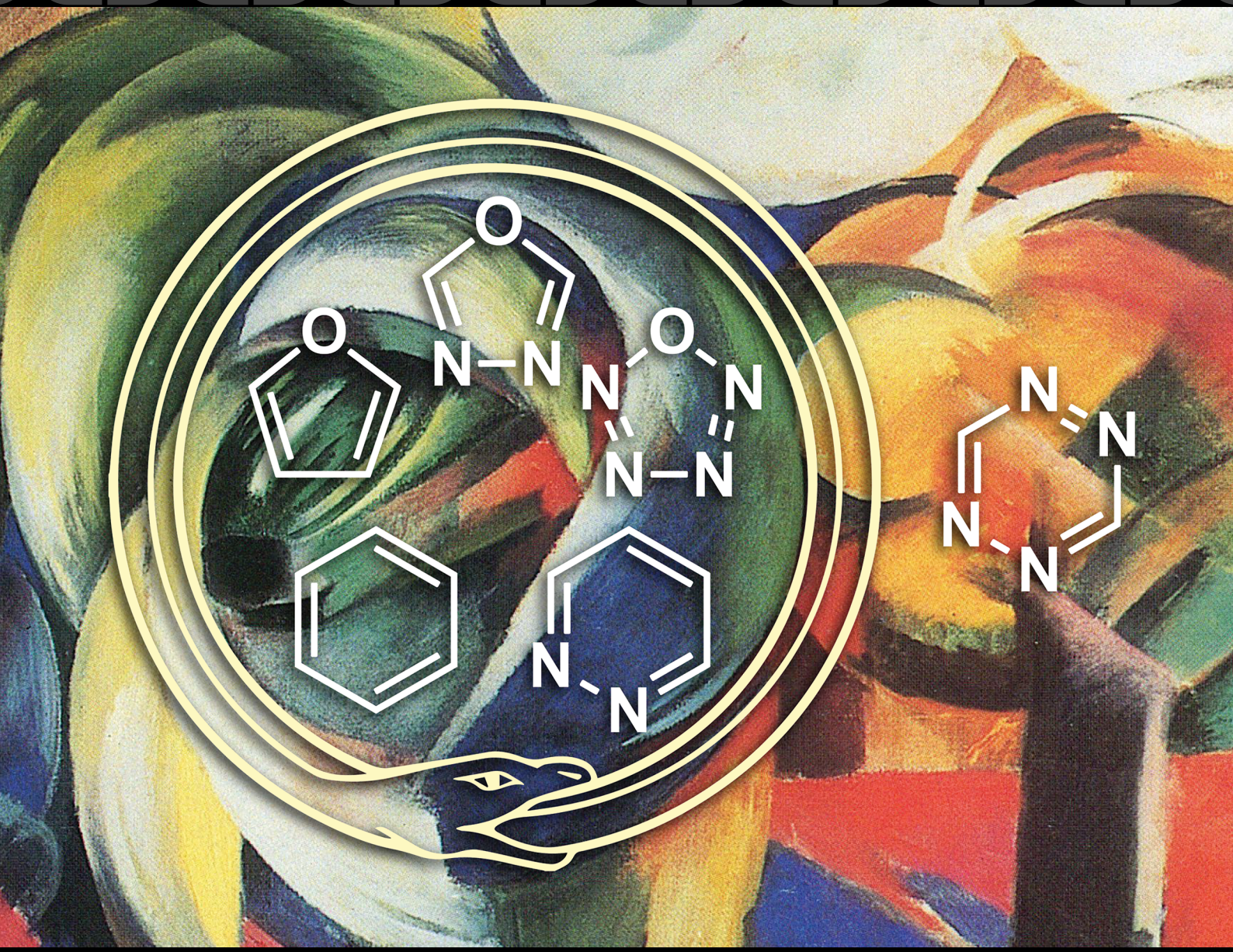
Chemistry
A European
Journal

Chemistry Europe
European Chemical
Societies Publishing

Check for updates

Front Cover:
R. T. Raines et al.
Differential Effects of Nitrogen-Substitution in 5- and 6-Membered Aromatic Motifs



41/2020

WILEY-VCH

Cover Profile
doi.org/10.1002/chem.202001542

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



Brian J. Levandowski Nile S. Abularrage Ronald T. Raines

Invited for the cover of this issue is the group of Ronald T. Raines at the Massachusetts Institute of Technology. The image depicts the consequence of replacing carbon with nitrogen in aromatic systems, represented by Kekulé's allegorical snake. Read the full text of the article at 10.1002/chem.202000825.

