HHS Public Access

Author manuscript

*Tetrahedron Lett*. Author manuscript; available in PMC 2023 October 25.

Published in final edited form as:

*Tetrahedron Lett*. 2023 October 25; 130: . doi:10.1016/j.tetlet.2023.154768.

# Computational study of an oxetane 4*H*-pyrazole as a Diels–Alder diene

**Brian J. Levandowski**[*],

**Nile S. Abularrage**,

**Brian J. Graham**,

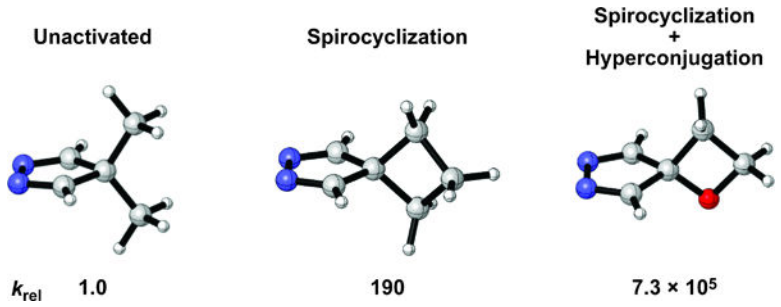
**Ronald T. Raines**[*]

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, MA 02139-4307, USA

## Abstract

We combine the effects of spirocyclization and hyperconjugation to increase the Diels–Alder reactivity of the 4*H*-pyrazole scaffold. A density functional theory (DFT) investigation predicts that 4*H*-pyrazoles containing an oxetane functionality at the saturated center are extremely reactive despite having a relatively high-lying lowest unoccupied molecular orbital (LUMO) energy.

## Graphical Abstract




Spirocyclization and hyperconjugation activate 4*H*-pyrazoles as Diels–Alder dienes. The harmonization of spirocyclization and hyperconjugation was used to design a 4*H*-pyrazole that is predicted to be 730,000 times more reactive than an unactivated 4*H*-pyrazole.

### Keywords

Click chemistry; cycloaddition; density functional theory (DFT)

[*]Corresponding authors: levandbj@ucla.edu (B. J. Levandowski); rtraines@mit.edu (R. T. Raines).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2023.xxxxxx.

## Introduction

Sauer and coworkers reported the rapid reactivity of 1,2,4,5-tetrazines as inverse-electron demand Diels–Alder dienes with strained dienophiles such as cyclopropene, *trans*-cyclooctene, cyclooctyne, and norbornadiene.[1,2] The Fox group took advantage of the reactivity of the tetrazine-*trans*-cyclooctene reaction, using it to modify a protein at low concentration.[3] Since then, efforts have been made to enhance the reactivity of the tetrazine and *trans*-cyclooctene scaffolds without sacrificing stability.[4,5]

We have focused on developing 4*H*-pyrazoles as bioorthogonal reagents. Fluorination of the saturated center in a 5-membered diene invokes antiaromatic electron delocalization and increases Diels–Alder reactivity.[6–9] We have reported a 4,4-difluoro-4*H*-pyrazole that reacts twice as fast as an equivalently substituted tetrazine towards the strained alkyne, bicyclononyne (BCN).[10] Although fluorination increased the reactivity, it also compromised the stability of the 4*H*-pyrazole scaffold.[11]

A purely computational study predicted that spirocyclic 4*H*-pyrazoles were more reactive than their acyclic analogs.[12,13] This study inspired the synthesis and experimental analysis of spirocyclic 4-oxo-4*H*-pyrazoles.[14] Whereas the spirocyclic 4-oxo-4*H*-pyrazoles were not as reactive as the 4,4-difluoro-4*H*-pyrazole, they showed robust biological stability, allowing them to be utilized in biological applications. Herein, we further optimize the spirocyclic 4-oxo-4*H*-pyrazole motif and disclose a new spirocyclic 4-oxo-4*H*-pyrazole with promising reactivity and suggestive stability.

