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Letter

Antiaromaticity Gain Activates Tropone and Nonbenzenoid Aromatics as Normal-Electron-Demand Diels–Alder Dienes

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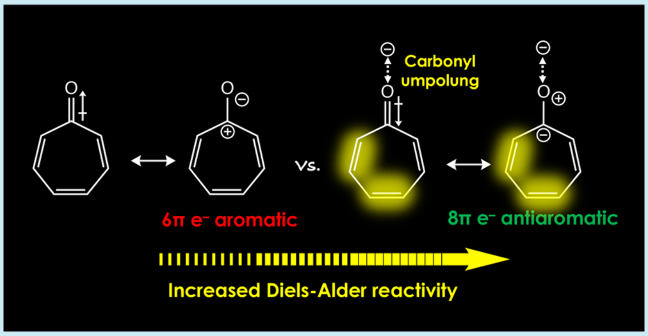
ABSTRACT: We propose a carbonyl umpolung strategy for activating tropone as a normal-electron-demand Diels–Alder diene. Tropone has low reactivity for Diels–Alder reactions because of its [4*n*+2] *π*-aromaticity. Conversion of the carbonyl group into a hydrazone ion (═N–NR$^-$) reverses the polarity of the exocyclic double bond, increases the [4*n*] ring *π*-antiaromaticity, and raises the HOMO energy. Computed gas-phase activation free energies for a Diels–Alder reaction with maleimide suggest a billion-fold rate increase when the tropone C═O is replaced by ═N–NR$^-$ (R = H or SO_2CH_3). Other nonbenzenoid aromatics can be activated as normal-electron-demand Diels–Alder dienes in the same way.



Aromaticity is a powerful force that, depending on circumstances, can either promote or impede chemical reactions. The Diels–Alder reactions of tropones as dienes provide direct access to bicyclo[3.2.2] structures that are frequently found in natural products and bioactive compounds. Unfortunately, the need to overcome the electron-deficient nature and [4*n*+2] *π*-aromatic character of the seven-membered ring often requires harsh conditions (e.g., high pressure or temperature)[1−4] or leads to low yields of these reactions. When tropones are made even more electron-deficient, for example, through Lewis acid catalysis,[5] they can react at room temperature with electron-rich dienophiles in an inverse-electron-demand Diels–Alder reaction.[6] But examples of converting tropones into electron-rich dienes for normal-electron-demand Diels–Alder reactions are limited to their donor-substituted derivatives. For example, tropolones have been activated with use of silica gel and triethylamine as base catalysts[7] or with the use of bifunctional Brønsted base catalysts.[8] In both cases, the tropolone hydroxyl group is deprotonated to generate an anion, thereby raising the HOMO energy of the diene.

Here we explore the activation of tropone as a Diels–Alder diene by umpolung (reversed polarity) of the carbonyl, converting the seven-membered ring into a [4*n*] *π*-antiaromatic cycle. Tropone is formally [4*n*+2] *π*-aromatic because the carbonyl is polarized toward the more electronegative oxygen, giving rise to a charge-separated aromatic resonance form.[9,10] (See Figure 1.) Thus the ring *π*-system is aromatic, and the double bonds show low reactivity for cycloaddition.[11,12] But what if the exocyclic double bond was polarized in the reversed direction? We hypothesize that such a change in polarization ("carbonyl umpolung") transforms tropone into a [4*n*] *π*-antiaromatic ring, raises its HOMO energy, and activates the ring double bonds as Diels–Alder dienes.

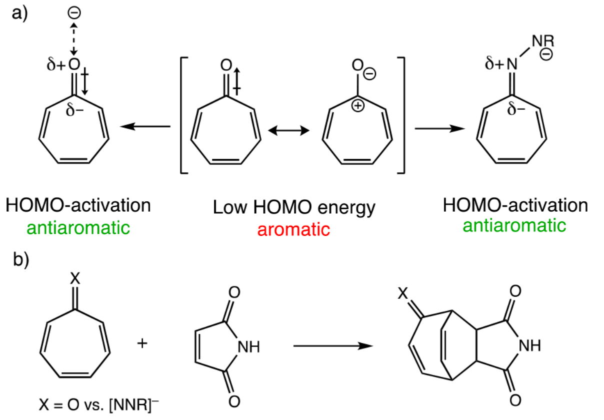


Figure 1. (a) Carbonyl umpolung increases [4*n*] *π*-antiaromaticity and raises the HOMO energy of tropone, making it a more effective Diels–Alder diene in a normalelectron-demand reaction. (b) Normal-electron-demand Diels–Alder reactions considered in this work.

