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Strong Conformational Preferences of Heteroaromatic Ethers and Electron Pair Repulsion

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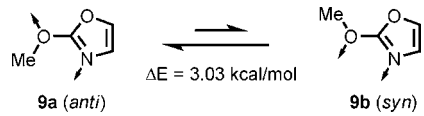
ABSTRACT

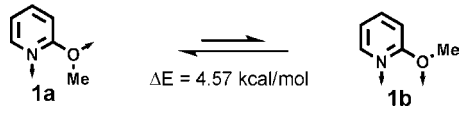


9a (*anti*) **9b** (*syn*)

Electron-pair repulsion in 2-methoxyheteroarenes is important for *N*, but not for *O* or *S* heteroatoms.

Structural factors which cause strong acyclic conformational preferences can be harnessed for the design of biologically active molecules or ligands which direct enantioselective catalysis. An ether oxygen which links a heteroaromatic ring to another subunit in a molecule can operate to orient a chain in conformational space by virtue of its lone pairs. 2-Methoxypyridine (**1**) provides a simple introduction to the issues involved, with its two planar conformations. These can be distinguished with regard to the orientation of the in-plane oxygen lone-pair electrons. In **1a**, the vectors corresponding to the axes of the lone pairs of N and O are at an angle of ca. 120°, whereas in **1b** the lone pair axes are parallel (ca. 0°) (Scheme 1).

Scheme 1



1a **1b**

This paper discusses energy differences and rotational barriers between such rotameric forms and the barriers to rotation for various heterocycles as determined by density functional calculations at the RB3LYP/6-31G* level.[1]

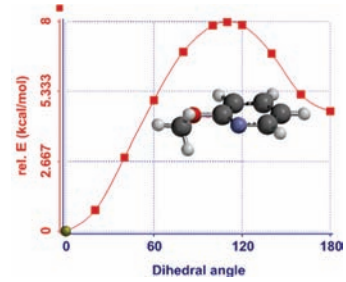


Figure 1. 2-Methoxypyridine (**1**).

For purposes of discussion in this paper, structure **1a** will be called the *anti* conformer, and structure **1b** will be called the *syn* conformer, using as reference the relative orientations of the hetero ring and OMe in-plane lone pairs. As will be evident, the energy differences between *syn*- and *anti*-rotamers can be large enough to ensure that one form, the *anti* conformer, predominates heavily for *N*-heteroarenes, providing a rational

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basis for ligand design with such compounds. A number of key compounds are considered herein and analyzed to afford a perspective that permits the assignment of conformational preference to many oxygen-substituted *N*-heteroarenes.

All our results are consistent with the physically reasonable proposition that repulsion between in-plane nonbonding electron lone pairs of *N*-heteroarenes is a significant destabilizing factor. All the calculated energies for the methoxy-substituted heteroarenes discussed below were obtained using the DFT method and the RB3LYP/6-31G* basis set.

2-Methoxypyridine (1). The results of DFT analysis of **1** are summarized graphically in Figure 1.[2] The *anti* form **1a** was found to be more stable than the *syn* form **1b** by about 4.57 kcal/mol. The barrier to rotation, which is fairly flat between 100° and 120° (degrees of rotation from the *anti* form), is about 7.98 kcal/mol at 110°. This barrier is greater than that for 3-methoxypyridine (3.03 kcal/mol)[2] or 4-methoxypyridine (4.33 kcal/mol) but less than that calculated for methoxybenzene which peaks at 3.0 kcal/mol at a dihedral angle of 90°.

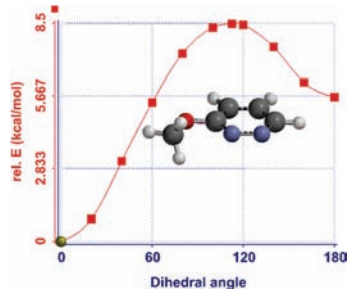


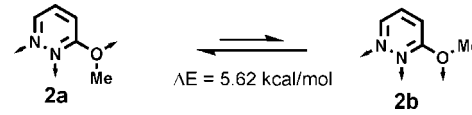
Figure 2. 3-Methoxypyridazine (**2**).

