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The Pauli Repulsion-Lowering Concept in Catalysis

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CONSPECTUS: Organic chemistry has undoubtedly had a profound impact on humanity. Day in and day out, we find ourselves constantly surrounded by organic compounds. Pharmaceuticals, plastics, fuels, cosmetics, detergents, and agrochemicals, to name a few, are all synthesized by organic reactions. Very often, these reactions require a catalyst in order to proceed in a timely and selective manner. Lewis acids and organocatalysts are commonly employed to catalyze organic reactions and are considered to enhance the frontier molecular orbital (FMO) interactions. A vast number of textbooks and primary literature sources suggest that the binding of a Lewis acid or an iminium catalyst to a reactant (R1) stabilizes its LUMO and leads to a smaller HOMO(R2)–LUMO(R1) energy gap with the other reactant (R2), thus resulting in a faster reaction. This forms the basis for the so-called LUMO-lowering catalysis concept. Despite the simplicity and popularity of FMO theory, a number of deficiencies have emerged over the years, as a consequence of these FMOs not being the operative factor in the catalysis. LUMO-lowering catalysis is ultimately incomplete and is not always operative in catalyzed organic reactions. Our groups have recently undertaken a concerted effort to generate a unified framework to rationalize and predict chemical reactivity using a causal model that is rooted in quantum mechanics. In this Account, we propose the concept of Pauli repulsion-lowering catalysis to understand the catalysis in fundamental processes in organic chemistry. Our findings emerge from state-of-the-art computational methods, namely, the activation strain model (ASM) of reactivity in conjunction with quantitative Kohn–Sham molecular orbital theory (KS-MO) and a matching energy decomposition analysis (EDA). The binding of the catalyst to the substrate not only leads to a stabilization of its LUMO but also induces a significant reduction of the two-orbital, four-electron Pauli repulsion involving the key molecular orbitals of both reactants. This repulsion-lowering originates, for the textbook Lewis acid-catalyzed Diels–Alder reaction, from the catalyst polarizing the occupied π orbital of the dienophile away from the carbon atoms that form new bonds with the diene. This polarization of the occupied dienophile π orbital reduces the occupied orbital overlap with the diene and constitutes the ultimate physical factor responsible for the acceleration of the catalyzed process as compared to the analogous uncatalyzed reaction. We show that this physical mechanism is generally applicable regardless of the type of reaction (Diels–Alder and Michael addition reactions) and the way the catalyst is bonded to the reactants (i.e., from pure covalent or dative bonds to weaker hydrogen or halogen bonds). We envisage that the insights emerging from our analysis will guide future experimental developments toward the design of more efficient catalytic transformations.

Pauli Repulsion-lowering Catalysis

KEY REFERENCES

- Hamlin, T.; Fernández, I.; Bickelhaupt, F. M. How dihalogens catalyze Michael addition reactions. *Angew. Chem., Int. Ed.* **2019**, 58, 8922–8926.¹ Dihalogen molecules ($X_2 = F_2, Cl_2, Br_2, I_2$) do not accelerate the aza-Michael reaction involving pyrrolidine and methyl acrylate by enhancing the HOMO(nucleophile)–LUMO(Michael acceptor) interaction, as traditionally accepted, but by reducing the Pauli repulsion between the lone pair of the nucleophile and the Michael acceptor's π -electron system.
- Vermeeren, P.; Hamlin, T.; Fernández, I.; Bickelhaupt, F. M. How Lewis acids catalyze Diels–Alder reactions. *Angew. Chem., Int. Ed.* **2020**, 59, 6201–6206.² We found that the Lewis acid induces a significant reduction

of the Pauli repulsion between the key π -molecular orbitals of the reactants. This Pauli lowering, and not the widely accepted LUMO-lowering catalysis, constitutes the actual electronic mechanism behind the catalysis mediated by Lewis acids.

- Vermeeren, P.; Hamlin, T.; Fernández, I.; Bickelhaupt, F. M. Origin of rate enhancement and asynchronicity in iminium catalyzed Diels–Alder reactions. *Chem. Sci.* **2020**,

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11, 8105–8112.³ Related to the above works, the acceleration of the Diels–Alder reactions induced by the formation of an iminium cation is mainly caused by significant Pauli lowering rather than by LUMO-lowering activation. The crucial impact of the asynchronicity on the process is also disclosed.

- Vermeeren, P.; Hamlin, T.; Bickelhaupt, F. M.; Fernández, I. Bifunctional hydrogen bond donor-catalyzed Diels–Alder reactions: origin of stereoselectivity and rate enhancement. *Chem.—Eur. J.* **2021**, *27*, 5180.⁴ In this work, we have focused on the related Diels–Alder cycloadditions catalyzed by (thio)urea organocatalysts. We established that the Pauli lowering concept described in the previous works seems general and can be also applied to the Diels–Alder reactions where the catalyst is more weakly bonded (through hydrogen bonds) to the dienophile.

