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## Origins of halogen effects in bioorthogonal sydnone cycloadditions<sup>†</sup>

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### Abstract

Halogen substituents increase sydnone cycloaddition reactivities substantially. Fluoro-sydnes are superior to bromo- and chloro-sydnes, and can achieve extremely high second-order rate constants with strained alkynes. Computational studies have revealed the fluorine substituent increases the reactivity of sydnone mainly by lowering its distortion energy.

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Sydnes are 1,3-dipolar azomethine imines bridged by a lactone, and react with dipolarophiles to give pyrazoles after carbon dioxide extrusion. Sydnone 1,3-dipolar cycloadditions were reviewed by Harrity,<sup>1</sup> and more recently Taran.<sup>2</sup> Sydnone chemistry has found application in organic synthesis, especially of natural products or drug molecules bearing pyrazole units,<sup>3</sup> as well as in materials science and biology.<sup>4</sup>

Pioneering work by Taran on copper catalyzed sydnone cycloaddition (Fig. 1a) demonstrated its high efficiency and biocompatibility and opened up the area of sydnone bioorthogonal chemistry.<sup>5</sup> Chin established a bioorthogonal sydnone cycloaddition with the use of a distorted bicyclononyne (BCN), and demonstrated its application in protein labeling (Fig. 1b).<sup>6</sup> Taran observed that halogen substituents on sydnes generally enhance the reactivities of sydnes in cycloadditions (Fig. 1c, X = Br, Cl, and F) except for the pseudohalogen CN, which decreases the rate constant by one order of magnitude compared to the parent sydnone, and is comparable to trifluoromethyl substituted sydnone (Fig. 1c, X

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<sup>†</sup>Electronic Supplementary Information (ESI) available: computational details see DOI: 10.1039/x0xx00000x

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= CN, CF<sub>3</sub>).<sup>7</sup> Fluorine significantly enhances the effectiveness of sydnone cycloaddition. The reaction of 4-fluoro-3-tolylsydnone with BCN has a second-order rate constant as high as 42 M<sup>-1</sup> s<sup>-1</sup>.<sup>7b</sup> If reacting with a much more distorted tetramethylthiacycloheptyne (TMTH), this fluorosydnone can achieve an extremely high second-order rate constant of 1500 M<sup>-1</sup> s<sup>-1</sup> (Fig. 1d).<sup>7b</sup>

We report here a theoretical study of the origins of sydnone activation by halogen, using DFT calculations carried out at the M06-2X level of theory.<sup>8</sup> It was showed earlier that this method gives relatively accurate energies for cycloadditions.<sup>9</sup> Solvent effects in water were evaluated at the M06-2X/6-311+G(d,p) level with the CPCM model. Computational details are provided in the Supplementary Information (ESI).

Fig. 2 summarizes the calculated LUMO energies of sydnones **1-6**, the activation free energies for their reactions with BCN **7**, and the transition-state structures (TSs) for cycloadditions. The forming C-C and C-N bond distances in TSs are shown in Å. Our computational results are in good agreement with the experimentally measured rate constants (Fig. 1c). According to the frontier molecular orbital theory, the primary orbital interaction in sydnone cycloaddition with BCN involves the LUMO of sydnone and the HOMO of BCN. The decrease in LUMO energy of sydnone **6** compared to sydnone **1** is small (0.81 versus 0.99 eV), whereas the surge in the reactivity upon fluorination is obvious (42 M<sup>-1</sup> s<sup>-1</sup> versus 0.03 M<sup>-1</sup> s<sup>-1</sup>, Fig. 1c). In comparison with sydnone **6**, sydnone **3** has a low-lying LUMO (0.40 versus 0.81 eV) but a high reaction barrier (22.6 versus 16.7 kcal mol<sup>-1</sup>). Fig. 3 presents the inconsistent relationships between LUMO energies of sydnones and activation free energies, implying that the R substituents alter the cycloaddition reactivities of sydnones through a more sophisticated mechanism.

To better understand the halogen effects in sydnone cycloadditions, we used the Distortion/Interaction Model (also known as the Activation Strain Model)<sup>10,11</sup> developed by Houk and Bickelhaupt to identify the origins of reactivity differences, and the results are shown below each TS structure in Fig. 2. The black arrows represent the activation barriers. The blue and green arrows correspond to the distortion energies, which are the energies required to distort the ground-state sydnone (blue) and BCN (green) into the geometries that they take in the transition-state structure. The stabilizing interaction between the distorted reactants is the interaction energy (red arrows), and the sum of distortion energy and interaction energy gives the activation energy of the reaction. Since dipolarophile (BCN) is highly pre-distorted, the BCN distortion energies (Fig. 2, green arrows) are only around 3 kcal mol<sup>-1</sup> and show minor fluctuations. Sydnone distortion energies (Fig. 2, blue arrows) and interaction energies (Fig. 2, red arrows) control the reactivity differences between substituted sydnones.