3-Methoxypyridazine (2). The results of the DFT calculations for **2** are displayed in Figure 2, which reveals that the *anti* form **2a** is more stable than the *syn* form **2b** by about 5.62 kcal/mol (Scheme 2), that is ca. 1 kcal/mol higher than the corresponding difference between the 2-methoxypyridines **1a** and **1b**. The difference probably reflects a somewhat higher *syn* destabilization of **2b** which has three lone pairs in a *syn* relationship. The barrier to interconversion of **2a** and **2b** is ca. 8.47 kcal/mol, peaking at a 112.7° rotation of C−OMe from **2a**. The barrier to rotation for **2a** ⇌ **2b** (8.47 kcal/mol) is slightly larger than that for **1a** ⇌ **1b** (7.98 kcal/mol), possibly as a result of greater MeO to ring electron delocalization for the more π-electron-deficient pyridazine ring relative to the pyridine system.

2,5-Dimethoxy-1,4-pyrazine (3), 4,6-Dimethoxy-1,3-pyrimidine (4), and 3,6-Dimethoxy-1,2-pyridazine (5). On the basis of the results outlined above demonstrating the greater stability of the *anti* conformers **1a** and **2a** vs the corresponding *syn* conformers, it is to be expected that the stable forms of **3**, **4**, and **5** could be the *anti* structures **3a**, **4a,** and **5a** rather than the *syn* structures **3b**, **4b**, and **5b**. The calculated energies for **3**, **4**, and **5** are shown in Figures 3−5.

(2) The energy difference between the two in-plane rotamers of 3-methoxypyridine (*syn* and *anti*) is less than 0.05 kcal/mol.

Scheme 2



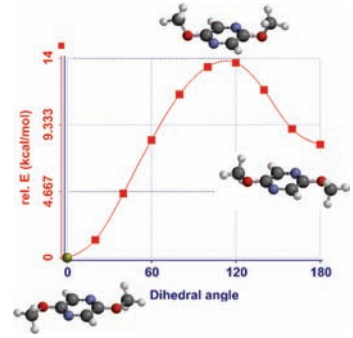


Figure 3. 2,5-Dimethoxy-1,4-pyrazine (**3**).

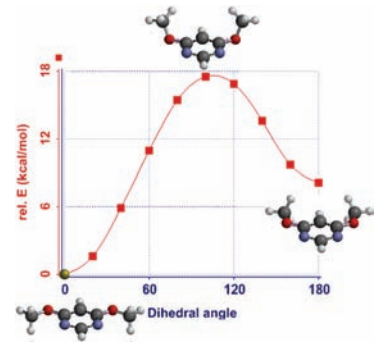


Figure 4. 4,6-Dimethoxy-1,3-pyrimidine (**4**).

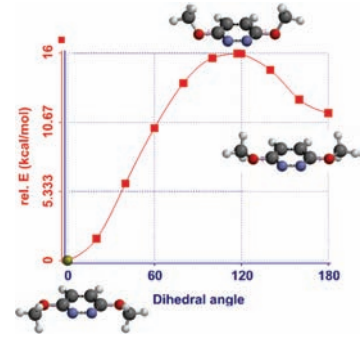
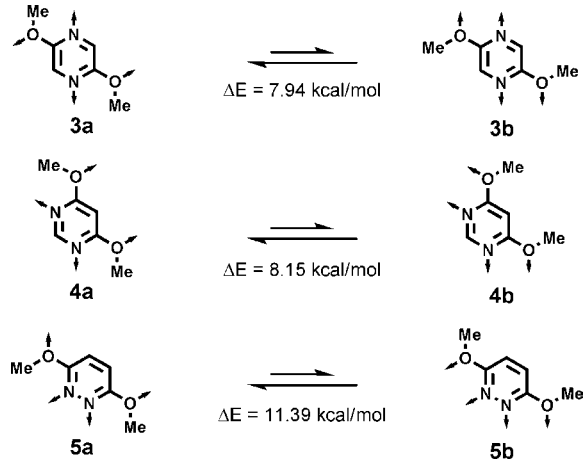


Figure 5. 3,6-Dimethoxy-1,2-pyridazine (**5**).

The *anti*,*anti*-forms **3a**, **4a**, and **5a** are more stable than the *syn*,*syn*-forms **3b**, **4b**, and **5b** by 7.94 kcal/mol, 8.15 kcal/mol, and 11.39 kcal/mol (Scheme 3). The difference in energy of the dimethoxypyridazine conformers **5a** and **5b** (11.39 kcal/mol) is just about two times that for the monomethoxypy-

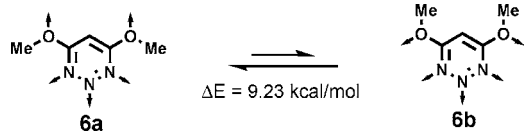
Scheme 3



ridazine conformers **2a** and **2b** (2 × 5.62 = 11.24 kcal/mol), which indicates the absence of unusually large electron pair repulsion for a series of four consecutive *syn* lone pairs.