Applying the principles of electrostatic catalysis,[13−15] we considered the effect of placing a negative charge close to the

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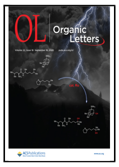

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carbonyl O atom of tropone. Because of repulsive interactions between the negative charge and the carbonyl O atom, the π-electrons would shift toward carbon, making tropone an electron-rich $[4n]$ π-antiaromatic ring. (See Figure 1a, left.) Nucleus-independent chemical shifts (NICS)[16,17] computations indicate that tropone, **1**, is modestly aromatic (NICS$(1)_{zz}$ = −5.0 ppm; negative value indicates aromaticity) but becomes increasingly antiaromatic when a point charge of −1 is positioned in a near-linear geometry at 4, 3, and 2 Å away from the carbonyl O atom (NICS$(1)_{zz}$ = −1.7 ppm at 4 Å, +0.3 ppm at 3 Å, and +4.7 ppm at 2 Å; positive values indicate antiaromaticity), and the HOMO energy is raised accordingly. (See the results in Table S1 of the Supporting Information (SI).) Whereas designing a catalyst that would maintain a negatively charged group in the vicinity of the carbonyl oxygen may be challenging, transforming carbonyl into a deprotonated hydrazone ion (=N−NR$^-$) offers a simple practical approach toward emulating this electronic effect for carbonyl umpolung. (See Figure 1a, right.)

Umpolung strategies using neutral hydrazone (=N−NR$_2$) to convert electrophilic carbonyl groups into nucleophilic sites[19,20] for cycloaddition reactions have been reported for inverse-electron-demand Diels−Alder reactions,[21−24] in which α,β-unsaturated carbonyls are converted to the corresponding hydrazones, giving rise to electron-rich dienophiles with a high HOMO energy. Menendez and coworkers reported the inverse-electron-demand aza-Diels−Alder reactions of an α,β-unsaturated hydrazone with aromatic imines.[21,22] Tamura and coworkers reported examples of inverse-electron-demand Diels−Alder reactions of α,β-unsaturated hydrazone with esters and pyrones, followed by dehydrazonation to recover the carbonyl.[23,24] However, hydrazone activation has never been applied to manipulate the aromaticity and umpolung of tropones. The only related example of a cycloheptatrienyl umpolung was reported by Machiguchi et al., who found that the carbon of the sulfine group (>C=S=O) of tropothione-*S*-oxide acquires a negative charge.[18] In a related work, Yamabe et al. showed that tropone undergoes a [4 + 2] cycloaddition with maleic anhydride, but the analogous reaction for tropothione is an [8 + 2] cycloaddition.[25]

We tested this concept with two examples: a deprotonated tropone hydrazone (**2**, =N−N$^-$−H) and its methanesulfonyl analog (**3**, =N−N$^-$−SO$_2$CH$_3$) (Figure 2). Remarkably, this umpolung makes the seven-membered ring electron-rich and $[4n]$ π-antiaromatic, converting it into an effective diene for a normal-electron-demand Diels−Alder reaction. (See the reaction considered in Figure 1b.) On the basis of the NICS computations, **1** is modestly aromatic (NICS$(1)_{zz}$ = −5.0 ppm), but hydrazone deprotonation converts the seven-membered ring into a highly antiaromatic cycle, as documented by enormous positive NICS$(1)_{zz}$ values for **2** (+105.4 ppm) and **3** (+61.4) ppm. (See Figure 2.) The nonplanar minima geometries of **2** and **3** also suggest increased $[4n]$ π-antiaromatic character. The HOMO energies of **2** (−1.4 eV) and **3** (−2.8 eV) are also much higher than the HOMO energy of **1** (−8.7 eV). (See Figure 2.) Computed natural population analysis (NPA)[26] charges document the effects of carbonyl umpolung. Note that the ring C1 position is positively charged in **1** but modestly negative in **2** and **3**.

Carbonyl umpolung is less pronounced in **3** because the electron-withdrawing methanesulfonyl stabilizes the negative charge on nitrogen, but from an experimental viewpoint, this also makes generating the hydrazone anion more feasible. Notably, the deprotonation of **2-prot** to give **2** (Δ*E* = 360.1 kcal/mol) is less endothermic than the deprotonation of hydrazone (Δ*E* = 374.7 kcal/mol). Likewise, the deprotonation of **3-prot** to give **3** (Δ*E* = 333.7 kcal/mol) gives nearly the same energy as methane sulfonohydrazone (Δ*E* = 336.6 kcal/mol). This comparison suggests that even though the resulting anionic rings (**2** and **3**) are largely antiaromatic, there appears to be no additional energetic penalty for deprotonation. For comparison, benzaldehyde phenylhydrazone has a modestly higher deprotonation energy, Δ*E* = 346.5 kcal/mol (pK_a = 21.6 in DMSO),[27] and may be deprotonated, for example, by an alkoxide base.

