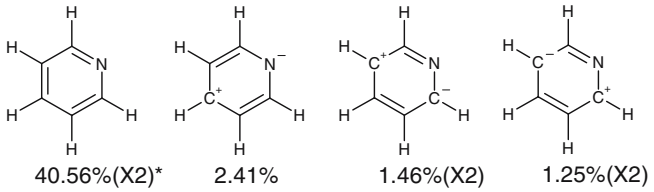
With one hydrogen substituted by an $–NH_2$ group, aniline has a slightly smaller NRT weightings than benzene for the covalent resonance structures, at 34.52% × 2. The lone pair of the N atom can participate in the conjugation with the adjacent C–C π-bonds, as shown by the 3.71% × 2 weighting for the third resonance structure. The ionic structures that result from C1 to C4 charge transfer continue to show large weightings. The resonance structure with the positive charge at C1 has slightly larger values than the other ionic structures.

The HF gives a larger weighting (37.63% × 2) for the covalent structure than the B3LYP functional, while MP2 and CCD give smaller weighting (∼29%). The ionic resonance structures seen in the B3LYP results also have weightings comparable to those of the other calculations. However, the MP2 and CCD results include a resonance structure in which C2 and N are bonded, forming a three-membered ring consisting of C1, C2, and N. This "strange" structure is a result of the inclusion of the electron correlation effect, which tends to enhance the vicinal donor–acceptor interactions [2,17]. Judged from this case and many cases that will be shown below, it seems that DFT is a good method to calculate electron density for the NRT analysis, whereas the presence of the "strange" structures obtained in many cases from the post-HF ab initio methods indicates that the NRT algorithm cannot be combined properly with these methods.



3.1.3 Pyridine

With one N atom substituted in the six-membered ring of benzene, pyridine has a similar resonance structure as benzene. Its covalent resonance structure has a large weighting (40.56% × 2) and the singly ionic resonance structures have significant weightings.



Due to the lack of branching heavy atoms, no "strange" resonance structures are obtained with the post-HF methods. The weighting of the covalent structure from the HF results is 41.37% × 2. It is 34% × 2 from both MP2 and CCD results. Again the B3LYP values are bracketed by the HF value on the upper side and the post-HF results on the lower side.

3.1.4 2-Aminopyridine

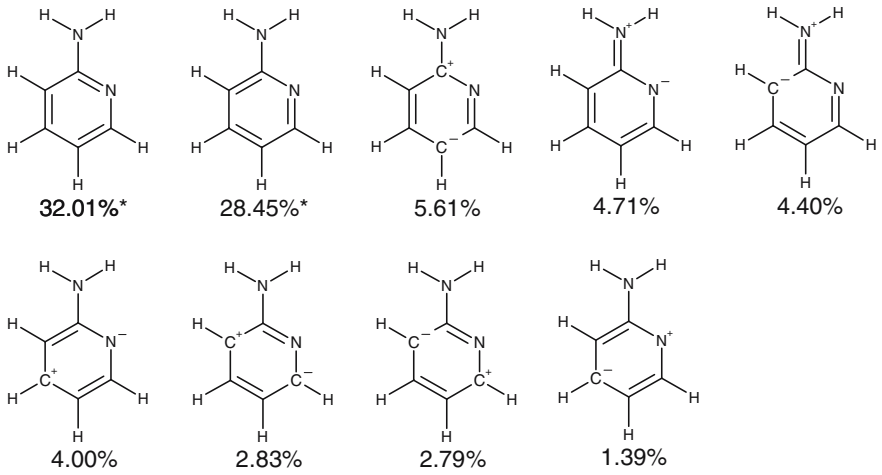
In 2-aminopyridine, the C_{2v} point group symmetry present in both aniline and pyridine is reduced to C_s symmetry. This differentiates the two covalent resonance structures from each other. As a result, their weightings are 32.01 and 28.45%, respectively. All ionic structures have weightings that are lower than 6%. The leading ionic contributions are from quinoid-like structures totaling 16.62% in weightings, and structures with charge transfer from the exocyclic NH_2 to N2 or C6 with total weighting of 9.11% (4.71% + 4.40%).

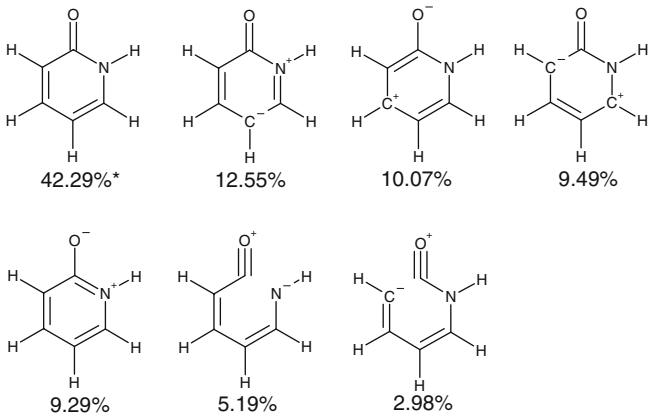
Again the weightings for the covalent structures calculated by HF are about 5% larger than B3LYP results, while the values obtained with MP2 and CCD are 4–5% lower. Also, vicinal atoms form bonds in MP2 and CCD results. Though these structures have weightings of less than 2% in the MP2 and CCD results, they are completely absent in the B3LYP and HF results.

3.1.5 2-Pyridone

An endocyclic NH and an exocyclic =O need to be simultaneously introduced in benzene to form 2-pyridone, or a –CH=N– segment in pyridine needs to change to –CO–NH–. This change causes the weighting of the single covalent resonance structure to decrease drastically to 42.29% from a total of 60.46% (32.01% + 28.45%) for pyridine. Conversely, the weightings for the ionic structures increase significantly. The leading ionic resonance structure (12.55%) has a quinoid-like structure resulting from a 1,5 charge transfer. This is followed closely by another quinoid-like structure with 10.05% weighting. The N lone pair can easily participate in the cyclic π conjugation, resulting in an aromatic structure with 9.29% weighting. Two structures with a triple CO bond and no bond between C2 and adjacent ring atoms have small but noticeable weightings.

The HF results closely follow those of B3LYP, with most resonance structures finding their counterparts. The weighting for the covalent structure is 53.36% by HF, while it is 22% by MP2 and 26% by CCD. Both post-HF methods produce "strange" structures with bonds between nonbonded atoms. Some of these strange structures have weightings as large as 10%.



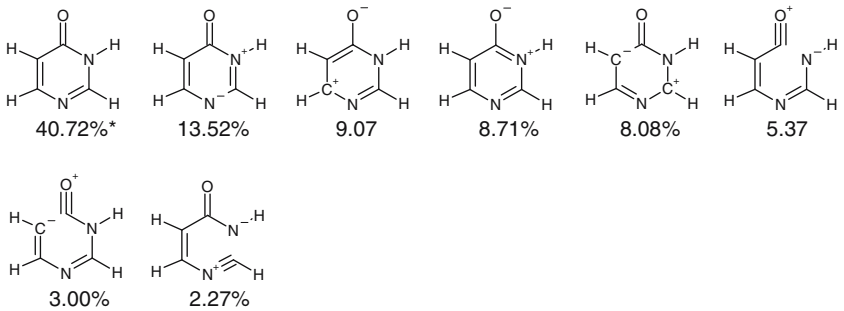


We carried out more calculations in addition to the standard treatment. When the geometries, optimized by either HF or MP2, are used, the weighting for the covalent resonance structure does not change for all four methods. For the ionic structures, there are noticeable changes for all methods. However, the changes for MP2 and CCD are more profound. Even larger changes are observed for the ionic resonance structures with vicinal bonds.

When basis sets ranging from STO-3G, 3-21G, 6-31G*, 6-311++G** to 6-311++G(3df, 2pd) were used with the B3LYP functional, the weighting of the covalent structure hardly changed. This was especially true for the basis sets larger than the minimal STO-3G. The weightings for the ionic structures were also very stable.

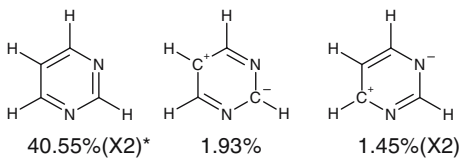
3.1.7 4-Pyrimidone

To arrive at the 4-pyrimidone, a –CH=N– segment in pyrimidine needs to change to a –CO–NH– segment. As shown in the case of 2-pyridone, this change causes a large decrease of the weighting of the covalent structure and a large increase in the weightings of the ionic structures. In 4-pyrimidone, the weighting for the covalent structure is 40.72%, a drastic decrease from 40.55% × 2 for pyrimidine. The ionic resonance structures resulting from intra-ring charge transfer all have much larger weightings than in pyrimidine. The charge transfer from the oxygen to ring atoms also results in ionic structures with large weightings.



3.1.6 Pyrimidine

With carbons 1 and 3 in benzene substituted by two N atoms, pyrimidine has a resonance structure very similar to benzene. Its covalent resonance structure has a large weighting (40.55% × 2) and the singly ionic resonance structures have significant weightings. As with benzene and pyridine, all methods give similar NRT expansions with some change in the weighting of the covalent structure.

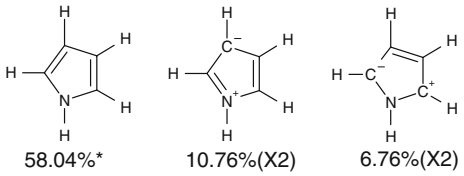


3.2 Pyrrole and derivatives

3.2.1 Pyrrole

For pyrrole, the covalent resonance structure has a weighting of 58.04%. This is much smaller than the weighting of the covalent structure for benzene (38.84% × 2), indicating significant charge transfer. Indeed, the large n → π^* interaction gives the singly ionic structures very large weightings of 10.76% × 2. Another singly ionic structure arises from charge transfer from C2 to C5 and has a weighting of 6.76% × 2. The HF, MP2, and CCD calculation all give NRT expansions consistent with that of B3LYP, although the weightings for the covalent structure are about 42% by

post-HF methods and 62.98% by HF, respectively. Again, due to the lack of branching heavy atoms, no strange resonance structure was observed in the MP2 or CCD results.

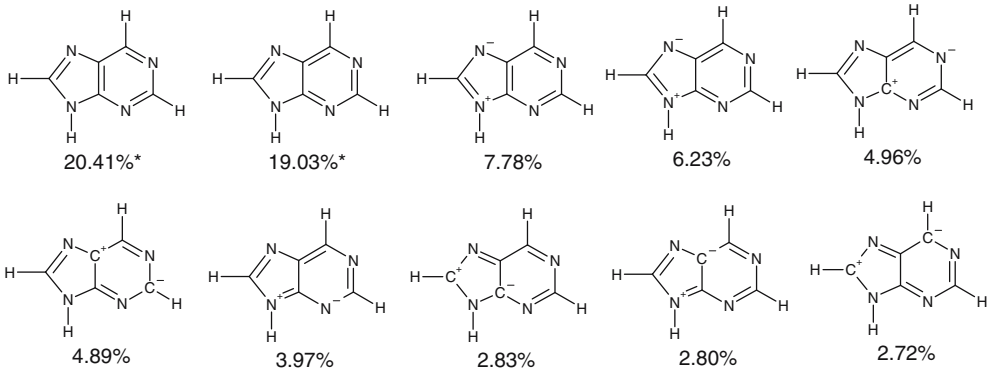


3.2.2 Imidazole

In imidazole, a nitrogen atom is introduced at the 3 position of pyrrole. The combination of the two heteroatoms slightly decreases the weighting of the covalent resonance structure in the NRT expansion to 56.82%. The ionic structure resulting from N1 to N3 charge transfer has a weighting of 12.67%, while the N1 to C4 charge transfer results in an ionic structure with weighting of 9.41%. The weightings for the singly ionic structure resulting from C2 to C5 charge transfer are about 6%. Therefore, the NRT expansion of imidazole is very similar to that of pyrrole in general, although the weighting for the covalent structure is smaller for imidazole in comparison, while the weightings for the ionic structures are larger. Among the results from HF, MP2, and CCD calculations, the weightings for all the major resonance structures are close to those of pyrrole. Again, the weighting for the covalent structure by B3LYP is bracketed by that of the HF results on the high end and by that of the MP2 and CCD results on the low end.