Fig. 4 shows that the activation energies correlate well with the distortion energies (both sydnone distortion and total distortion energies) for all six reactions of sydnones **1-6**. Cyanosydnone **3** has the highest activation barrier, an overall result of favorable interaction exceeded by the greatest distortion energy due to its extremely late transition state. The reaction of fluorosydnone **6** involves a much earlier transition state compared to the parent

sydnone **1**, and therefore has a much smaller distortion energy and less favorable interaction energy, with the overall effect causing it to be the most reactive substituted sydnone.

We evaluated the thermodynamic consequence of the R substituents on the sydnone nucleus (Fig. 5). The hydrogenation reaction of sydnone shown in Fig. 5 resembles the transformation from  $sp^2$  to  $sp^3$  hybridization involved in the sydnone cycloaddition. In comparison to the parent sydnone, a less negative hydrogenation enthalpy implies stabilization (cyanosydnone **3**), while a more negative hydrogenation enthalpy suggests destabilization (fluorosydnone **6**). Sydnone distortion energies correlate with the hydrogenation enthalpies, revealing the fact that stabilization (or destabilization) prevents (or assists) the distortion of sydnone toward its geometry in transition-state structure during cycloaddition.

To compare directly how R substituents alter the distortion energies of sydnones, a scan of the out-of-plane distortion (Fig. 6, top left), a prominent distortion in the transition state, was carried out. For each substituted sydnone, the out-of-plane dihedral angle  $\omega$ , which is nearly  $1^\circ$  for ground-state structures and  $23\text{--}27^\circ$  for transition-state structures, was gradually increased to  $30^\circ$  at intervals of  $2.5^\circ$ . The remaining geometrical parameters were optimized with  $\omega$  fixed. Fig. 6 shows the plots of  $E_{\text{dist}}$  versus the dihedral angle  $\omega$ . The distortion energy increases as the dihedral angle increases. At a certain angle within the transition zone (highlighted with a yellow box in Fig. 6 with  $\omega = 23\text{--}27^\circ$ ), the distortion energy of sydnone **6** ( $R = F$ ) is significantly lower than that of **3** ( $R = CN$ ). The out-of-plane distortion converts an  $sp^2$  C into an  $sp^3$  C; this is unfavorable for CN, which provides better conjugation for the planar system. The strongly electronegative F prefers to be attached to the  $sp^3$  hybridized carbon, which better releases electron density (Bent's Rule).<sup>12</sup> Chlorine and bromine, which are less electronegative compared to fluorine, have less significant effects on lowering the out-of-plane distortion of sydnones **4** and **5** (Fig. 6).

In conclusion, we have computed activation free energies and analyzed them with the Distortion/Interaction model to explore the origins of halogen effects on the cycloaddition reactivities of sydnones. Fluorine substituent at the sydnone C4 position lowers the LUMO energy, and more importantly, makes it much easier to distort, decreasing the activation barrier dramatically. Our results provide new understandings of the role of halogens in cycloadditions. The distortion-assisted acceleration in reactivity will inspire the future design of new bioorthogonal reactions.

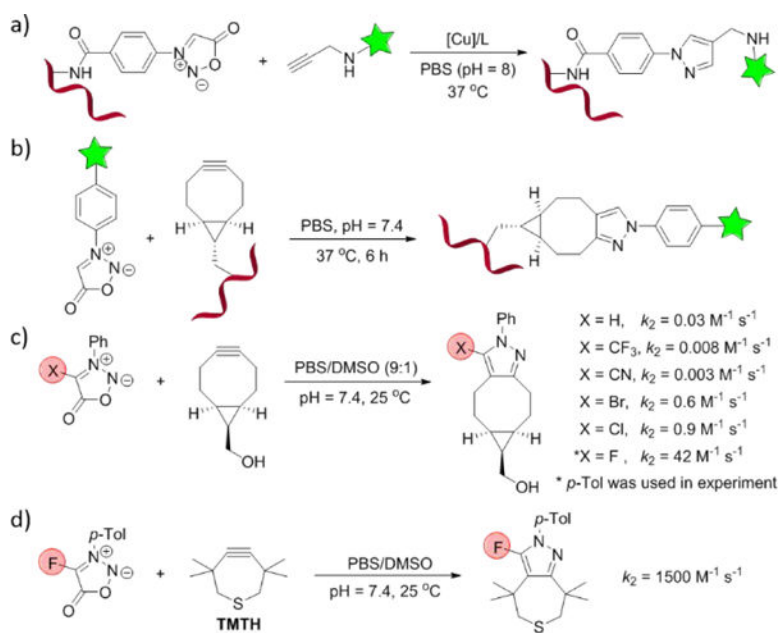
This work was financially supported by the National Thousand Young Talents Program, Jiangsu Specially-Appointed Professor Plan, and the NSF of Jiangsu Province (BK20170631) in China. K.N.H. is grateful to the National Institute of General Medical Sciences, National Institutes of Health (R01 GM109078) for support. Y.C. acknowledges the support from the Shenzhen Peacock Plan (No.1208040050847074).