What was the inspiration for this cover design?

Our manuscript is dedicated to the memory of Rolf Huisgen (1920–2020) and his contributions to cycloaddition chemistry. We sought to design a cover that highlights our key findings while paying homage to Professor Huisgen. The background is from *The Mandrill,* a 1913 cubist painting by Franz Marc. This painting, which likewise serves as the backdrop in a common photograph of Professor Huisgen, hangs in the Pinakothek der Moderne, a Munich museum that he experienced and enjoyed often. An ouroboros snake, like that in August Kekulé's allegorical dream about the structure of benzene, has become a symbol of aromaticity. In our design, the snake is wrapped around diene systems that are aromatic according to nucleus-independent chemical shift calculations. 1,2,4,5-Tetrazine is outside of the snake because it is not aromatic.

What was the biggest surprise (on the way to the results presented in this paper)?

Chemical reactivity was the first of many criteria used to assess aromaticity and continues to be useful in predicting aromaticity today. In our search for Diels–Alder reactions with reactivity suitable for applications in "click" chemistry, we were surprised to discover that the effects of nitrogen substitution in 5-membered heteroaromatic dienes differed markedly from those in 6-membered aromatic dienes. The loss of aromaticity upon nitrogen substitution in 6-membered dienes is paralleled by a remarkable increase in reactivity, as with 1,2,4,5-tetrazine. This increased reactivity upon nitrogen substitution is not mimicked in 5-membered heteroaromatic dienes, such as furan, pyrrole, and thiophene.

What other topics are you working on at the moment?

Our research group is seeking to use ideas and methods from chemistry to understand and control life processes, especially those related to enzymes and other proteins. For example, we are developing processes to modify proteins chemoselectively, catalyze their folding, and facilitate their entry into human cells. We are characterizing fundamental forces, such as the n→π* interaction, that stabilize proteins and alter the conformation and reactivity of biomolecules. A favorite enzyme is human ribonuclease 1, which can be cytotoxic and which we have modified to become a clinical anti-cancer agent. Finally, we are creating hyperstable and human-scale synthetic collagens for the detection and treatment of wounds and in applications as biomaterials.

© 2020 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Aromaticity | *Hot Paper*

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

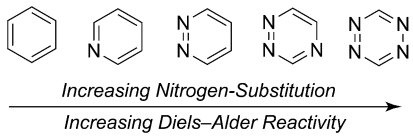
Brian J. Levandowski, Nile S. Abularrage, and Ronald T. Raines*[a]

Dedicated to the memory of Rolf Huisgen and his 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 10^{11}-fold increase in reactivity upon nitrogen substitution at the 4- and 5-positions, whereas a 5-membered heteroaromatic diene, furan, experiences a comparatively incidental 10^{2}-fold increase in reactivity upon nitrogen substitution at the 3- and 4-positions.

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[1] and 3-substituted cyclopropenes[2] are related to the hyperconjugative aromaticity or antiaromaticity[3] induced by the substituent at the saturated center. Hyperconjugative antiaromaticity has since been applied to develop highly reactive cyclopentadienes for click-chemistry applications.[4]

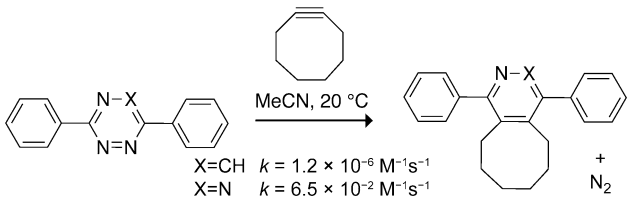
How nitrogen substitution affects aromaticity is an unsettled affair of great interest to theoretical and organic chemists. Computational chemistry groups have extensively studied the Diels–Alder reactivity trend of the azabenzene series shown in Scheme 1.[5] Computationally, the Diels–Alder reactivity increases by 10^{4}- to 10^{5}-fold with each nitrogen substitution. Houk and co-workers 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.[5b] Other aromaticity indices such as NICS(1),[6] isomerization stabilization energies,[7] and harmonic oscillator models of aromaticity (HOMA) based on bond-length equalization[8] 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.



