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Differential Effects of Nitrogen-Substitution in 5- and 6-Membered Aromatic Motifs

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Dedicated to Rolf Huisgen in honor of his 100th birthday and contributions to cycloaddition chemistry

Abstract

The replacement of carbon with nitrogen can affect the aromaticity of organic rings. Nucleus-independent chemical shift (NICS) calculations at the center of the aromatic π-systems reveal that incorporating nitrogen into 5-membered heteroaromatic dienes has only a small influence on aromaticity. In contrast, each nitrogen incorporated into benzene results in a sequential and substantial loss of aromaticity. The contrasting effects of nitrogen-substitution in 5-membered dienes and benzene are reflected in their Diels–Alder reactivities as dienes. 1,2-Diazine experiences a 99 billion-fold increase in reactivity upon nitrogen-substitution at the 4- and 5-positions, whereas a 5-membered heteroaromatic diene, furan, experiences a comparatively incidental 62-fold increase in reactivity upon nitrogen-substitution at the 3- and 4-positions.

Graphical Abstract

Unusual reactivity of azadienes! The Diels–Alder reactivity of a 1,2-diazine increases by 10^{11}-fold upon nitrogen-substitution, whereas in furan, nitrogen-substitution results in only a 10^2-fold rate-enhancement. NICS calculations reveal that this dichotomy is related to how nitrogen-substitution affects the aromaticity of the azadienes.
Aromaticity is a central concept in organic chemistry as a congener of chemical reactivity. For example, aromaticity manifests in the diene character of aromatic dienes that participate in Diels–Alder reactions. In this regard, Levandowski and Houk have shown that the Diels–Alder reactivities of 5-substituted cyclopentadienes and 3-substituted cyclopropenes are related to the hyperconjugative aromaticity or antiaromaticity induced by the substituent at the saturated center. Hyperconjugative antiaromaticity has since been applied to develop highly reactive cyclopentadienes for click-chemistry applications.

How nitrogen-substitution affects aromaticity is an unsettled affair of great interest to theoretical and organic chemists. Computational chemistry groups have extensively studied the Diels–Alder reactivity trend of the azabenzenes shown in Scheme 1. Computationally, the Diels–Alder reactivity increases by $10^4$- to $10^5$-fold with each nitrogen-substitution. Houk and coworkers have shown that the aromaticity of the azabenzenes measured by nucleus-independent chemical shift (NICS) calculations at the center of the ring and isodesmic aromatic stabilization energies correlates with the Diels–Alder reactivity of the azabenzenes. Other aromaticity indices such as NICS(1), isomerization stabilization energies, and harmonic oscillator models of aromaticity (HOMA) based on bond-length equalization suggest that the azabenzenes have aromaticities similar to that of benzene. These indices have inspired alternative explanations for the azabenzene reactivity trend that do not invoke aromaticity.

Ess, Bickelhaupt, and coworkers attributed the Diels–Alder reactivity trend in Scheme 1 to nitrogen polarizing the diene electrons away from the carbon atoms involved in bond formation. They postulated that this polarization increases the Diels–Alder reactivity by reducing the closed-shell (Pauli) repulsion between the occupied π-molecular orbitals of the diene and dienophile. The lower energy of the tetrazine unoccupied molecular orbitals is similar aromaticity
Diels–Alder $k_{rel} = 68$

different aromaticity
Diels–Alder $k_{rel} = 9.9 \times 10^{10}$

Keywords
aromaticity; cycloaddition; density functional calculations; kinetics
Diels–Alder reactions of furans and 1,3,4-oxadiazoles have widespread use in organic synthesis. Despite the synthetic utility of furans and 1,3,4-oxadiazoles as dienes, little is known about their relative Diels–Alder reactivities. Sauer (who was a student of Rolf Huisgen) and coworkers studied the Diels–Alder reaction of a 2,5-bis(methoxycarbonyl)-1,3,4-oxadiazole with cyclooctyne shown in Scheme 3. When less than one equivalent of cyclooctyne is used, the furan cycloadduct is obtained in 73% yield. Excess cyclooctyne results in the formation of a 2:1 cycloadduct in a similar 66% yield. The subsequent cycloaddition of the furan cycloadduct following the 1,3,4-oxadiazole cycloaddition is in contrast to tetrazine and triazine cycloadditions, in which the pyridine and 1,2-diazine cycloadducts do not undergo subsequent cycloadditions with cyclooctyne. This observation led Sauer and coworkers to suggest that furans and 1,3,4-oxadiazoles have similar reactivities.