4,6-Dimethoxy-1,2,3-triazine (6). A conformational analysis of this structure was undertaken to investigate further the question of whether the energy difference between the *anti,anti*- and *syn,syn*-forms **6a** and **6b** might be enhanced by the alignment of *five* consecutive lone pairs in **6b**.

Scheme 4



The results, which are summarized in Scheme 4 and Figure 6, clearly indicate that there is no such enhancement, since the energy difference between **6a** and **6b** is just 9.23 kcal/mol, somewhat smaller than the difference for the corresponding dimethoxypyridazine conformers **5a** and **5b** (11.39 kcal/mol). The barrier to simultaneous rotation of the two methoxy groups starting with the *anti,anti*-form **6a** is 18.06 kcal/mol at 100°.

2-Methoxyfuran (7) and 2-Methoxythiophene (8). We next studied the conformational preferences and rotational barriers for the *anti*- and *syn*-coplanar forms of 2-methoxyfuran (**7**) and 2-methoxythiophene (**8**) with interesting results. The results of calculations on *anti*-2-methoxyfuran (**7a**) and its *syn*-rotamer (**7b**) are shown in Scheme 5 and Figure 7.

The *anti*-form (**7a**) is less stable than the *syn*-form (**7b**) in the 2-methoxyfuran case. The barrier to rotation is 2.09 kcal/mol, somewhat lower than that for anisole and considerably lower than for, e.g., 2-methoxypyridine (7.98 kcal/mol). The case of the 2-methoxythiophene (**8**) (Figure 8) is similar to the furan series: the *anti*-form **8a** again is less stable than the *syn*-form **8b** by 0.99 kcal/mol. The barrier to rotation from **8b** is 1.90 kcal/mol, nearly the same as for the furan analogue. These results for the furan **7** and the thiophene **8** indicate that the lone

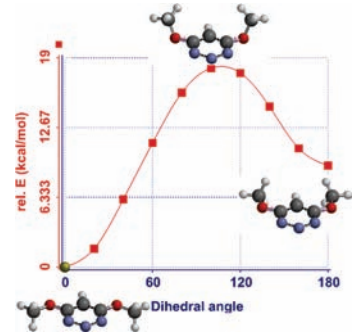
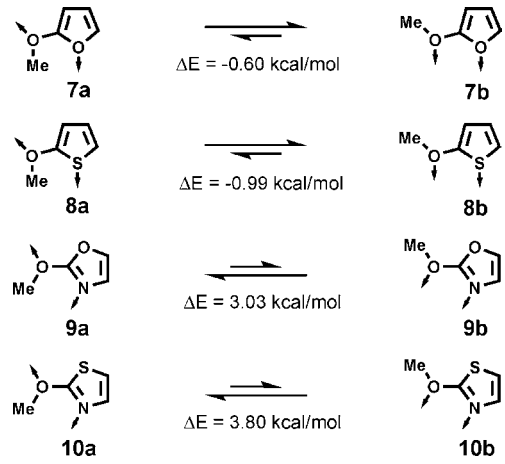


Figure 6. 4,6-Dimethoxy-1,2,3-triazine (**6**).

Scheme 5



pair repulsive interaction that destabilizes the *syn*-form relative to the *anti*-rotamer is insignificant, possibly because the lone pair at O of furan and that at S of thiophene are held much more tightly (i.e., lower-energy nonbonding orbital) than is the case for N of pyridine and related N-heteroaromatic structures.

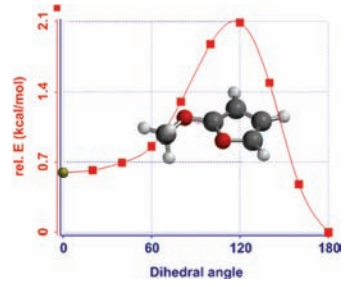


Figure 7. 2-Methoxyfuran (**7**).

2-Methoxy-1,3-oxazole (9) and 2-Methoxy-1,3-thiazole (10). The results outlined above for the methoxy *N*-heteroarenes **1**−**6** and for 2-methoxyfuran (**7**) and 2-methoxythiophene (**8**) suggest that the *N-anti,O-syn*-planar rotamer of 2-methoxy-1,3-

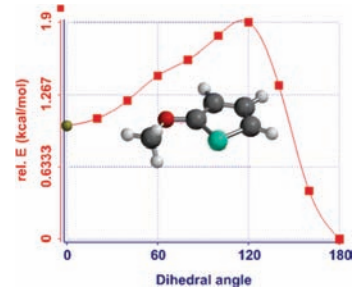


Figure 8. 2-Methoxythiophene (**8**).