Scheme 1. Diels–Alder reactivity trend in azabenzenes.

Ess, Bickelhaupt, and co-workers attributed the Diels–Alder reactivity trend in Scheme 1 to nitrogen polarizing the diene electrons away from the carbon atoms involved in bond formation.[5a] 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 also thought to play a role in the increased reactivity of tetrazines.[9] Scheme 2 shows the magnitude of the rate-enhancement. The Diels–Alder reaction of cyclooctyne with a tetrazine proceeds ≈50,000 times faster than with an equivalent triazine.[10] This rapid reactivity has made tetrazine a valuable reagent for bioorthogonal coupling reactions.[11]

Diels–Alder reactions of furans and 1,3,4-oxadiazoles have widespread use in organic synthesis.[12] Despite the synthetic utility of furans and 1,3,4-oxadiazoles as dienes, little is known



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.[10]

[a] *Dr. B. J. Levandowski, N. S. Abularrage, Prof. Dr. R. T. Raines*
Department of Chemistry
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139 (USA)
E-mail: rtraines@mit.edu
Homepage: http://raineslab.com

Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/chem.202000825.

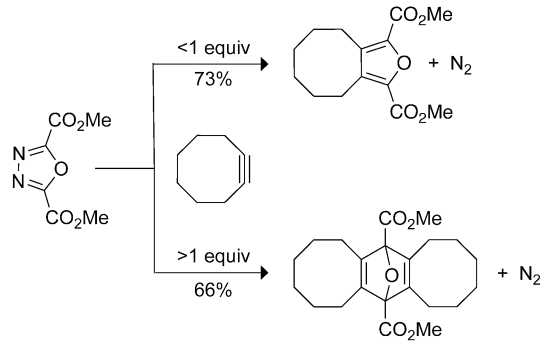
© 2020 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

about their relative Diels–Alder reactivities. Sauer (who was a student of Rolf Huisgen) and co-workers studied the Diels–Alder reaction of a 2,5-bis(methoxycarbonyl)-1,3,4-oxadiazole with cyclooctyne shown in Scheme 3.[13] 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.[10] This observation led Sauer and co-workers to suggest that furans and 1,3,4-oxadiazoles have similar reactivities.[13]

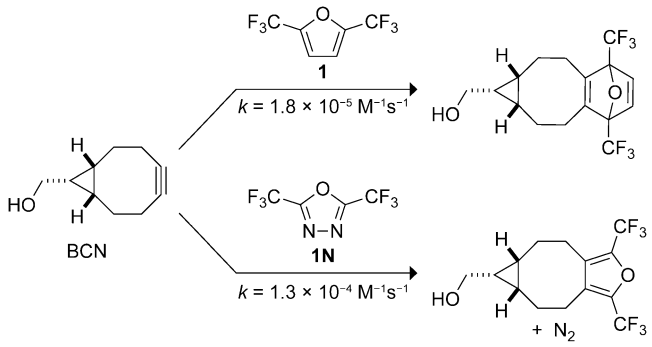
Whereas the effects of nitrogen substitution on the Diels–Alder reactivity of 6-membered cyclic dienes have been studied thoroughly, the extension of these effects to Diels–Alder reactions of 5-membered heteroaromatic dienes is unknown. To discern how nitrogen substitution at the 3- and 4-positions of 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 (**1 N**) with *endo*-bicyclo[6.1.0]non-4-yne (BCN) with NMR spectroscopy (Scheme 4). We found the second-order rate constants to be $1.8\times10^{-5}\,\text{M}^{-1}\,\text{s}^{-1}$ for **1** and $1.3\times10^{-4}\,\text{M}^{-1}\,\text{s}^{-1}$ for **1 N**. 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 (**1 N**-**3 N**), the 5- and 6-membered non-aromatic dienes cyclopentadiene (**4**) and cyclohexadiene (**5**), their 2,3-diaza analogs (**4 N** and **5 N**), and the 6-membered aromatic dienes benzene (**6**), 1,2-diazine (**6 N**), and 1,2,4,5-tetrazine (**6NN**) (Scheme 5). Calculations were performed with the M06-2X[14] 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 4600-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.