Whereas the effects of nitrogen-substitution on the Diels–Alder reactivity of 6-membered cyclic dienes have been studied thoroughly, the extension of these effects to Diels–Alder reactions of 5-membered heteroaromatic dienes is unknown. To discern how nitrogen-substitution at the 3- and 4-positions of furan affects Diels–Alder reactivity, we measured the experimental second-order rate constants for the Diels–Alder reactions of 2,5-bis(trifluoromethyl)furan (1) and 2,5-bis(trifluoromethyl)-1,3,4-oxadiazole (1N) with endo-bicyclo[6.1.0]non-4-ynyl (BCN) with NMR spectroscopy (Scheme 4). We found the second-order rate constants to be $1.8 \times 10^{-5}$ M$^{-1}$s$^{-1}$ for 1 and $1.3 \times 10^{-4}$ M$^{-1}$s$^{-1}$ for 1N. These rate constants differ by only 7.2-fold, indicating that the extraordinary rate-enhancement observed in the azabenzene series does not extend to the furan scaffold.

To understand how nitrogen-substitution affects the Diels–Alder reactivity of 5- and 6-membered aromatic dienes, we studied computationally the Diels–Alder reactivities of ethylene with the 5-membered heteroaromatic dienes furan (1), pyrrole (2), thiophene (3), their 3,4-diaza analogs (1N–3N), the 5- and 6-membered non-aromatic dienes cyclopentadiene (4) and cyclohexadiene (5), their 2,3-diaza analogs (4N and 5N), and the 6-membered aromatic dienes benzene (6), 1,2-diazine (6N), and 1,2,4,5-tetrazine (6NN) (Scheme 5). Calculations were performed with the M06–2X functional using the 6–31G(d) basis set for geometry optimizations and the 6–311++G(d,p) basis set for energetic values. The transition states and the calculated energetics for the Diels–Alder reactions of the 5-membered heteroaromatic and non-aromatic diene series with ethylene are shown in Figure 1. The calculated Gibbs free energies of activation suggest that incorporating nitrogen at the 3- and 4-positions of furan, pyrrole, and thiophene increase the Diels–Alder reactivity towards ethylene by 68-, 7.6-, and 4,600-fold, respectively. The reactivity of non-aromatic dienes (cyclopentadiene and cyclohexadiene) increases by 440- and 610-fold, respectively. Figure 2 shows the activation energies and transition-state geometries for the Diels–Alder reactions of the benzene series with ethylene. Nitrogen-substitution at the 1- and 2-positions of benzene results in a 360-million-fold rate-enhancement. Incorporating nitrogen at the 4-
and 5-positions of the 1,2-diazine results in an additional 99-billion-fold rate-enhancement. The calculations show that the reactivity increase upon nitrogen-substitution in the 5-membered heteroaromatic dienes is more similar to that of the non-aromatic dienes, cyclopentadiene and cyclohexadiene, than with benzene.

Nitrogen-substitution has an effect on the position of the transition state. The transition states of the diaza analogs of the 5-membered heteroaromatic dienes and the non-aromatic dienes shift by 0.02–0.03 Å towards a later transition state. Aza substitution in the 6-membered dienes results in an opposite shift towards an earlier transition state. The transition state with 1,2-diazine is 0.04 Å earlier than with benzene, and the transition state of 1,2,4,5-tetrazine is 0.08 Å earlier than with 1,2-diazine.

The reaction energies of the nitrogen-substituted dienes are more exergonic than those of the parent dienes. In the heteroaromatic diene series, nitrogen-substitution decreases the reaction energies by 2.8, 0.9, and 4.5 kcal/mol for furan, pyrrole, and thiophene, respectively. The reaction energies of the non-aromatic dienes, cyclopentadiene and cyclohexadiene, decrease by 4.8 and 2.0 kcal/mol, respectively. For benzene and 1,2-diazine, the reaction energies decrease by 15.2 and 17.2 kcal/mol, respectively. The increase in the reaction exergonicities of the heteroaromatic and the non-aromatic dienes is significantly less than that of benzene and 1,2-diazine. Figure 3 shows a plot of the difference in the activation free energies and reaction energies between the dienes and their aza analogs. The decrease in activation energy is paralleled by a similar decrease in reaction energy. This strong correlation suggests that the factors affecting the activation energies also affect the reaction energies.

The studied reactions are inverse electron-demand Diels–Alder reactions in which the key stabilizing FMO interactions are between the HOMO of ethylene and the LUMO of the diene. Classically, the azabenzene reactivity trend has been attributed to a lowering of the LUMO energy upon nitrogen-substitution.\[15] We calculated the LUMO energies from the diene transition-state geometries at the M06–2X/6–311++G(d,p) level of theory to see the effect of nitrogen-substitution on the LUMO energies of dienes. Upon nitrogen-substitution, the LUMO energies of 1, 2, 3, 4, 5, 6, and 6N are lowered by 1.0, 0.9, 0.9, 0.9, 0.7, 0.8, and 0.8 eV, respectively. In other words, the LUMO energies of all the dienes are lowered to a similar extent (0.7–1.0 eV) and do not follow the reactivity trend.