1. INTRODUCTION

A great number of reactions in organic chemistry have been (and still are) rationalized in terms of Fukui's frontier molecular orbital (FMO) theory⁵ and Woodward–Hoffmann rules.⁶ Indeed, these approaches have become powerful conceptual frameworks for interpreting the reactivity and regioselectivity patterns of different fundamental transformations such as pericyclic reactions.⁷ FMO theory focuses on the interactions between the HOMO and LUMO of reactants, and the strongest interactions occur between orbitals that are closest in energy and have the largest overlap.

In this regard, FMO theory has also been used to rationalize catalytic organic transformations. For instance, the acceleration observed in Lewis acid (LA)-catalyzed Diels–Alder (DA) reactions with respect to the corresponding uncatalyzed processes is typically explained in terms of the stabilization of the LUMO of the dienophile upon binding to the LA. This, in turn, results in a lower HOMO(diene)–LUMO(dienophile) energy gap as compared to that occurring in the uncatalyzed process which is translated into the observed acceleration.^{7,8} This is the typical explanation that can be found in most organic chemistry textbooks⁹ and is known as LUMO-lowering catalysis. This concept has been extended to other synthetically useful transformations such as iminium-catalyzed (cyclo)additions.¹⁰

Despite the usefulness and popularity of FMO theory, a significant number of deficiencies have been identified,¹¹ mainly due to the lack of quantitative significance of these FMO interactions. We have also recently found that the above-mentioned FMO-based LUMO-lowering catalysis concept is rather incomplete and does not constitute the ultimate reason behind the catalysis in fundamental processes in organic chemistry.^{1–4} In this Account, we shall highlight our recent results rooted in state-of-the-art quantum chemical calculations, which allowed us to propose a new concept called Pauli repulsion-lowering catalysis. We will show herein that this physical mechanism is of general applicability regardless of the type of reaction and the way the catalyst is bonded to the reactants.

2. LEWIS ACID-CATALYZED DIELS–ALDER REACTIONS²

We first focused on the textbook and synthetically useful LA-catalyzed Diels–Alder reactions.¹² To this end, we selected the cycloaddition reaction involving isoprene and methyl acrylate

(MA), which, in the presence of an LA such as AlCl_3 , leads to the almost selective formation of the corresponding 1,4-cycloadduct (Scheme 1).¹³

Scheme 1. Uncatalyzed and LA-Catalyzed DA Reactions That Were Considered

The activation barrier computed for the cycloadditions depicted in Scheme 1 steadily decreases with the increasing Lewis acidity of the LA (Table 1),¹⁴ which is consistent with the

Table 1. Computed Activation Barriers ($\Delta E^\ddagger$ in kcal/mol),^a LUMO(Dienophile) Energies (ϵ_{LUMO} , in eV), Instantaneous Interaction Energies (ΔE_{int} , in kcal/mol),^b and Experimentally Determined Lewis Acidities^c

LA	$\Delta E^\ddagger$	ϵ_{LUMO}	ΔE_{int}	Lewis acidity
none	16.2	−2.6		
SnCl_4	12.3	−4.0	−10.0	0.52 ± 0.04
TiCl_4	11.8	−4.3	−14.5	0.66 ± 0.03
ZnCl_2	10.8	−3.7	−17.2	
BF_3	10.0	−3.8	−25.6	0.77 ± 0.02
AlCl_3	7.6	−4.2	−37.5	0.82

^aComputed as $\Delta E^\ddagger = E(\text{TS}) - E(\text{diene}) - E(\text{dienophile})$ at the (TightPNO)DLPNO-CCSD-(T)/CBS(3,4/def2)//ZORA-BP86/TZ2P level. ^bComputed (ZORA-BP86/TZ2P level) as $\Delta E_{\text{int}} = E(\text{LA-dienophile}) - E(\text{dienophile}) - E(\text{LA})$ using the geometries in the LA-acrylate complex. ^cRelative Lewis acidity scale based on $\Delta\delta$ values of H3 resonances of various bases related to methyl crotonate, with data taken from ref 14.

rate enhancement observed experimentally.^{12,13} Should the widely accepted LUMO-lowering catalysis apply, then a clear correlation between the computed barriers and the energy of the LUMO(dienophile) should exist. However, although the energy of the LUMO of these LA–ester complexes, which corresponds to the reactive π^* -molecular orbital, is indeed lower (i.e., more negative) than that of the parent MA, it does not follow the same reactivity trend (Table 1).² This is a somewhat surprising result if we take into account that the strength of the dative bond established between the lone pair of the carbonyl group of MA and the vacant (atomic d or p) orbital of the LA, measured by the instantaneous interaction energy between the LA and the ester (ΔE_{int}), also follows the same trend in reactivity as the activation barriers. This finding therefore suggests that the relative reactivity of these dienophiles is not directly related to the corresponding HOMO(diene)–LUMO(ester) interaction.