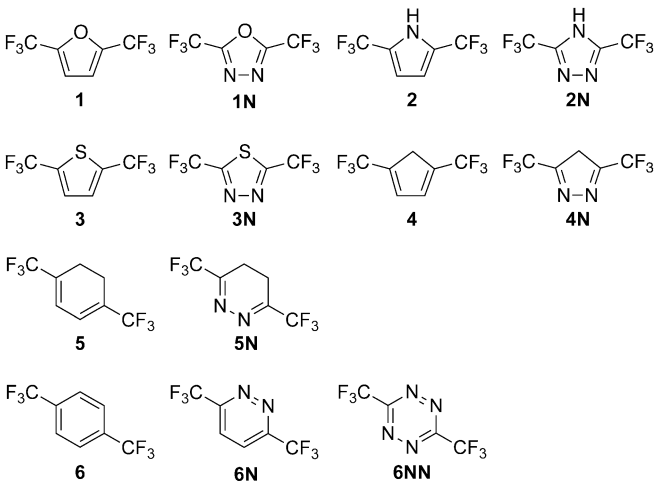
Nitrogen substitution has an effect on the position of the transition state. The transition states of the diaza analogs of the 5-membered heteroaromatic dienes and the non-aromatic dienes shift by 0.02–0.03 Å towards a later transition state. Aza substitution in the 6-membered dienes results in an opposite



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]

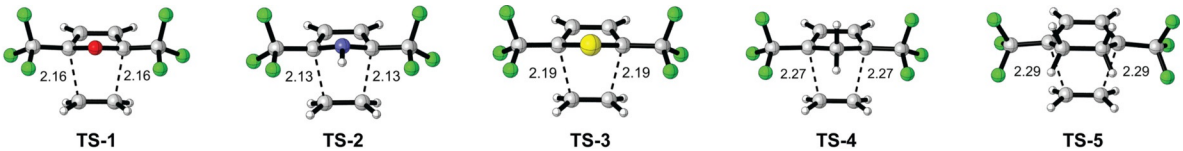


Scheme 4. Diels–Alder reactions of BCN (8.3 mM) with **1** (83 mM) or **1 N** (83 mM) in MeOD at 60 °C.

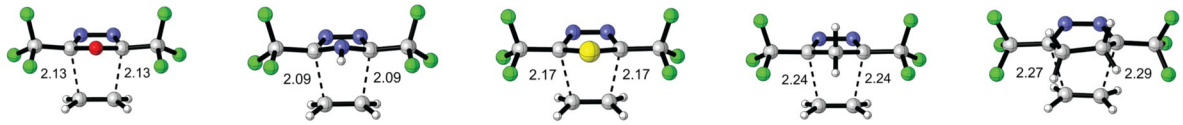


Scheme 5. Structures of dienes **1**–**6** and their aza analogs **1 N**–**6 N** and **6NN**.

© 2020 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

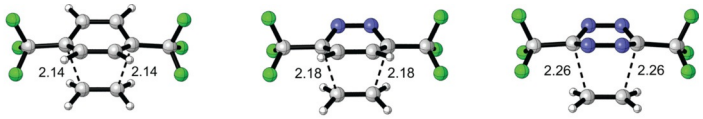


	TS-1	TS-2	TS-3	TS-4	TS-5
$\Delta G^{\ddagger}$ (kcal/mol)	30.2	36.2	38.5	27.7	31.9
ΔG_{rxn} (kcal/mol)	−6.7	5.6	−2.9	−19.4	−26.2



	TS-1N	TS-2N	TS-3N	TS-4N	TS-5N
$\Delta G^{\ddagger}$ (kcal/mol)	27.7	35.0	33.5	24.1	28.1
k_{rel}	68	7.6	4.6×10^3	4.4×10^2	6.1×10^2
ΔG_{rxn} (kcal/mol)	−9.5	4.7	−7.4	−24.2	−28.1

Figure 1. Transition-state structures with Gibbs free energies of activation ($\Delta G^{\ddagger}$) and Gibbs free reaction energies (ΔG_{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.