## Supplementary Material

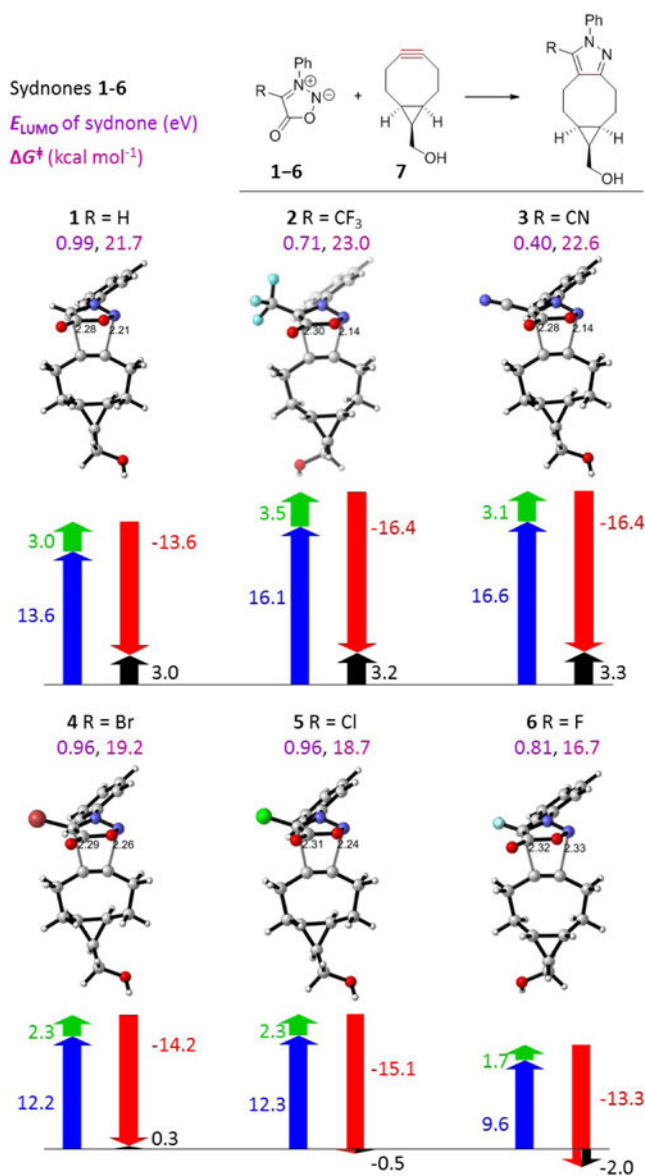
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## Notes and references

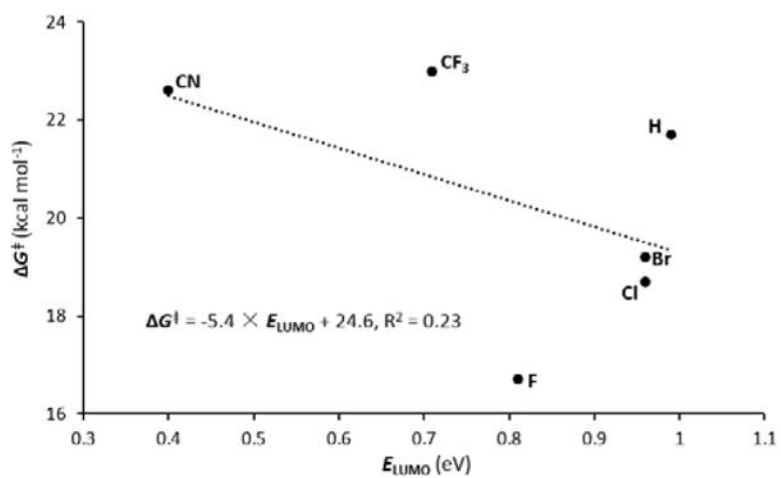
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**Fig 1.**  
Sydnone cycloaddition in bioorthogonal chemistry.

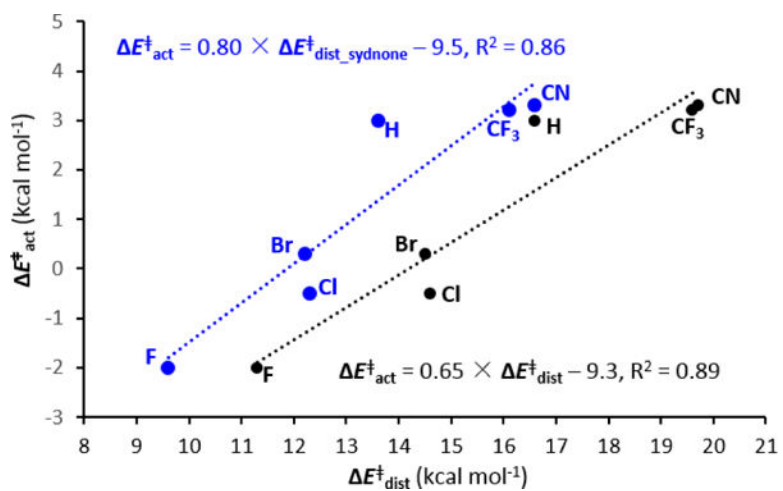


**Fig. 2.** Transition-state structures and D/I analysis of the cycloadditions of sydnones **1-6** with BCN **7**. Computed LUMO energies of sydnones and activation free energies are shown above each TS structure. D/I analysis is shown below each TS structure, in which the black arrows represent activation energies, the blue and green arrows represent the distortion energies for sydnones and BCN, respectively, and the red arrows represent the interaction energies. The activation energy is the sum of distortion energy and interaction energy.

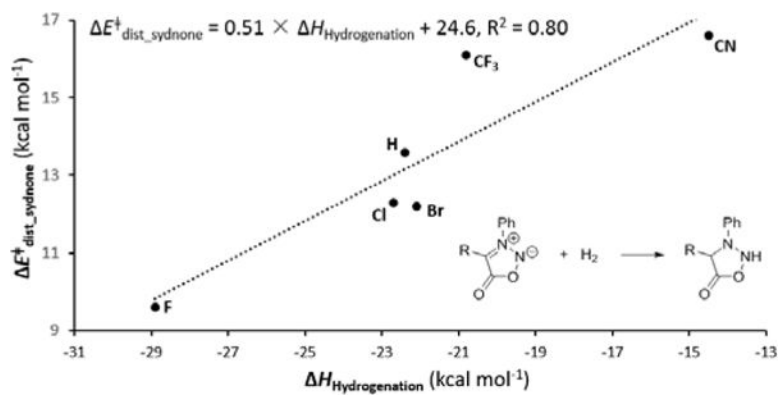


**Fig. 3.** Plot of activation free energies versus LUMO energies of sydnones **1-6**.

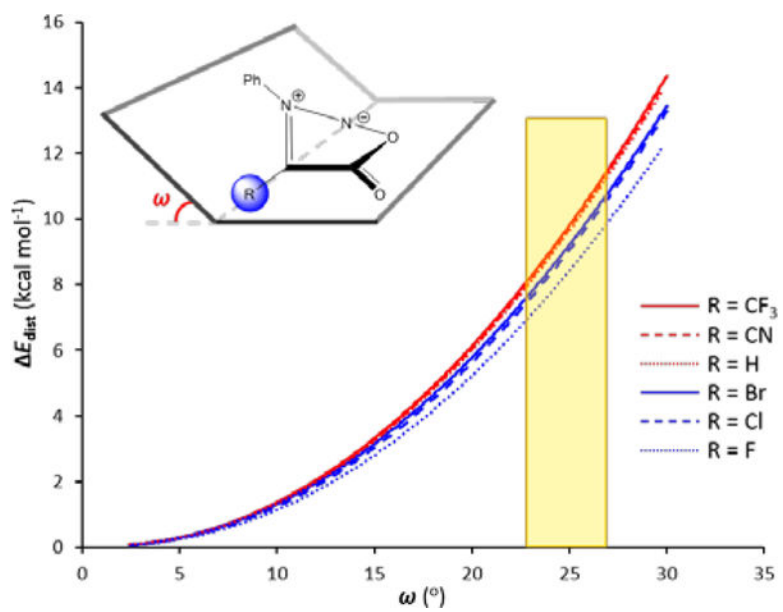




**Fig. 4.** Plots of activation energies versus distortion energies (blue: sydnone distortion energies; black: total distortion energies) for reactions of sydnones **1-6**.



**Fig. 5.** Plot of syndnone distortion energies versus syndnone hydrogenation enthalpies.



**Fig. 6.** Sydnone distortion energies as a function of out-of-plane bending angle.