To quantitatively understand the factors which ultimately control the catalysis in these LA-mediated DA reactions, we applied the so-called activation strain model (ASM)¹⁵ of reactivity. This method, also known as the distortion–interaction model,^{15b} decomposes the electronic energy (ΔE) into two terms, namely, the strain (ΔE_{strain}) that results from the distortion of the individual reactants and the interaction (ΔE_{int}) between the deformed reactants along the reaction coordinate

defined as the projection of the intrinsic reaction coordinate (IRC) on a critical geometry parameter that directly defines the progress of the studied reaction, which in this case is the shorter C...C bond-forming distance. Figure 1a shows the correspond-

Figure 1. (a) Comparative activation strain analyses of the DA reactions between isoprene and uncoordinated (none) as well as TiCl_4 - and AlCl_3 -coordinated methyl acrylate complexes projected onto the shorter C...C bond-forming distance. (b) Optimized geometries of the corresponding transition states. Bond distances are given in angstroms.

ing activation strain diagrams (ASDs) for the uncatalyzed (none), TiCl_4 -catalyzed, and AlCl_3 -catalyzed cycloadditions along the reaction coordinate from the initial stages of the process up to the respective transition states. It is found that the lower barrier computed for the LA-catalyzed cycloadditions originates mainly from a much stronger interaction between the deformed reactants along the entire transformation and to a less destabilizing strain energy, albeit to a much lesser extent. The latter can be ascribed to the higher asynchronicity of the LA-catalyzed cycloadditions (none, $\Delta r_{\text{C}\cdots\text{C}}^{\text{TS}} = 0.46 \text{ \AA}$; TiCl_4 , $\Delta r_{\text{C}\cdots\text{C}}^{\text{TS}} = 0.72 \text{ \AA}$; and AlCl_3 , $\Delta r_{\text{C}\cdots\text{C}}^{\text{TS}} = 0.78 \text{ \AA}$, where $\Delta r_{\text{C}\cdots\text{C}}^{\text{TS}}$ is the difference between the newly forming C...C bond lengths in the TS; see Figure 1b), which leads to a lower degree of deformation of the diene since one C–C bond forms ahead of the other C–C bond.

The origin of the stronger interaction between the reactants computed for the LA-catalyzed cycloadditions can be further quantitatively understood by using the canonical energy decomposition analysis (EDA) method (employed for all studies highlighted in this Account).¹⁶ The EDA decomposes

the ΔE_{int} between the reactants into three chemically meaningful energy terms, namely, the classical electrostatic interaction (ΔV_{elstat}), the Pauli repulsion (ΔE_{Pauli}) between closed-shell orbitals which is responsible for steric repulsion, and the stabilizing orbital attractions (ΔE_{oi}) that account, among others, for HOMO–LUMO interactions. The evolution of these EDA terms along the reaction coordinate, once again from the initial stages of the processes up to the respective TSs, is shown in Figure 2a. It becomes evident that the differences in the ΔV_{elstat} curves and, in particular, in the ΔE_{oi} curves are minimal, which sharply contrasts with the commonly accepted view. At variance, ΔE_{Pauli} is significantly less destabilizing for the LA-catalyzed reactions; therefore, it constitutes the sole factor responsible for the stronger interaction between the reactants along the transformation. This Pauli repulsion lowering is the result of a significant reduction of the electron density at the reactive C=C bond of the ester induced by the LA, which is reflected in a reduction of the overlap between the key occupied π -molecular orbitals (MOs) of the diene and the dienophile (Figure 2b). Therefore, it can be concluded that the ultimate factor controlling the LA-catalyzed DA reactions is the reduction of the four-electron (Pauli) repulsion between the π -systems of the dienophile and the incoming diene rather than the stabilization of the LUMO of the dienophile.