	TS-6	TS-6N	TS-6NN
$\Delta G^{\ddagger}$ (kcal/mol)	41.5	29.8	14.8
k_{rel}	2.7×10^{-9}	1	9.9×10^{10}
ΔG_{rxn} (kcal/mol)	8.2	−7.0	−24.2

Figure 2. Transition-state structures with Gibbs free energies of activation ($\Delta G^{\ddagger}$) and Gibbs free reaction energies (ΔG_{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_{rel} were calculated at 298 K with the Arrhenius equation.

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^{-1} 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^{-1}, respectively. For benzene and 1,2-diazine, the reaction energies decrease by 15.2 and 17.2 kcal mol^{-1}, 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 **6 N** 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.

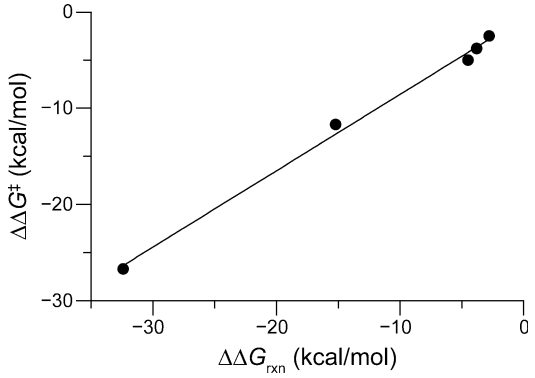


Figure 3. Plot of the difference in the activation energies ($\Delta\Delta G^{\ddagger}$) between each diene and its aza analog against the difference in the reaction energies ($\Delta\Delta G_{rxn}$) between each diene and its aza analog. The data are fitted to the equation: $\Delta\Delta G^{\ddagger} = 0.78 \cdot \Delta\Delta G_{rxn} - 0.76$ with $R^2 = 0.99$.

© 2020 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

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 co-workers 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 sub-

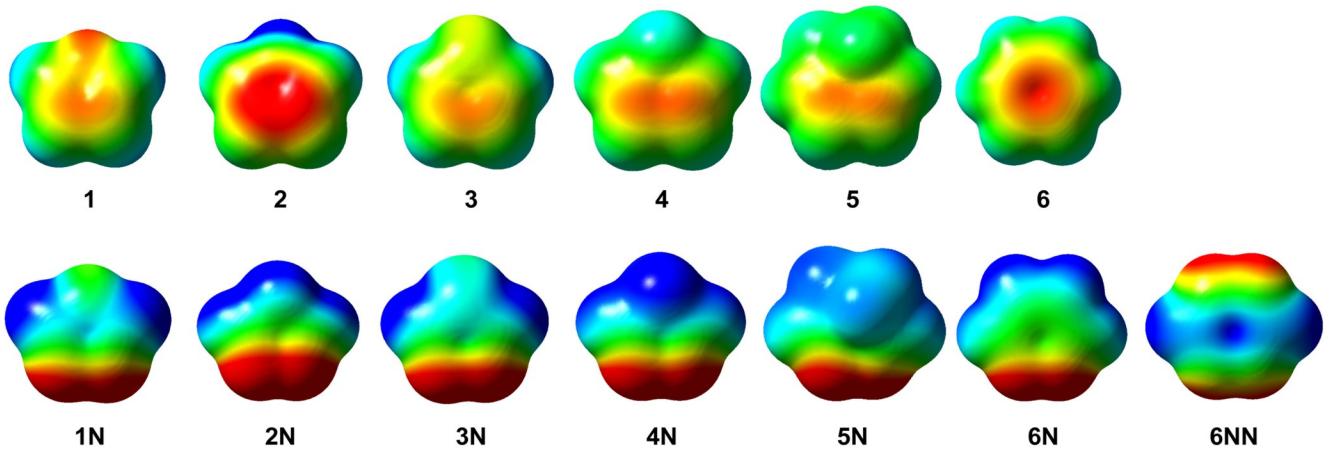


Figure 4. Ground-state molecular electrostatic potentials (ESPs) for unsubstituted dienes **1**–**6** and their aza analogs. M06-2X/6-31G(d) values are plotted from $-3.0\ e^{-2}$ (red) to $+3.0\ e^{-2}$ (blue) Hartree.