## Results and discussion

The structures of the 4*H*-pyrazoles included in this study are shown in Scheme 1. The lowest unoccupied molecular orbital (LUMO) energies of these compounds as well as their activation energies towards the strained alkyne BCN are reported in Figure 1. All calculations were carried out at the M06-2X/6-311++G(d,p)-SMD($H_2O$)//M06-2X/6-31G(d) level of theory.[15] The M06-2X functional has been shown to accurately predict the reactivity of bioorthogonal cycloaddditions.[16–20]

The dimethyl 4*H*-pyrazole, **1**, is the least reactive 4*H*-pyrazole with an activation energy of 24.9 kcal/mol. The difluoro 4*H*-pyrazole, **4**, is predicted to be $6.2 \times 10^5$ times more reactive than **1** with an activation energy of 17.0 kcal/mol. The cyclobutane 4*H*-pyrazole, **2**, has a calculated activation energy of 21.8 kcal/mol and is predicted to be 190 times more reactive than dimethyl 4*H*-pyrazole **1**. The oxetane 4*H*-pyrazole, **3**, combines the effects of spirocyclization and hyperconjugation in an optimal fashion to promote reactivity. This diene has a predicted activation energy of 16.9 kcal/mol, which is comparable to that of highly reactive difluoro 4*H*-pyrazole **4**.

The computed LUMO energies are −1.3, −1.4, −1.5, and −2.1 eVs for 4*H*-pyrazoles **1**, **2**, **3**, and **4**, respectively. It has been shown that the relevant unoccupied molecular orbitals of appropriate symmetry in 1,2,4,5-tetrazines correlate with their stability in biological media.[5] 4*H*-Pyrazoles **3** and **4** have similar predicted reactivities towards BCN, but the LUMO of **3** is 0.55 eVs higher lying than the LUMO of **4**. This increase suggests that oxetane

4*H*-pyrazole **3** will have greater stability towards biological nucleophiles relative to difluoro 4*H*-pyrazole **4**[10,11] and could expand the scope of bioorthogonal reactions based on the Diels–Alder reaction.[21]

## Conclusions

We find that oxetane 4*H*-pyrazole **3** is a promising motif worthy of experimental study. The harmonization of spirocyclization and hyperconjugation in the oxetane 4*H*-pyrazole induces a synergetic effect that promotes the reactivity of the 4*H*-pyrazole scaffold without significantly disturbing the electronic properties of the diene. This computational studyx suggests that oxetane 4*H*-pyrazole **3** will have similar Diels–Alder reactivity and increased biological stability relative to 4*H*-pyrazoles that are activated by fluorination.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

B.J.L. was supported by postdoctoral fellowship F32 GM137543 from the NIH. N.S.A. was supported by a Graduate Research Fellowship from the NSF. This work was supported by Grants R01 GM044783 and R35 GM148220 from the 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 from the NSF.

## References

[1]. Thalhammer F, Wallfahrer U, Sauer J J, Tetrahedron Lett 31 (1990) 6851–6854.

[2]. Sauer J, Heinrichs G, Tetrahedron Lett 7 (1966) 4979–4984.

[3]. Blackman ML, Royzen M, Fox JM, J. Am. Chem. Soc 130 (2008) 13518–13519. [PubMed: 18798613]

[4]. Taylor MT, Blackman ML, Dmitrenko O, Fox JM, J. Am. Chem. Soc 133 (2011) 9646–9649. [PubMed: 21599005]

[5]. Svatunek D, Wilkovitsch M, Hartmann L, Houk KN, Mikula H, J. Am. Chem. Soc 144 (2022) 8171–8177. [PubMed: 35500228]

[6]. Fernández I I, Wu JI, von R Schleyer P. , Org. Lett 15 (2013) 2990–2993. [PubMed: 23724938]

[7]. Levandowski BJ, Zou L, Houk KN, J. Comput. Chem 37 (2016) 117–123. [PubMed: 26444427]

[8]. Levandowski BJ, Zou L, Houk KN, J. Org. Chem 83 (2018) 14658–14666. [PubMed: 30395708]

[9]. Nyulászi L, von R P. Schleyer, J. Am. Chem. Soc 121 (1999) 6872–6875.