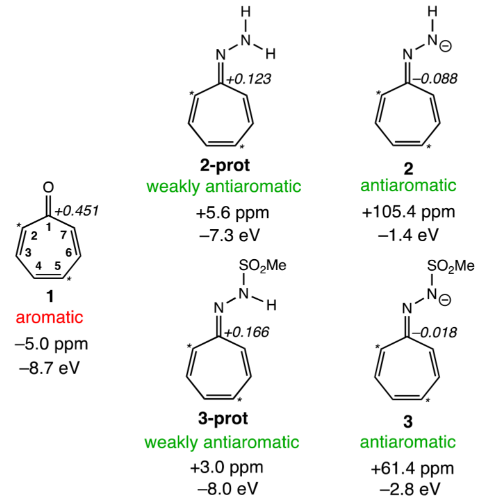

Figure 2. Computed NICS$(1)_{zz}$ values, HOMO energies, and NPA charges for the ring atoms of tropone (**1**), the neutral hydrazone analogs **2-prot** and **3-prot**, deprotonated tropone hydrazone (**2**), and deprotonated methanesulfonyl tropone hydrazone (**3**). Carbon centers involved in the Diels−Alder reaction considered are indicated by an asterisk (*).

The computed gas-phase activation free energies for the *endo*-Diels−Alder reaction of **1** and maleimide ($\Delta G^{\ddagger}$ = 26.5 kcal/mol) decrease by 19.1 kcal/mol when **2** is the diene (stepwise pathway, $\Delta G_1^{\ddagger}$ = 7.4 kcal/mol, $\Delta G_2^{\ddagger}$ = 4.8 kcal/mol; Figure 3a) and by 10.4 kcal/mol when **3** is the diene ($\Delta G^{\ddagger}$ = 16.9 kcal/mol; Figure 3b), suggesting at least a billion-fold rate increase. Activation free energies computed in implicit dichloromethane solvent show the same barrier lowering effects for the reactions with **2** and **3**, albeit to a lesser extent. (See Figure 3, values in brackets.) Computed NICS values along the points on the intrinsic reaction coordinate (IRC) leading to the transition-state structure document the effects of antiaromaticity relief. (See the example for **2** in Figure S1 of the SI.)

Both **1** and **3** undergo concerted Diels−Alder reactions with maleimide (although **3** is noticeably more asynchronous; see the text later), but the reaction with **2** proceeds through a stepwise mechanism (see Figure 3), forming a σ bond first at C5 and then at C2. (See the Figure 2 carbons labeled by an asterisk.) As shown in Figure 3, the reaction of **2** and maleimide is stepwise because a partial positive charge on C2, formed as a consequence of the C−C σ bond at C5, is stabilized by the resonance of the negative charge on the hydrazone group, and this leads to the formation of the intermediate (**2-Inter**). (See Figure 4.) This Diels−Alder reaction can be considered as a sequence of two Michael additions. The reaction of **3** with maleimide is asynchronous