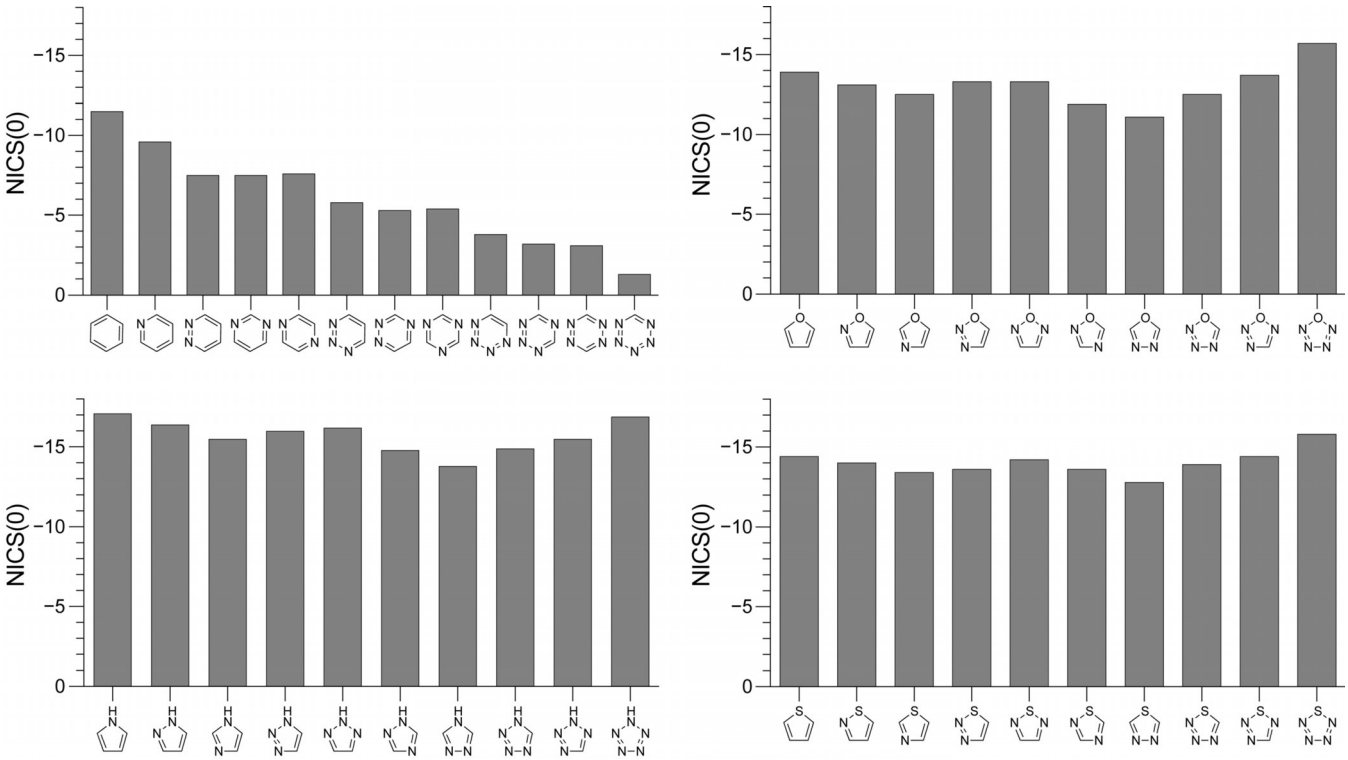


Figure 5. NICS(0) values calculated at the MP2/6-31G(d)//M06-2X/6-31G(d) level of theory for benzene, furan, pyrrole, thiophene, and their aza analogs.

© 2020 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

stitution 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.