Bickelhaupt and Ess attributed the increase in diene reactivity upon nitrogen-substitution to the reduced closed-shell repulsion that arises from the polarization of the diene electrons away from the carbon atoms involved in bond formation.\[5a] The electrostatic surface potentials of dienes 1–6 and their aza analogs 1N–6N and 6NN are shown in Figure 4. The electrostatic surface potentials in Figure 4 show that nitrogen-substitution polarizes the electrons away from the carbon atoms involved in bond formation for all dienes. The change in the diene polarization and LUMO energies are comparable for all dienes. In contrast, if closed-shell repulsions between the occupied orbitals of the diene and dienophile or FMO interactions were the origin of the significant rate-enhancement in the benzene series, then a similarly large rate-enhancement would also be expected in the 5-membered heteroaromatic and the non-aromatic dienes upon nitrogen-substitution.
Houk and coworkers attributed the rate-enhancement of the azabenzene series to a decrease in aromaticity upon nitrogen-substitution.\[5b]\ Figure 5 shows how the NICS values calculated at the center of the 5-membered heteroaromatic dienes and benzene change as nitrogen atoms are substituted into the scaffolds. Nitrogen-substitution in benzene results in a systematic loss of aromaticity that parallels the increase in diene reactivity. An analogous loss of aromaticity upon nitrogen-substitution is not apparent with nitrogen-substitution in the 5-membered heteroaromatic dienes. Instead, the 5-membered heteroaromatic dienes and their aza analogs have similar aromaticities. The similar aromaticity of the 5-membered heteroaromatic dienes and their aza analogs explains why the rate-enhancement upon nitrogen-substitution in the 5-membered heteroaromatic dienes is similar to that of the non-aromatic dienes, and significantly less than in the azabenzene series.

We conclude that the contrasting effect of nitrogen-substitution on the aromaticity of the 5-membered heteroaromatic dienes and benzene are supported by NICS(0) calculations and their chemical reactivity as dienes. The slight rate-enhancement observed in the Diels–Alder reactions of 5-membered heteroaromatic dienes upon nitrogen-substitution is comparable to the rate-enhancement of non-aromatic dienes. This modest rate-enhancement is the result of reduced closed-shell repulsion and increased FMO interactions between the diene and dienophile. In marked contrast, nitrogen-substitution in benzene results in a significantly larger increase in Diels–Alder reactivity. NICS(0) calculations show that this significant increase in reactivity is the result of the systematic loss of aromaticity that occurs upon nitrogen-substitution, in addition to the reduced closed-shell repulsion and increased strength of the FMO interactions. This significant, systematic loss of aromaticity that occurs with nitrogen-substitution in benzene is not apparent in 5-membered heteroaromatic dienes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Transition-state structures with Gibbs free energies of activation (Δ$G^f$) and Gibbs free reaction energies (Δ$G_{rxn}$) for the Diels–Alder reactions of ethylene with dienes 1–5 and their diaza analogs (1N–5N). The lengths (Å) of forming bonds are shown. Values of $k_{rel}$ for the analogs were calculated at 298 K with the Arrhenius equation.
Figure 2.
Transition-state structures with Gibbs free energies of activation ($\Delta G^\ddagger$) and Gibbs free reaction energies ($\Delta G_{\text{rxn}}$) for the Diels–Alder reactions of ethylene with dienes 6, 6N, and 6NN. The lengths (Å) of forming bonds are shown. Values of $k_{\text{rel}}$ were calculated at 298 K with the Arrhenius equation.
Figure 3.
Plot of the difference in the activation energies ($\Delta \Delta G^\ddagger$) between each diene and its aza analog against the difference in the reaction energies ($\Delta \Delta G_{\text{rxn}}$) between each diene and its aza analog. The data are fitted to the equation: $\Delta \Delta G^\ddagger = 0.78 \cdot \Delta \Delta G_{\text{rxn}} - 0.76$ with $R^2 = 0.99$. 
Figure 4. Ground-state molecular electrostatic potentials (ESPs) for unsubstituted dienes 1–6 and their aza analogs. M06–2X/6–31G(d) values are plotted from $-3.0 \, e^2$ (red) to $+3.0 \, e^2$ (blue) Hartree.
Figure 5.
NICS(0) values calculated at the MP2/6–31G(d)/M06–2X/6–31G(d) level of theory for benzene, furan, pyrrole, thiophene, and their aza analogs.
Scheme 1.
Diels–Alder reactivity trend in azabenzenes
Scheme 2.
Second-order rate constants for the Diels–Alder reaction of 3,6-diphenyl-1,2,4-triazine and 3,6-diphenyl-1,2,4–5-tetrazine with cyclooctyne at 20 °C in acetonitrile.\textsuperscript{[10]}
Scheme 3.
Diels–Alder reactions of a 2,5-bis(methoxycarbonyl)-1,3,4-oxadiazole with cyclooctyne at <1 equiv and in excess. Reactions were performed in dioxane at 60 °C.[13]
Scheme 4.
Diels–Alder reactions of BCN (8.3 mM) with 1 (83 mM) or 1N (83 mM) in MeOD at 60 °C.
Scheme 5.
Structures of dienes 1–6 and their aza analogs 1N–6N and 6NN.