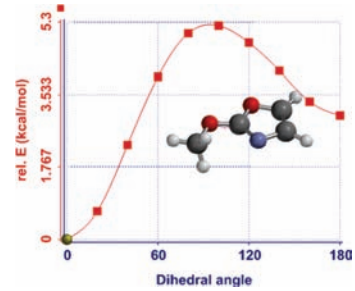


Figure 9. 2-Methoxy-1,3-oxazole (**9**).

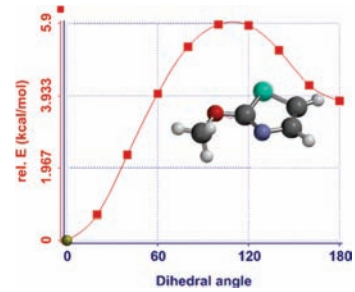


Figure 10. 2-Methoxy-1,3-thiazole (**10**).

oxazole (**9a**) and 2-methoxy-1,3-thiazole (**10a**) should be more stable than the corresponding *N-syn*,*O-anti*-rotamers **9b** and **10b**. Computations fully support this expectation. The results for 2-methoxy-1,3-oxazole (**9**) are summarized in Scheme 5 and Figure 9, and those for 2-methoxy-1,3-thiazole are summarized in Scheme 5 and Figure 10.

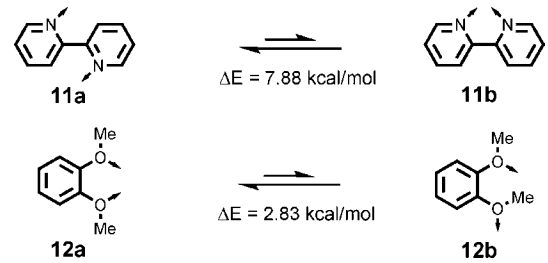
Discussion. The DFT calculations (RB3LYP/6-31G* basis set), the key results of which are summarized above in Figures 1−10, suggest that 2-substituted ethers of 1-*N*-azaheteroaromatic compounds have a strong preference for the planar conformation in which the in-plane nonbonding electrons avoid one another, thus favoring the anti arrangement. Detailed numerical results are provided in the Supporting Information. In a physical sense, the greater stability of the *anti*- vs *syn*-rotamer can be thought of as the result of electrostatic repulsion between those in-plane *n*-electrons. The effect is large enough (>3 kcal/mol) to provide a basis for designing protein binding or catalytic ligands. There is no such preference with O or S as heteroatoms, as shown for the results obtained for the furan, thiophene, oxazole, and thiazole derivatives **7**−**10**. We believe that this conformational preference for N-heteroaromatic systems containing the subunit **11** may be very general. It plays a significant role, for example, in the demonstrated preference for a U-shaped binding pocket for pyridazine diether derivatives of cinchona alkaloids in the catalytic enantioselective dihydroxylation of olefins.[3]

Electron-pair repulsion in directly bonded atoms is generally regarded as responsible for bond weakening (e.g., the peroxide O−O bond) and the gauche effect[4] (e.g., for acyclic hydrazines and peroxides). It also provides a basis for explaining the lower acidity of the conjugate acid of pyridazine (2.33) vs pyrimidine (1.30) or pyrazine (0.6) and the lower energy $n \rightarrow \pi^*$ electronic transition for pyridazine (29 740 cm^{-1}) vs pyrimidine (34 250 cm^{-1}) or pyrazine (31 620 cm^{-1}).[5]

Electron pair electron repulsion is significant between two sp^2 nitrogens, even if the connecting atom path is increased from one to two, since calculations show that the stable conformer of 2,2′-bipyridyl is the *anti* coplanar from **11a** rather than the *syn* structure **11b** (see Supporting Information).[6,7]

On the other hand, calculations also show that the stable planar conformer of 1,2-dimethoxybenzene is **12a**, not **12b** (Scheme 6). In this case, attenuation of electron pair repulsion is expected not only because of the oxygen heteroatoms but also because of the larger intervening path. In the case of the much studied dimethoxyethane, the gauche rotamer is the global energy minimum, as expected from the anomeric effect (or in frontier orbital terms $n \rightarrow \sigma^*$ delocalization).[7] This case illustrates another important instance of a sizable (2.6 kcal/mol) acyclic conformational preference that can be useful in molecular design.

Scheme 6



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Supporting Information Available: Tables of numerical results and figures for all DFT calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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