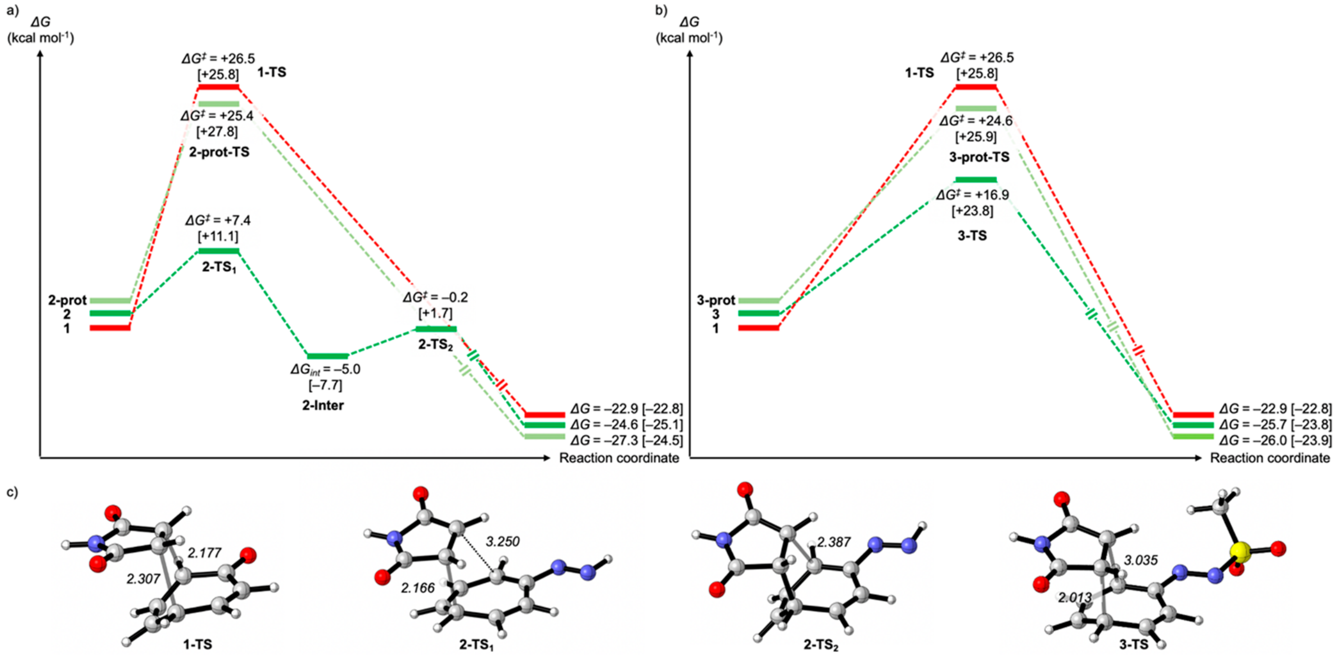

Figure 3. Computed gas-phase reaction pathway for the Diels−Alder reaction of maleimide with **1** compared with (a) **2** and **2-prot** as well as (b) **3** and **3-prot**. Relevant transition state (TS) and intermediate (Inter) structures are shown. Relative free energies (ΔG and $\Delta G^{\ddagger}$) are in kilocalories per mole. Relative free energies computed in implicit dichloromethane solvent are in brackets. Labeled bond distances are in angstroms.

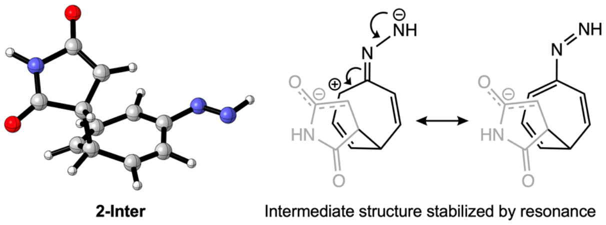

Figure 4. Schematic illustration showing the resonance stabilization for **2-Inter**.

but concerted because the effects of resonance stabilization are less pronounced. (The negative charge on hydrazone is delocalized to the methanesulfonyl group.) Deprotonation giving the alternative conformer of **2** (N lone pair antiperiplanar to C═N) also follows a stepwise Diels−Alder reaction pathway with low activation free energies for each step. (See the details in the SI.) Alternatively, maleimide could add to the C4 and C7 positions of **2**, giving a comparably low activation free energy. (See the SI.)

In sharp contrast, *endo*-Diels−Alder reactions with *neutral* tropone hydrazone analogs as the dienes, **2-prot** ($\Delta G^{\ddagger}$ = 25.4 kcal/mol; Figure 3a) and **3-prot** ($\Delta G^{\ddagger}$ = 24.6 kcal/mol; Figure 3b), show little barrier lowering effect compared with the reaction with tropone (Figure 3; see the details in the SI). Note that both **2-prot** (NICS$(1)_{zz}$ = +5.6 ppm) and **3-prot** (NICS$(1)_{zz}$ = +3.0 ppm) are nonaromatic to weakly antiaromatic and have HOMO energy levels close to **1** (−7.3 eV for **2-prot**, −8.0 eV for **3-prot**, cf. −8.7 eV for **1**). (See Figure 2.) These results suggest that merely having a lone pair of π-electrons delocalize into the imine C═N bond does not reverse-polarize the exocyclic double bond enough to significantly activate the ring double bonds.

Similar to tropone, nonbenzenoid aromatic compounds like pyrones and pyridones also show low reactivity for cycloaddition reactions because of their electron-deficient nature and $[4n+2]$ π-aromatic character. Examples of activating 3-hydroxy-pyrone[28] and *N*-tosyl-3-hydroxy-2-pyridone[29] base catalysis have been reported, in which triethylamine was used to deprotonate the hydroxyl groups, producing an anionic diene with a raised HOMO energy. Using 2-pyrone, **4**, as an example, we show that umpolung strategies using the hydrazone ion (see Figure 5) can also activate other nonbenzenoid aromatics as electron-rich dienes for Diels−Alder reactions.

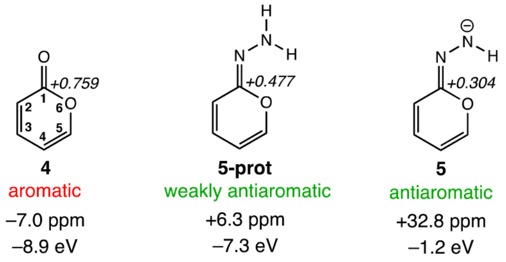

Figure 5. Computed NICS$(1)_{zz}$ values, HOMO energies, and NPA charges for the ring atoms of 2-pyrone (**4**), 2-pyrone hydrazone (**5-prot**), and deprotonated 2-pyrone hydrazone (**5**).

2-Pyrone, **4**, displays a negative NICS$(1)_{zz}$ value (−7.0 ppm), a low HOMO energy (−8.9 eV), and a high activation barrier ($\Delta G^{\ddagger}$ = 24.0 kcal/mol) for a Diels−Alder reaction with maleimide. The hydrazone **5** exhibits a positive NICS$(1)_{zz}$ value (+32.8 ppm) and increased HOMO energy (−1.2 eV). As a result, the activation free energy for the corresponding Diels−Alder reaction is dramatically reduced (stepwise pathway, $\Delta G_1^{\ddagger}$ = 4.7 kcal/mol and $\Delta G_2^{\ddagger}$ = 15.6 kcal/mol for **5**). (See the results in the SI.) Computed NPA charges at the C1 positions of **4** and **5** document the effects of carbonyl umpolung; note the less positive C1 charge for **5** (Figure 5). In contrast, 2-pyrone hydrazone, **5-prot**, is only modestly antiaromatic (NICS$(1)_{zz}$ = +6.3 ppm), has a low HOMO energy (−7.3 eV), and shows no barrier-lowering effect ($\Delta G^{\ddagger}$ = 24.3 kcal/mol).

Temporarily introducing antiaromaticity offers a way to convert [4*n*+2] π-aromatic, electron-deficient dienes into electron-rich dienes that have high HOMO energies suitable for normal-electron-demand Diels−Alder reactions. We show here that this transformation may be achieved through a carbonyl umpolung strategy using the hydrazone ion. By analogy to the use of iminium ions to catalyze cycloadditions (i.e., decreasing the LUMO energies of dienophiles),[30,31] the reversible transformation of carbonyl groups into anionic derivatives (i.e., increasing the HOMO energies of dienes with low reactivity) can open interesting possibilities for organocatalysis. We note that in the reported examples of HOMO-raising strategies for activating tropolone,[7,8] deprotonating OH also increases the electron density and decreases the aromatic character of the seven-membered ring, much like the effects of carbonyl umpolung discussed here. Conceptually, this work offers a new approach to achieving reactivity control through the relief of reactant antiaromaticity.[32−40]

COMPUTATIONAL DETAILS

Geometry optimizations in the gas-phase and in implicit dichloromethane solvent were performed at ωB97X-D/6-311+G(d,p) employing the Gaussian16 program.[41] Vibrational frequency analyses and intrinsic reaction coordinate (IRC) computations verified the nature of the minima and transition-state structures. Activation free energies were computed at the same level of theory based on the energy of the transition-state structures minus the energy of the reactant complex and include basis set superposition error (BSSE) corrections. Data for the exo pathways of all reactions considered are included in Table S2 and support a preferred endo reaction. Natural bond orbital (NBO)[26] calculations were performed at the ωB97X-D/6-311+G(d,p) level. Nucleus-independent chemical shifts, NICS$(1)_{zz}$, were computed at the PW91/IGLOIII level at 1 Å above the seven-membered ring centers, including only magnetic tensor components in the direction perpendicular to the ring plane.[16,17] 3-D structures were produced with the CYLView 1.0.1 software.[42]

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02343.

> Gas-phase activation free energies for relevant reactions, analyses of electron demand for all reactions, and Cartesian coordinates of all optimized structures. Contents of the SI were partly generated by ESIgen[43] (PDF)

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Notes

The authors declare no competing financial interest.

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