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A computational study on substituted diazabenzenes

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The results of computational calculations on the aromaticity of the monosubstituted diazabenzenes (pyridazine, pyrimidine, and pyrazine) are reported herein. The aromaticity of the parent heterocycle was enhanced by substitution of strong electron-withdrawing groups. The effects of the position of the substituent on the aromaticity and the stability of the system were also investigated by studying all possible derivatives of the systems.

Key Words: Aromaticity, NICS, pyridazine, pyrimidine, pyrazine

Introduction

In organic chemistry, the structures of some rings of atoms are more stable than expected. Aromaticity can be considered as the stronger stabilization of conjugated unsaturated bonds, lone pairs, or empty orbitals in a ring, which cannot be due to only conjugation alone. It can also be a result of cyclic delocalization and of resonance.[1−3]

This is usually considered to be the case because the electrons are free to move around circular arrangements of atoms that are alternately single- and double-bonded to one another. These bonds may be seen as a hybrid of a single bond and a double bond; each bond in the ring can be considered as identical to the others. This commonly seen model of aromatic rings, based on the idea that benzene is formed from a carbon ring with 6 members and alternating single and double bonds (cyclohexatriene), was developed by Kekulé. The model for benzene consists of 2 resonance forms, which corresponds to the double and single bonds superimposing to give rise to 6 bonds, each a 1.5 bond. Benzene is a more stable compound than would be expected without accounting for charge delocalization.

Pyridazine (1,2-diazabenzene), pyrimidine (1,3-diazabenzene), and pyrazine (1,4-diazabenzene) are diaza analogs of the benzene molecule. They are isoelectronic with benzene as they contain 6π electrons for aromatic delocalization. However, the perfect aromaticity of benzene is disturbed by centric substitution of 2 nitrogen

atoms in the case of the systems under consideration, such that the electronegative nitrogens hold some of the ring electrons to prevent the perfect delocalization of the 6π electrons.

A literature survey suggests that the diamino-dinitro pyridazine derivatives were not examined before. However, 2,6-diamino-3,5-dinitropyrazine was considered theoretically by Klapötke's group as a candidate for a high energy density material.[4] Millar et al.[5] intensively studied the nitration and N-oxidation of diaminopyrimidines, with a goal of synthesizing novel insensitive high energy materials as target molecules. They achieved the synthesis of 5-nitro-2,4,6-triamino-pyrimidine-1,3-dioxide and 5-nitro-4,6-diaminopyrimidine-1,3-dioxide successfully.

Method of calculation

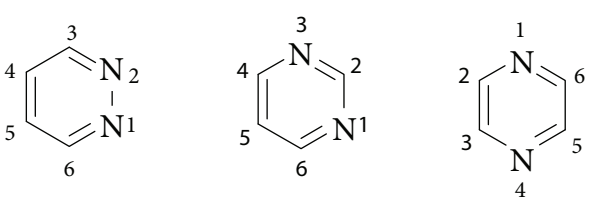
All computations were performed according to the density functional theory method using the hybrid functional B3LYP with 6-31G(d,p) and cc-PVTZ basis sets as implemented in the Gaussian 03 package.[6] The geometry-optimized structures are obtained by restricted closed-shell formalism and without any symmetry restrictions.

The vibrational analysis for each structure does not yield any imaginary frequencies, which indicates that the structure of each molecule corresponds to at least a local minimum on the potential energy surface. The normal mode analysis was performed for $3N-6$ vibrational degrees of freedom, N being the number of atoms forming the system.

Absolute NMR shielding values[7] were calculated using the gauge-independent atomic orbital method[8] employing the 6-31G(d,p) basis set over B3LYP/6-31G(d,p) and cc-PVTZ optimized geometries. Nucleus-independent chemical shift (NICS) data were obtained by computing the absolute NMR shielding at the ring center, NICS(0), and at 0.5 Å NICS(0.5) and 1.0 Å NICS(1.0) above the center of the ring, respectively.

Results and discussion

The present work deals with the aromaticities of diaza analogs of benzene and their monofluoro-, nitro- and amino-substituted derivatives. The effects of fluoro (an activating electron-withdrawing group), nitro (deactivating group), and amino (activating group) substitution on the aromatic character of the parent pyridazine (**1**), pyrimidine (**2**), and pyrazine (**3**) systems were investigated in terms of stability (total electronic energies) and magnetic (NICS) criteria. The numbering of the heterocycles can be seen in the Figure. The molecules studied here are named by indicating the number of the parent heterocyclic compound (**1**-**3**) together with the position and the type of the substituent. The short name for 5-nitropyrimidine is **2_5_NO$_2$**.



1 **2** **3**

Figure. The numbering of pyridazine (**1**), pyrimidine (**2**), and pyrazine (**3**).

Aromaticity is a combination of some properties in cyclic delocalized systems. In general, aromaticity is discussed in terms of energetic, structural, and magnetic criteria.[1,9–13] The NICS was introduced by Schleyer in 1996 as a simple and efficient probe for aromaticity.[14] It is expressed by the computed value of the negative magnetic shielding at some selected point in space, usually at a ring or cage center. It is based on a probe without any basis functions (Bq), which is placed at or above the geometric center of a conjugated ring. Its calculated isotropic NMR chemical shift indicates the aromaticity of the ring, either as an individual moiety in a polycyclic compound or as a molecule. The B3LYP/6-31G(d) method was applied by Schleyer[14] for the computation of aromaticities for a series of aromatic, antiaromatic, or nonaromatic compounds; it was proposed that negative NICS values denote aromaticity (–11.5 for benzene, –11.4 for each ring of naphthalene), whereas large positive NICS values denote antiaromaticity (28.8 for cyclobutadiene) and small NICS values indicate nonaromaticity (–3.1 for 1,3-cyclopentadiene). NICS data for the present systems were calculated with the B3LYP/6-31G(d,p) method. The justification of the applied method was achieved by obtaining –11.0, 26.1, and –3.0 for benzene, cyclobutadiene, and cyclopentadiene, respectively.