[10]. Levandowski BJ, Abularrage NS, Houk KN, Raines RT, Org. Lett 21 (2019) 8492–8495. [PubMed: 31589054]

[11]. Abularrage NS, Levandowski BJ, Raines RT, Int. J. Mol. Sci 21 (2020) 3964. [PubMed: 32486503]

[12]. Levandowski BJ, Abularrage NS, Raines RT, J. Phys. Org. Chem 36 (2023) e4478. [PubMed: 36968255]

[13]. Levandowski BJ, Abularrage NS, Raines RT, Tetrahedron 91 (2021) 132160. [PubMed: 34290459]

[14]. Abularrage NS, Levandowski BJ, Giancola JB, Graham BJ, Raines RT, Chem. Commun 59 (2023) 4451–4454.

[15]. Zhao Y, Truhlar DG, Theor. Chem. Acc 120 (2008) 215–241.

[16]. Yang J, Liang Y, Šečkutė J, Houk KN, Devaraj NK, Chem. Eur. J 20 (2014) 14893–14902.

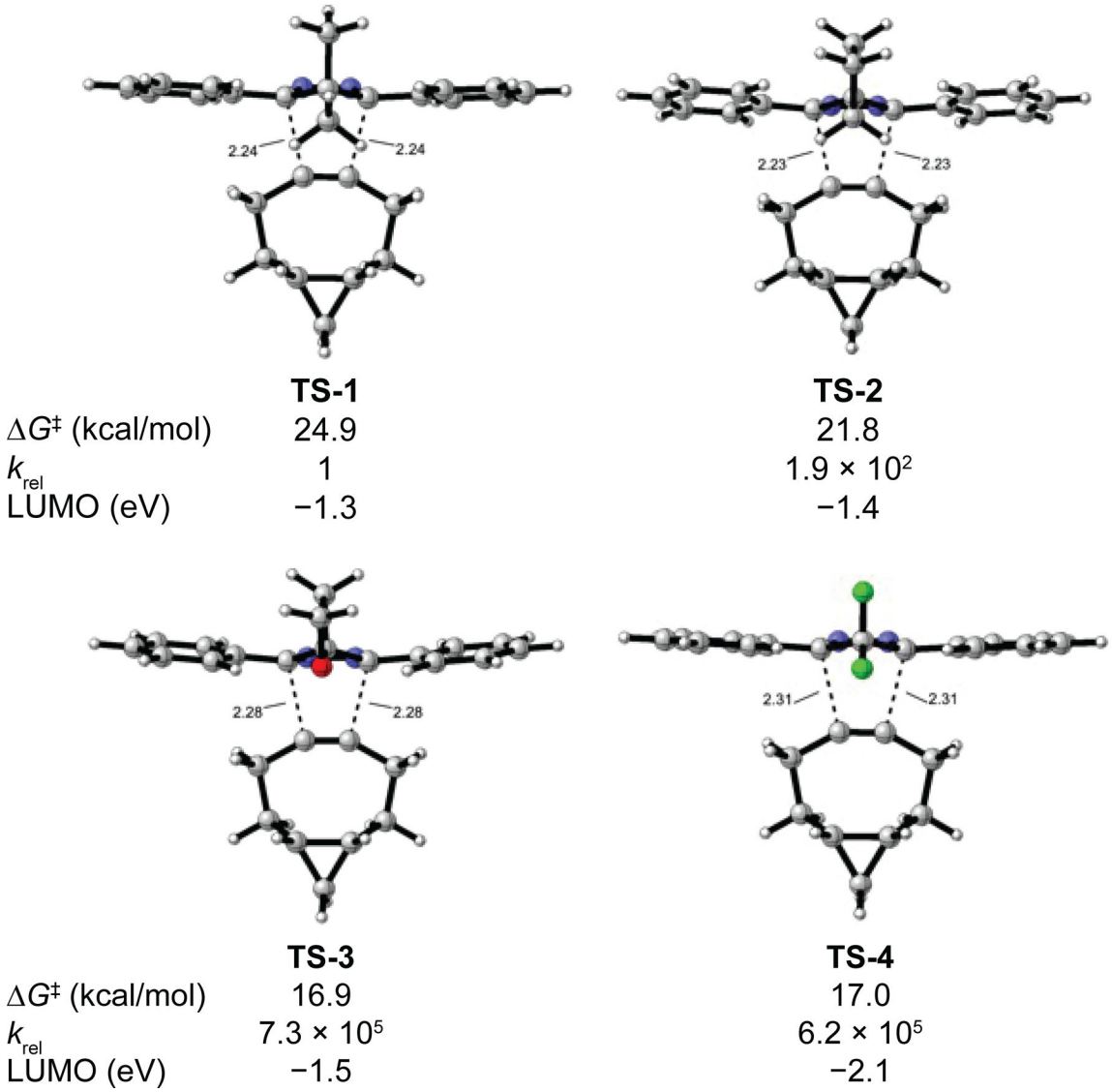
[17]. Kamber DN, Liang Y, Blizzard RJ, Liu F, Mehl RA, Houk KN, Prescher JA, J. Am. Chem. Soc 137 (2015) 8388–8391. [PubMed: 26084312]