Acknowledgements

B.J.L. was supported by postdoctoral fellowship F32 GM137543 (NIH). This work was supported by Grant R01 GM044783 (NIH). Computational resources were provided by the Extreme Science and Engineering Discovery Environment (XSEDE) Bridges at the Pittsburgh Supercomputing Center through allocation TG-CHE190066. XSEDE is supported by Grant ACI-1548562 (NSF).[16]

Conflict of interest

The authors declare no conflict of interest.

Keywords: aromaticity · cycloaddition · density functional calculations · kinetics

[1] a) B. J. Levandowski, L. Zou, K. N. Houk, *J. Comput. Chem.* **2016**, *37*, 117 – 123; b) B. J. Levandowski, L. Zou, K. N. Houk, *J. Org. Chem.* **2018**, *83*, 14658 – 14666.
[2] B. J. Levandowski, K. N. Houk, *J. Am. Chem. Soc.* **2016**, *138*, 16731 – 16736.
[3] a) L. Nyulászi, P. v. R. Schleyer, *J. Am. Chem. Soc.* **1999**, *121*, 6872 – 6875; b) I. Fernández, J. I. Wu, P. v. R. Schleyer, *Org. Lett.* **2013**, *15*, 2990 – 2993.
[4] a) B. J. Levandowski, R. F. Gamache, J. M. Murphy, K. N. Houk, *J. Am. Chem. Soc.* **2018**, *140*, 6426 – 6431; b) B. J. Levandowski, N. S. Abularrage, K. N. Houk, R. T. Raines, *Org. Lett.* **2019**, *21*, 8492 – 8495.
[5] a) A. Talbot, D. Devarajan, S. J. Gustafson, I. Fernández, F. M. Bickelhaupt, D. H. Ess, *J. Org. Chem.* **2015**, *80*, 548 – 558; b) Y.-F. Yang, Y. Liang, F. Liu, K. N. Houk, *J. Am. Chem. Soc.* **2016**, *138*, 1660 – 1667.
[6] Z. Chen, C. S. Wannere, C. Corminboeuf, R. Puchta, P. v. R Schleyer, *Chem. Rev.* **2005**, *105*, 3842 – 3888.
[7] Y. Wang, J. I.-C. Wu, Q. Li, P. v. R. Schleyer, *Org. Lett.* **2010**, *12*, 4824 – 4827.
[8] a) T. M. Krygowski, M. Cyrański, *Tetrahedron* **1996**, *52*, 10255 – 10264; b) C. W. Bird, *Tetrahedron* **1997**, *53*, 13111 – 13118.
[9] D. N. Kamber, Y. Liang, R. J. Blizzard, F. Liu, R. A. Mehl, K. N. Houk, J. A. Prescher, *J. Am. Chem. Soc.* **2015**, *137*, 8388 – 8391.
[10] J. Balcar, G. Chrisam, F. X. Huber, J. Sauer, *Tetrahedron Lett.* **1983**, *24*, 1481 – 1484.
[11] a) M. L. Blackman, M. Royzen, J. M. Fox, *J. Am. Chem. Soc.* **2008**, *130*, 13518 – 13519; b) S. Mayer, K. Lang, *Synthesis* **2017**, *49*, 830 – 848.
[12] a) H. Wu, N. K. Devaraj, *Top. Curr. Chem.* **2016**, *374*, 3; b) J. Zhang, V. Shukla, D. L. Boger, *J. Org. Chem.* **2019**, *84*, 9397 – 9445.
[13] F. Thalhammer, U. Wallfahrer, J. Sauer, *Tetrahedron Lett.* **1988**, *29*, 3231 – 3234.
[14] Y. Zhao, D. G. Truhlar, *Theor. Chem. Acc.* **2008**, *120*, 215 – 241.
[15] D. L. Boger, *Chem. Rev.* **1986**, *86*, 781 – 793.
[16] J. Towns, T. Cockerill, M. Dahan, I. Foster, K. Gaither, A. Grimshaw, V. Hazlewood, S. Lathrop, D. Lifka, G. D. Peterson, R. Roskies, J. R. Scott, N. Wilkins-Diehr, *Comput. Sci. Eng.* **2014**, *16*, 62 – 74.

Manuscript received: March 10, 2020
Accepted manuscript online: March 13, 2020
Version of record online: June 12, 2020

© 2020 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim