# Hyperconjugative Antiaromaticity Activates 4H-Pyrazoles as Inverse-Electron-Demand Diels−Alder Dienes

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S *Supporting Information*

ABSTRACT: The Diels−Alder reactivity of 4,4-difluoro-3,5-diphenyl-4H-pyrazole was investigated experimentally and computationally with *endo*-bicyclo[6.1.0]non-4-yne. The computationally predicted rate enhancement from hyperconjugative antiaromaticity induced by fluorination of cyclopentadienes at the 5-position extends to five-membered heterocyclic dienes containing a saturated center. 4,4-Difluoro-4H-pyrazoles are new electron-deficient dienes with rapid reactivities toward strained alkynes.

R = Me, no reaction
R = F, fast reaction
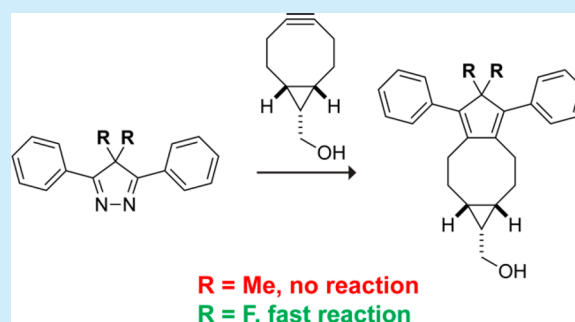
C yclopentadienes have been explored as a new class of bio-orthogonal dienes with rapid reactivities and robust biological stabilities.[1] Tetrachlorocyclopentadiene ketal (TCK) does not dimerize[2] and can be synthesized in one step from readily available starting materials. As an ambiphilic diene, TCK reacts with both electron-deficient and electron-rich dienophiles and is stable toward biological nucleophiles. The rate constant for the Diels−Alder reaction of TCK with *endo*-bicyclo[6.1.0]non-4-yne (BCN) at room temperature in methanol is 0.26 M^{-1} s^{-1}. TCK cycloadditions are as fast as the most rapid azide−alkyne cycloadditions[3] but slower than the inverse-electron-demand Diels−Alder reactions of 3,6-diphenyl- and 3,6-dipyridyl-1,2,4,5-tetrazines with BCN, which have rate constants in MeOH at room temperature of 3.3 and 44.8 M^{-1} s^{-1}, respectively.[4]

The rapid Diels−Alder reactivity of cyclopentadienes is the result of the minimal distortion of the cyclopentadiene ground-state geometry required to achieve the transition-state geometry.[5] The Diels−Alder reactivities of cyclopentadienes can be tuned by substitution at the 5-position.[6] Negative hyperconjugation at the saturated center of a cyclopentadiene enhances the Diels−Alder reactivity of the diene by producing antiaromatic 4π-electron destabilization.[7] This destabilization, which is especially strong when a fluoro group is the substituent, attracted our attention to the 4,4-difluoro-4H-pyrazole scaffold. Hünig[8] and Adam[9] have studied the Diels−Alder reactions of 3,5-dimethyl- and 3,5-diaryl-substituted 4,4-dimethyl-4H-pyrazoles extensively and found that acid catalysis is needed to promote the reaction, even with highly strained and electron-rich dienophiles. As shown in Scheme 1, the Diels−Alder reaction of 4,4-dimethyl-3,5-dimethyl-4H-pyrazole with cyclopentadiene (Cp) proceeds only in the presence of an acid catalyst.[8a] Though Diels−Alder reactions of 4,4-difluoro-4H-

Scheme 1. Diels−Alder Reaction of 4,4-Dimethyl-3,5-diphenyl-4H-pyrazole and Cyclopentadiene (Cp) with or without an Acid Catalyst[9]
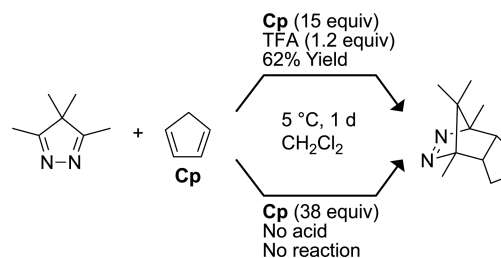
pyrazoles have yet to be studied, the destabilizing effects of hyperconjugative antiaromaticity invoked by the geminal fluoro groups suggest that 4,4-difluoro-4H-pyrazoles would be highly reactive as Diels−Alder dienes.

We have studied computationally and experimentally the Diels−Alder reactivity of 4,4-dimethyl-3,5-diphenyl-4H-pyrazole (DMP), 4,4-difluoro-3,5-diphenyl-4H-pyrazole (DFP), and 3,6-diphenyl-1,2,4,5-tetrazine (Tz) with BCN (Scheme 2). We find that fluorine substitution enhances the Diels−Alder reactivity of DFP, making it more reactive than Tz toward BCN.

We began by evaluating the aromaticity of the 4H-pyrazole scaffold by using nuclear independent chemical shift (NICS)[10] calculations. Our intent was to determine if the hyperconjugative aromaticity and antiaromaticity observed in cyclopentadienes extends to 4H-pyrazoles. NICS(0) calculations measure the magnetic shielding at the center of the ring and have been shown to correlate well with the Diels−Alder reactivities of

Scheme 2. Structures of 4,4-Dimethyl-3,5-diphenyl-4H-pyrazole (DMP), 4,4-Difluoro-3,5-diphenyl-4H-pyrazole (DFP), 3,6-Diphenyl-1,2,4,5-tetrazine (Tz), and *endo*-Bicyclo[6.1.0]non-4-yne (BCN)
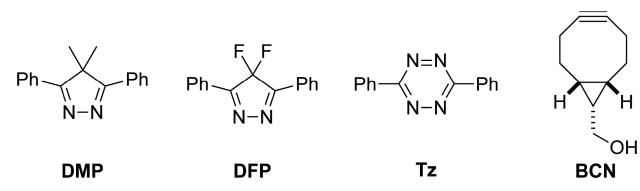
heteroaromatic azadienes.[11] Negative NICS values are associated with a diatropic (aromatic) ring current, whereas positive NICS values are indicative of a paratropic (antiaromatic) ring current. The NICS(0) value of 0.5 ppm for the unsubstituted 4H-pyrazole suggests that the 4H-pyrazole scaffold is not aromatic (Table S1). Fluorination of the 4H-pyrazole leads to antiaromatic electron delocalization (NICS(0) = 6.2 ppm), whereas silylation induces aromatic electron delocalization (NICS(0) = −3.3 ppm).

The antiaromaticity of 4,4-difluoro-4H-pyrazoles led us to believe that they would be highly reactive as inverse-electron-demand Diels−Alder dienes. We computationally surveyed the Diels−Alder reactivities of DFP, DMP, and Tz toward BCN at the M06-2X/6-31G(d)//M06-2X/6-311++(d,p)-SMD(H$_2$O) level of theory.[12] Gas-phase energies are listed in Table S2. Our calculations reveal that fluorine substitution significantly enhances the reactivity of the 4H-pyrazole scaffold. The reaction of DFP with BCN is predicted to be 5.2 × 10^5 faster and 12.5 kcal/mol more exergonic than the cycloaddition of DMP with BCN (Figure 1). The increased reactivity and exergonicity of the DFP cycloaddition are consistent with DFP being antiaromatic. The lowest unoccupied molecular orbital (LUMO) energies of DFP and DMP were calculated to be −2.1 and −1.3 eV, respectively. Decreasing the LUMO results in more favorable frontier molecular orbital interactions and is an additional factor that contributes to the increased reactivity of DFP as an inverse-electron-demand diene.