[18]. Narayanam MK, Liang Y, Houk KN, Murphy JM, Chem. Sci 7 (2016) 1257–1261 [PubMed: 29910881]

[19]. Levandowski BJ, Gamache RF, Murphy JM, Houk KN, J. Am. Chem. Soc 140 (2018) 6426–6431. [PubMed: 29712423]

[20]. Levandowski BJ, Svatunek D, Sohr B, Mikula H, Houk KN, J. Am. Chem. Soc 141 (2019) 2224–2227. [PubMed: 30693769]

[21]. Levandowski BJ, Raines RT, Chem. Rev 121 (2021) 6777–6801. [PubMed: 33651602]

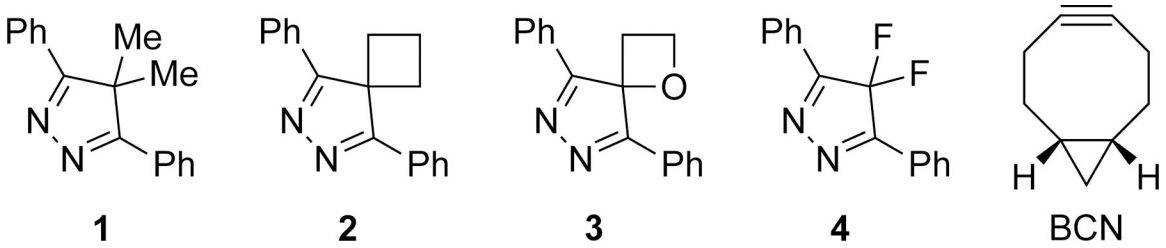



| | TS-1 | TS-2 |
|---|---|---|
| $\Delta G^{\ddagger}$ (kcal/mol) | 24.9 | 21.8 |
| $k_{rel}$ | 1 | $1.9 \times 10^2$ |
| LUMO (eV) | −1.3 | −1.4 |

| | TS-3 | TS-4 |
|---|---|---|
| $\Delta G^{\ddagger}$ (kcal/mol) | 16.9 | 17.0 |
| $k_{rel}$ | $7.3 \times 10^5$ | $6.2 \times 10^5$ |
| LUMO (eV) | −1.5 | −2.1 |

**Figure 1.**

Gibbs free energies of activation in kcal/mol for the Diels–Alder reaction of dienes **1**–**4** with BCN. Relative rates were obtained from the Arrhenius equation. LUMO energies are reported in electron volts calculated from the diene ground state geometries. Forming bond lengths of the transition state structures are reported in Ångstroms.




**Scheme 1.**
Structures of 4*H*-pyrazoles **1**–**4** and BCN.