3.2.3 Purine

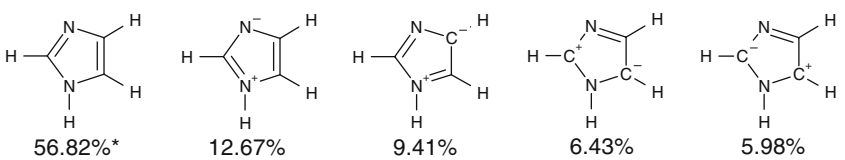
Before discussing the results for nucleobases, we look at an intermediate structure that is common to adenine and guanine, purine. Purine consists of a pyrimidine and an imidazole fused together, both of which satisfy the $4n+2$ rule. The two covalent structures of purine have weightings of 20.41 and 19.03%, respectively, whose sum is roughly the product of the weightings of the covalent structures of the two substructures individually, i.e. the value for pyrimidine (40.55%×2) times that for imidazole (56.82%). The major singly ionic structures include those resulting from an N1 to N3 charge transfer in imidazole and 1–4 charge transfer in pyrimidine.

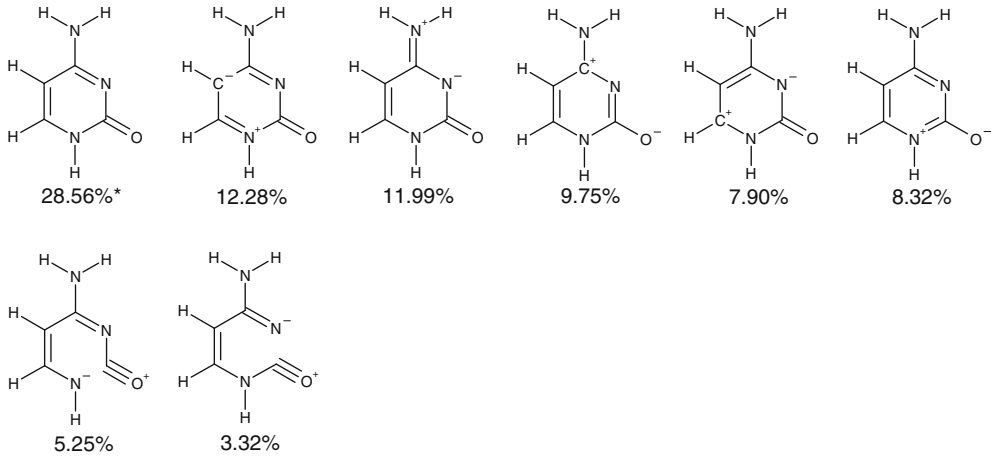


3.3 Nucleobases

3.3.1 Cytosine

We now analyze the NRT expansions for nucleobases, first for nucleobases with a single six-membered ring. The NRT expansion for cytosine is quite similar to that of 2-pyridone. All seven major resonance structures of 2-pyridone find their counterparts in the NRT expansion of cytosine. However, the covalent structure of cytosine has a weighting of 28.56%, which is much smaller than that of 2-pyridone (42.29%). All leading ionic structures of 2-pyridone can be found in the NRT expansion of cytosine, albeit some with larger weightings. One resonance structure with a weighting of 11.99% shows the charge transfer between the exocyclic NH_2 and N3.





Among the different methods, the HF result closely follows that of B3LYP, though with larger weighting for covalent structures and smaller weightings for ionic structures. The results from post-HF ab initio calculations fail to show the covalent structure as the dominant resonance structure at all. Instead, the structure with the largest weighting has an N1–C4 bond in the CCD results, and the covalent structure has only the second largest weighting (12.33%). In the MP2 results, the structure with the largest weighting has an N1–N3 bond, four other ionic structures have larger weightings than the covalent structure, and the covalent structure has only the sixth largest weighting (8.06%).

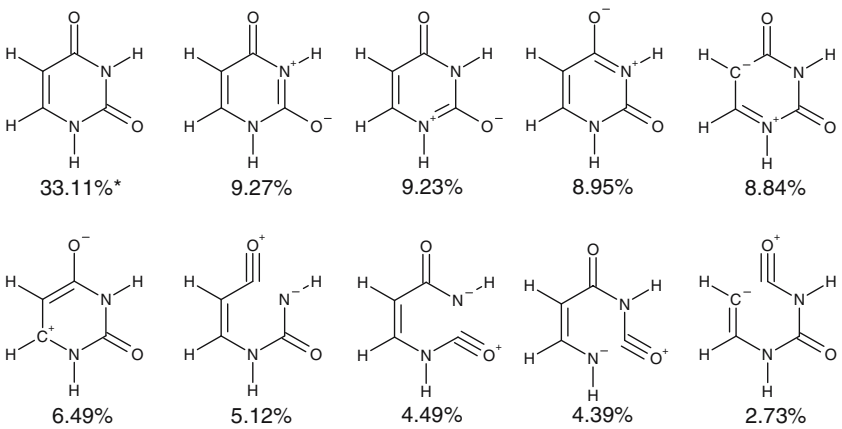
3.3.2 Uracil

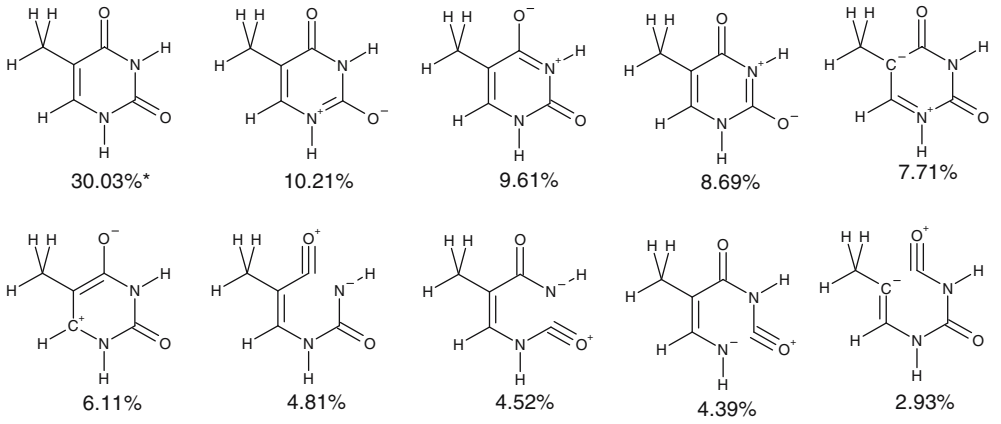
For uracil, the dominant resonance structure is the covalent structure with a weighting of 33.11%. Four of the five leading ionic structures involve charge transfer between one of the two exocyclic oxygens and an endocyclic atom, mostly nitrogen. The other major ionic structure shows charge transfer from N1 to C5, which is similar to the leading ionic structure in 2-pyridone. Other ionic resonance structures have a CO triple bond and a negative charge on an atom adjacent to the carbon in the triple bond.

The HF result again has all major resonance structures present, with larger weighting for the covalent structure (48.18%) and smaller weightings for the ionic structures. In the MP2 and CCD results, the covalent structure has the largest weighting. However, the weighting for the covalent structure is only slightly larger than those of the major ionic structures in both results, and the leading ionic structure is a "strange" structure with vicinal atoms connected in both results.

3.3.3 Thymine

The extra exocyclic $-CH_3$ group in thymine has very limited effect on the NRT expansion when compared with uracil. All covalent and ionic resonance structures in the NRT expansion of uracil appear in the NRT expansion for thymine, with only slight changes in their weighting values.



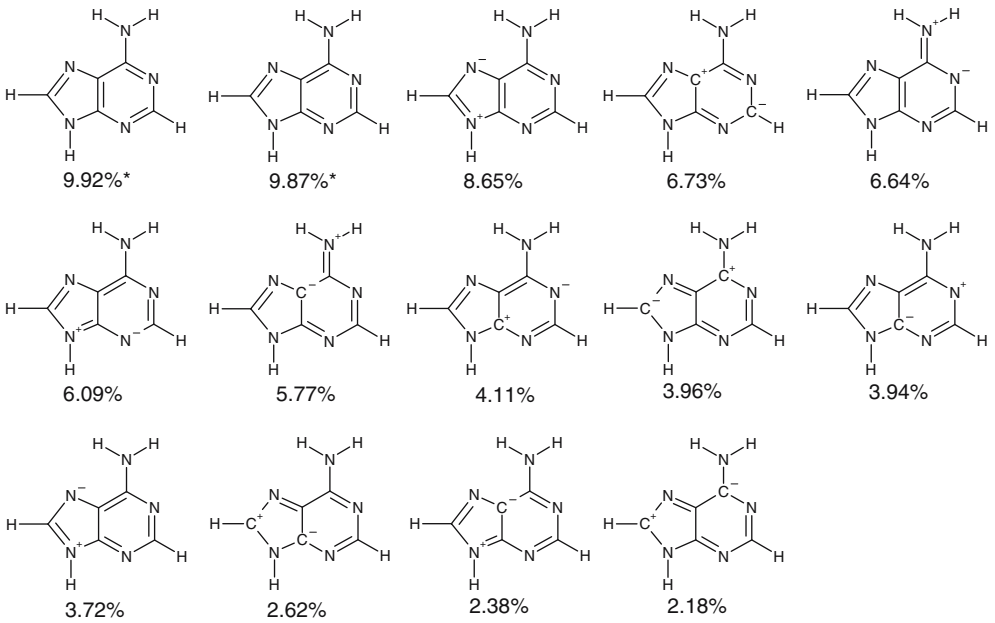


The HF result is comparable to the B3LYP result, with larger weighting for the covalent structure and smaller weightings for ionic structures. In the CCD result, the covalent structure is only the third contributor, and the two leading ionic structures that were found in the B3LYP results have larger weightings than the covalent structure here. In the MP2 result, a normal ionic structure and an ionic structure with N1 and O4 connected have larger weightings than the covalent structure. In both the CCD and MP2 results, other structures with vicinal atoms connected have weightings as large as 4.9%.

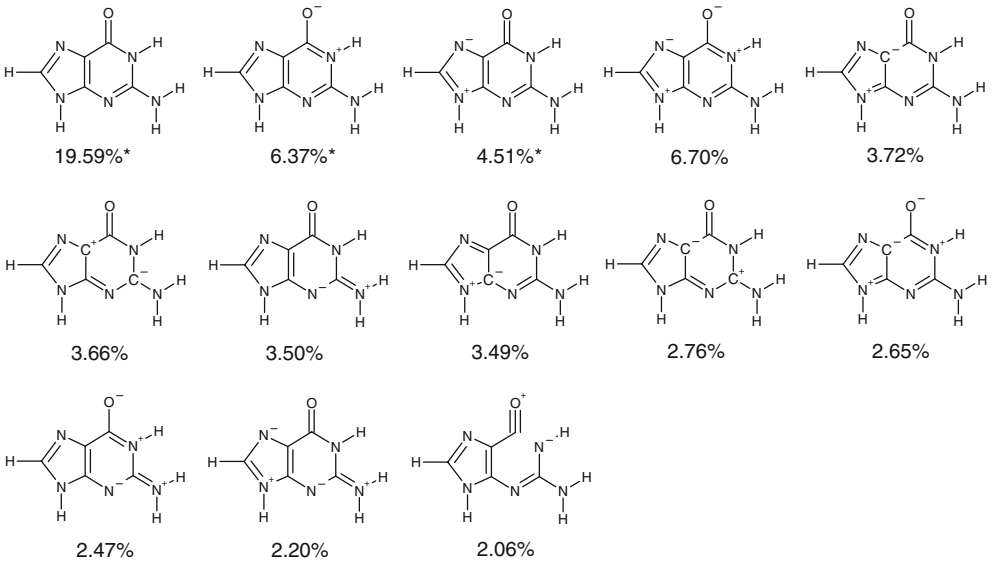
3.3.4 Adenine

The NRT structures of adenine that have weightings of more than 2% are listed below. Many more resonance structures with yet smaller weightings exist but are not listed here. The two covalent resonance structures have weightings of 9.92 and 9.87%, respectively, which are much smaller than those seen before for the single-ring systems and purine. However, considering that the covalent structure has a 56.82% weighting for imidazole, and about 30% for each of the two covalent structures of 2-aminopyridine, the low weighting for the covalent structure of adenine would naturally follow as the result of fusing a five-membered ring with a six-membered ring.

The 12 ionic resonance structures in the NRT expansion of adenine can be categorized into four groups. Group 1 involves charge transfer within the five-membered ring. There are four such structures, all of which have a counterpart in the imidazole NRT expansion. Group 2 comprises three structures resulting from charge transfer within the six-membered ring. The ionic structures resulting from charge transfer from N6 to the adjacent ring atoms form group 3. All structures in groups 2 and 3 have a counterpart in the NRT expansion of 1-aminopyridine. Group 4 has three structures featuring charge transfer between the five- and six-membered rings. Similar resonance structures exist in the NRT expansion of purine. Therefore, all leading ionic resonance structures of adenine can be traced to one or the other of its constitutive structural moieties.



In the HF results, the covalent structures are only the 3rd and 9th contributors with weightings of 8.81 and 4.42%, respectively. Instead, two ionic structures with charge transfer within the six-membered ring have the largest weightings. The post-HF ab initio methods give slightly larger weightings for the covalent structures than B3LYP. Some of the major ionic structures in the B3LYP result also have large weightings in the CCD and MP2 results, but others do not. Again, the CCD and MP2 results include structures with unbonded vicinal atoms connected to each other.



3.3.5 Guanine

The NRT expansions of 2-pyridone and 4-pyrimidone have demonstrated that the structural change from –CH=N– to –CO–NH– introduces a large disturbance in the molecular electron density and consequently a drastic decrease in the weightings of the covalent structures. Since guanine is characterized by a similar change with respect to adenine, we expected to see a large reduction in the weighting of guanine's covalent structure. Indeed, when we used the covalent structure as the only reference structure, all leading resonance structures are ionic. After some tests, we realized that two singly ionic structures are important, one with charge transfer from N1 to O6 and one with charge transfer from N9 to N7. Reasonable NRT expansions, more in keeping with standard organic chemistry concepts, were obtained when the covalent structure and the two ionic structures were used as reference. Since a different set of reference structures is used, the NRT expansion of guanine cannot be directly compared with that of adenine [5].

In the B3LYP result, the covalent structure has a weighting of 19.59%, which is about three times the value of that for the leading ionic structure. The reference ionic structure with charge transfer from N1 to O6 has a weighting of 6.37% and the ionic structure with charge transfer from N9 to N7 has a weighting of 4.51%. A doubly ionic structure that combines the above charge transfer modes has a similar weighting at 6.7%. Other major ionic resonance structures result from charge transfer within the five-membered ring, charge transfer within the six-membered ring, charge transfer between the exocyclic substituents and the six-membered ring, and combinations of the above.

As in all other cases, the HF result shows slightly larger weighting for the covalent structure. The two reference ionic structures both have large weightings at about 4%, although other ionic structures also have comparable weightings. In the MP2 result, the weighting for the covalent structure is 12.39%, while both reference ionic structures have weightings of less than 1%. Some of the major ionic structures in the B3LYP and HF results have large weightings in the MP2 results, too, but others do not, and structures occur in MP2 with connections between unbonded vicinal atoms.

To find the largest weighting for the covalent structure(s) in the HF results, smaller ones with B3LYP, yet smaller ones with MP2 and CCD, has been a running theme for all the molecules studied here. Guanine's "strange" ionic structures with significant weightings are also paralleled in the other molecules' MP2 and CCD results. This study therefore allows us to propose that the DFT method is a good approach to calculate the electron density for NRT analysis.

3.4 Aromaticity of heterocycles and nucleobases

Starting from the undecorated benzene and pyrrole molecules, we studied the effect of the structural modifications, i.e. the endocyclic heteroatoms and exocyclic substituents, on the aromaticity of the nucleobases. We calculated the NICS at the center of all rings for the nucleobases and for benzene, pyrrole, and many intermediate structures, as shown in Fig. 1.

The NICS values we calculated for benzene (−9.7 ppm) and pyrrole (−15.0 ppm) are in excellent agreement with literature values reported earlier by Schleyer et al. [6]. Substitut-

ing one H atom in benzene by an $–NH_2$ group in aniline yields a slight increase of 0.1 ppm in the NICS value. This is consistent with the small change in the weighting of the covalent structures in the NRT expansion. Substituting a CH group in benzene by an N atom reduces the NICS by about 1.5 ppm for pyridine, while the change is 2.5 ppm by going from aniline to 2-aminopyridine. Pyrimidine has a NICS value of −6.5 ppm, which constitutes a 1.7 ppm decrease from pyridine. 4-Aminopyrimidine is still aromatic with a NICS of −5.5 ppm. The NICS increases to −7.3 ppm in adenine after fusing the imidazole ring to 4-aminopyrimidine. On the other hand, the change from –CH=CH– in benzene to –NH–CO– in 2-pyridone drastically reduced aromaticity of the latter, as indicated by its NICS of −3.1 ppm. As a consequence, cytosine, uracil and thymine all are nonaromatic with NICS values within a range of −1.2 to −1.6 ppm. Compared with adenine, the aromaticity of guanine is much reduced (NICS = −3.1 ppm), also a result of the –NH–CO– fragment. The change in NICS from benzene to the nucleobases is consistent with the changes in their NRT expansions.

Pyrrole has a NICS of −15.0 ppm, which is due to its smaller size. Substituting its 3-CH group with an N atom to yield imidazole slightly reduces the aromaticity (NICS = −14.0 ppm). Fusing this with pyrimidine further reduces the aromaticity of the five-membered ring in purine to −11.7 ppm. The NICS of the five-membered rings in adenine (−11.9 ppm) and guanine (−12.5 ppm) demonstrates similar aromaticity as in purine.

4 Conclusions

We have studied the resonance structures and aromaticity of the five nucleobases. The NRT analysis indicates that, starting from benzene, progressive structural modifications toward the nucleobases introduce disturbances of various degrees. The substitution of –CH– by an aromatic N atom, and substitution of an H atom by an $–NH_2$ group are associated with only a small change in the weighting of the covalent structure. On the other hand, changing –CH=N– to –CO–NH– yields a large decrease in the weighting of the covalent structure and large increase in the weightings of the ionic structures. For cytosine, uracil, and thymine, the covalent structures have weightings of about 30% and the leading ionic resonance structures have weightings as large as 10%. Even further down this trend, the covalent structures for adenine and guanine have weighting of only about 20%.

Comparing the results calculated with different methods, the weightings of the covalent structures in the B3LYP results are typically bracketed by those from the HF calculations on the higher side and by those from the MP2 and CCD results on the lower side. This is consistent with the fact that DFT methods include electron correlation effects to some extent, while HF does not. The MP2 and CCD methods, however, seem to "overemphasize" electron correlation effects in this context, yielding "strange" ionic structures with connections between unbonded vicinal atoms with significant weightings for molecules with branching skeletons. For this reason, DFT seems to be an appropriate choice for calculating the molecular electron density needed for NRT analysis.

The calculated NICS indicate that the six-membered rings in cytosine, uracil, thymine and guanine are essentially nonaromatic with NICS values falling within a range of −1 to −3 ppm, presumably as the result of the heavy structural modifications from benzene. The six-membered ring in adenine retains much of the aromaticity of benzene with a calculated NICS value of −7.3 ppm. On the other hand, the five-membered rings in both adenine and guanine have NICS values of about −12 ppm. This is only marginally less negative than that of pyrrole, indicating little change in their electronic configurations.

Acknowledgements The authors wish to thank Prof. Frank A. Weinhold for helpful discussions. This research was supported by the Intramural Research Program of the NIH, National Cancer Institute, Center for Cancer Research. Access to the high-performance Biowulf Linux cluster of CIT, NIH, for part of the calculations is gratefully acknowledged. GYS thanks the Pittsburgh Supercomputing Center for computer time (MCB030011P).

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