We also compared the reactivity of the 4,4-difluoro-4H-pyrazole scaffold to the highly reactive tetrazine scaffold. We found that the 4,4-difluoro-4H-pyrazole and tetrazine scaffolds have similar predicted reactivities toward BCN, with the
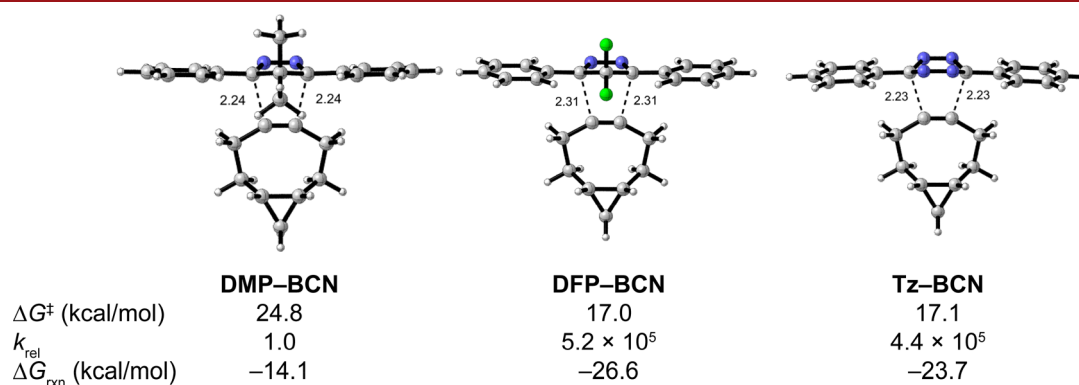
computed activation free energies differing by only 0.1 kcal/mol in favor of DFP.

We synthesized DFP in one step and high yield (93%) from commercial starting materials by a route reported previously.[13] To evaluate how the reactivity of the 4,4-difluoro-4H-pyrazole scaffold compares to that of the tetrazine scaffold, we measured pseudo-first-order kinetics for the Diels−Alder reactions of DFP and Tz with BCN in 9:1 methanol/water at room temperature. A plot of the observed rate constants with respect to the BCN concentration is shown in Figure 2. The 4,4-difluoro-4H-pyrazole scaffold is more reactive than is the tetrazine scaffold toward BCN, with second-order rate constants of 5.2 and 3.2 M^{-1} s^{-1} for DFP and Tz, respectively. The rapid reactivity of DFP arises from the antiaromatic 4π-electron delocalization invoked by negative hyperconjugation of the fluoro substituents.[7] To provide confirmation for hyperconjugative antiaromaticity as the source of the high reactivity of DFP, we stirred DMP with BCN; we detected no reaction after 2 h by NMR spectroscopy.

To discern if hyperconjugative antiaromaticity compromises the stability of DFP in a biological context, we incubated DMP and DFP in phosphate-buffered saline (PBS) containing fetal bovine serum (FBS; 10% v/v) at 37 °C. After 8 h, 42% of the DFP and 98% of the DMP remained intact (Figure S1). Thus, hyperconjugative antiaromaticity also increases the reactivity of the diene toward biological nucleophiles but not to a substantial detriment.

The DFP−BCN cycloadduct loses N$_2$(g) spontaneously to yield a 5,5-difluorocyclopentadiene product that we characterized by NMR spectroscopy and mass spectrometry. The geminal fluoro groups at the saturated cyclopentadiene center of the 5,5-difluorocyclopentadiene product induce hyperconjugative antiaromaticity.[6] To see if this hyperconjugative antiaromaticity compromises stability, we incubated the cycloadduct in PBS containing FBS (10% v/v) at 37 °C. After 8 h, no decomposition of the cycloadduct was apparent by UV−vis spectroscopy (Figure S1).