NICS may be considered as a useful indicator of the aromatic character of a system and usually correlates well with the other energetic, structural, and magnetic criteria for aromaticity.[15–18] Resonance energies and magnetic susceptibilities are measures of the overall aromaticity of polycyclic compounds, but they do not provide information about the individual rings. However, NICS is an effective probe for the local aromaticity of individual rings of polycycles.

The relative zero-point-corrected electronic energies and NICS data for the compounds are given in the Table. Pyrimidine was found to be most stable isomer among the 3 diazabenzene systems with the 2 methods applied. Although the instability of pyridazine was expected with respect to the others due to the existence of vicinal aza substitution, a consideration of the polar contributors helps to explain the difference between pyrazine and pyrimidine. The same order of stability is followed by the substituted derivatives, as well. Substituted pyrimidines possess lower energies than the others. A similar theoretical outcome was reported about the aromaticity of substituted diazanaphthalenes.[19]

NICS data were calculated at the ring center (NICS(0)) and above the center at NICS(0.5) and NICS(1.0). The NICS value can be affected by other structural features that are not directly related to the aromatic ring current. The maximum ring current is located somewhat above the ring, where the other factors are found to be minimized.[20] This argument is confirmed by the findings here, as greater NICS indices were calculated above the ring. A drastic decrease from –11.5 to around –6.0 ppm was observed with double aza substitution on benzene. The idea of substitution of the hydrogens with a heteroatom or group withstands the fact that electron-withdrawing groups can pull the electrons located on the electronegative nitrogens of the ring, and thus they can participate in the ring current, leading a better conjugation. Therefore, the decreased aromaticity could be gained back. Recently, NICS data have been confirmed to be strongly dependent on the method and the basis set applied, although the trend of aromaticity does not change.[21] This is further confirmed by the present study. The aromaticities of compounds **2** and **1** were calculated to be the greatest and the smallest among the series, respectively, but absolutely smaller values were obtained with the cc-PVTZ basis set.

In fact, the data in the Table indicate parallel results with the above argument. In the case of pyridazine (**1**), greater aromaticity indices were obtained by the location of **F** or $\mathbf{NO}_2$ on position 3 than on position 4. On the other hand, amino substitution, as an activating group, decreased the aromaticity of the heterocycle.

Table. Relative energies (kcal/mol) and NICS data (ppm) for the substituted heterocyclic systems.

Structure	Energy	Energy	NICS(0)	NICS(0.5)	NICS(1.0)	NICS(0)
	6-31G(d,p)	cc-PVTZ	6-31G(d,p)	6-31G(d,p)	6-31G(d,p)	cc-PVTZ
1	22.5	22.4	–5.84	–7.73	–7.32	–5.02
2	0.0	0.0	–6.5	–8.61	–7.95	–5.56
3	4.1	4.1	–6.32	–8.11	–8.09	–5.25
1_3_F	24.1		–7.39	–9.41	–9.23	
1_4_F	26.3		–7.13	–9.85	–9.81	
2_2_F	0.0		–7.92	–10.03	–10.02	
2_4_F	0.0		–8.4	–10.39	–10.38	
2_5_F	6.3		–8.02	–9.89	–10.33	
3_2_F	4.7		–8.32	–10.27	–10.21	
1_3_NO_2	22.9		–7.37	–9.33	–9.17	
1_4_NO_2	21.8		–7.19	–9.1	–9.01	
2_2_NO_2	3.2		–8.1	–10.33	–10.18	
2_4_NO_2	0.6		–8.37	–10.41	–10.41	
2_5_NO_2	0.0		–7.5	–9.86	–9.86	
3_2_NO_2	3.8		–8.02	–9.97	–9.89	
1_3_NH_2	27.1		–5.01	–6.65	–6.44	
1_4_NH_2	30.3		–6.04	–7.68	–7.66	
2_2_NH_2	0.0		–4.86	–6.71	–6.53	
2_4_NH_2	2.4		–5.71	–7.22	–7.12	
2_5_NH_2	11.8		–6.94	–9.01	–8.87	
3_2_NH_2	8.3		–5.76	–7.34	–7.16	

The unpaired electrons on the amino nitrogen join the conjugation with the main ring; however, the disturbed aromatic ring current cannot be repaired. These findings also hold for the other 2 cases. Another outcome of the present computational calculations is that the position of the substituent has a great effect on the aromaticity of the system. In the case of the pyrimidine (**2**) system, **F** or $\mathbf{NO}_2$ substitution on position 2 is less effective than the substitution on position 4. Because point 2 has already become quite positive by being situated between 2 aza points, the electron-withdrawal from 2 nitrogens by **F** or $\mathbf{NO}_2$ is not that efficient.

In conclusion, the effect of a monoheteroatom or group substitution on the aromaticity of pyridazine, pyrimidine, and pyrazine was investigated by computational calculations at the level of the density functional theory. The B3LYP/6-31G(d,p) and B3LYP/cc-PVTZ methods were applied to obtain geometry-optimized structures, energies, and the aromaticity indices (NICS). NICS data were calculated both at the center and above the ring. The results indicated that the decrease of aromaticity by double aza substitution on benzene can be gained back by strong electron-withdrawing groups. However, activating groups have an opposite and unfavorable effect on the aromaticity of the system. Moreover, the closer the position of the substituent to the aza points, the greater the aromaticity of the system.

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