In conclusion, we have experimentally confirmed the computationally predicted rate-enhancing effects of hyperconjugative antiaromaticity on the Diels−Alder reactivity of five-membered cyclic dienes. The use of hyperconjugative antiaromaticity to tune the Diels−Alder reactivity of five-membered cyclic dienes and three-membered cyclic dieno-

	DMP−BCN	DFP−BCN	Tz−BCN
$\Delta G^\ddagger$ (kcal/mol)	24.8	17.0	17.1
k_{rel}	1.0	5.2 × 10^5	4.4 × 10^5
ΔG_{rxn} (kcal/mol)	−14.1	−26.6	−23.7

Figure 1. Transition-state geometries and calculated Gibbs free energies of activation ($\Delta G^\ddagger$) and reaction (ΔG_{rxn}) computed at the M06-2X/6-31G(d)//M06-2X/6-311++G(d,p)-SMD(H$_2$O) level of theory for the Diels−Alder reactions of 4,4-dimethyl-3,5-diphenyl-4H-pyrazole (DMP), 4,4-difluoro-3,5-diphenyl-4H-pyrazole (DFP), and 3,6-diphenyl-1,2,4,5-tetrazine (Tz) toward BCN. The lengths (Å) of forming bonds are shown. Values of k_{rel} were calculated at 298 K with the Arrhenius equation.
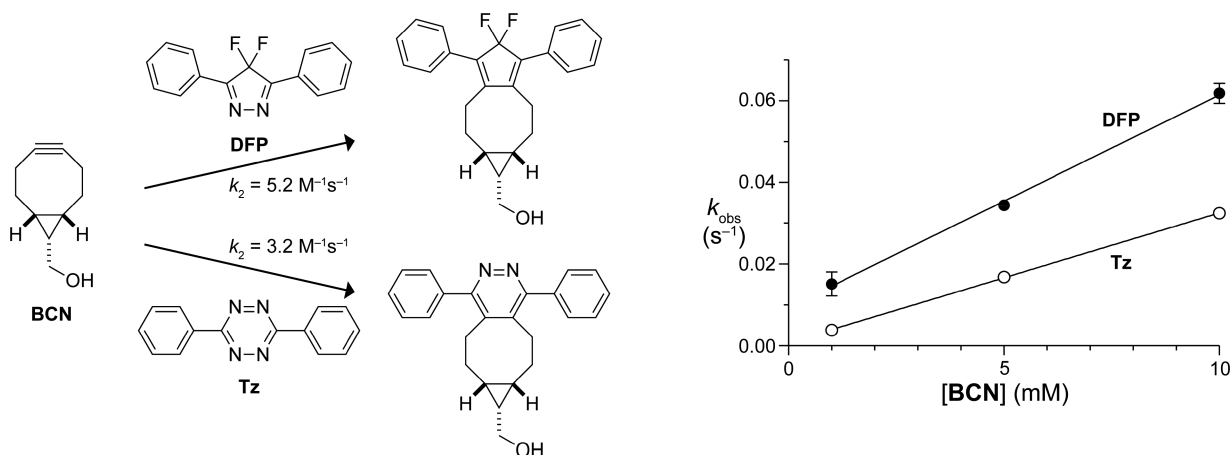
Figure 2. Reaction of BCN (1, 5, or 10 mM) with DFP (0.1 mM) or Tz (0.1 mM) in 9:1 methanol/water. Values of k_{obs} are the mean $\pm$ SEM for reactions performed in triplicate. Second-order rate constants as calculated from a linear fit of the data were $k_2 = 5.2$ M^{-1} s^{-1} for DFP ($R^2 = 0.97$) and $k_2 = 3.2$ M^{-1} s^{-1} for Tz ($R^2 = 0.99$).

philes[14] will be useful to click chemistry applications that require rapid and tunable kinetics.

ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03351.

Tables S1 and S2; Figure S1; computational methods and additional computational data, Cartesian coordinates, and energies; and synthetic methods and analytical data (PDF)

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Notes

The authors declare no competing financial interest.

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