Finally, the NOCV (natural orbitals for chemical valence)¹⁷ extension of the EDA method can be applied to reveal the origin of the counterintuitive finding that the total orbital interactions (ΔE_{oi}) are nearly identical for both the uncatalyzed and catalyzed reactions, despite the latter benefits from a more stabilized LUMO(dienophile) (see above). For the extreme situations represented by the uncatalyzed and AlCl_3 -catalyzed cycloadditions, this method identifies two main orbital interactions that dominate the total orbital interactions, namely, the normal electron demand (NED) HOMO(diene) $\rightarrow$ LUMO(dienophile) and the inverse electron demand (IED) LUMO(diene) $\leftarrow \pi$ -HOMO(dienophile) interactions (ρ_1 and ρ_2 , respectively, Figure 3). Not surprisingly, $\rho_1 > \rho_2$ in both cases, which agrees with the NED nature of these cycloadditions. The direct ρ_1 interaction is, as expected, stronger in the AlCl_3 -catalyzed process ($\Delta\Delta E(\rho_1) = -5.8 \text{ kcal/mol}$), consistent with the stabilization of the LUMO(dienophile). Strikingly, the LA also weakens the inverse ρ_2 to a nearly identical extent ($\Delta\Delta E(\rho_2) = +6.1 \text{ kcal/mol}$), which offsets the stabilization gained in the direct NED interaction, therefore resulting in the

Figure 2. (a) Comparative energy decomposition analyses of the DA reactions between isoprene and uncoordinated (none) as well as TiCl_4 - and AlCl_3 -coordinated methyl acrylate complexes projected onto the shorter C...C bond-forming distance. (b) Molecular orbital diagram and the most significant occupied orbital overlaps of the cycloadditions computed at a consistent geometry with a shorter C...C bond-forming distance of 2.097 Å.

Figure 3. Contour plots of NOCV deformation densities $\Delta\rho$ and associated energies $\Delta E(\rho)$ for the (a) uncatalyzed and (b) AlCl_3 -catalyzed DA reactions between isoprene and methyl acrylate computed at a consistent geometry with a shorter C...C bond-forming distance of 2.097 Å.

computed rather similar total orbital interactions. Thus, the widely accepted LUMO-lowering concept is correct in the sense that the LUMO(dienophile) indeed becomes stabilized upon binding to the LA but is rather incomplete because this traditional concept does not consider the remarkable impact of the LA on the IED interaction.

3. IMINIUM CATALYSIS

The term iminium catalysis (or iminium ion catalysis) typically refers to the formation of a transient iminium ion via the condensation of enals with (chiral) primary or secondary amine catalysis, which facilitates the nucleophilic attack at the β -carbon atom.¹⁸ This procedure has been widely used in the synthesis of a vast number of products including complex natural products and pharmaceuticals.^{18,19}

By analogy with the LA-catalysis mentioned above, McMillan and co-workers proposed in 2000 that “the reversible formation of the iminium ions from α,β -unsaturated aldehydes and amines might emulate the equilibrium dynamics and π -orbital electronics that are inherent to Lewis acid catalysis”.¹⁰ This seminal work rationalized the way that iminium catalysis works (i.e., by lowering the LUMO of the reactant), and since then, it has been widely used to explain the rate enhancements observed in these processes.

Given this proposed LA/iminium ion catalysis analogy, we hypothesized that a reduction in the Pauli repulsion between the reactants rather than a LUMO-lowering mechanism becomes the actual mechanism behind the iminium catalysis as well.³ To check this, we focused on the DA cycloadditions involving cyclopentadiene (CP) and various α,β -unsaturated iminium cations (NMe_2^+ , $\text{N}(\text{C}_4\text{H}_8)^+$, and $\text{N}(\text{C}_4\text{H}_8\text{O})^+$) as dienophiles, similar to the processes initially described by MacMillan and co-workers,¹⁰ and compared them with the analogous (uncatalyzed) reaction involving the neutral parent imine (NMe, Scheme 2).

Table 2 gathers the computed activation barriers for the preferred endo-cycloadditions (the corresponding *exo*-trans-

Scheme 2. Uncatalyzed ($\text{X} = \text{NMe}$) and Iminium Ion-Catalyzed DA Reactions That Were Considered

Table 2. Computed Activation Barriers ($\Delta E^\ddagger$, in kcal/mol)^a and HOMO(Diene)–LUMO(Dienophile) Energy Gaps ($\Delta\epsilon_{\text{H-L}}$, in eV)^b

X	NMe	NMe-AlCl ₃	N(C ₄ H ₈) ⁺	N(C ₄ H ₈ O) ⁺	NMe ₂ ⁺
$\Delta E^\ddagger$	17.1	10.5	0.7	1.1	−0.6
$\Delta\epsilon_{\text{H-L}}$	7.37	5.52	1.59	1.51	1.38

^aComputed as $\Delta E^\ddagger = E(\text{TS}) - E(\text{diene}) - E(\text{dienophile})$ at the DLPNO-CCSD(T)/def2-QZVPP//M06-2X/def2-TZVP level.
^bComputed at the M06-2X/def2-TZVP level.

tion states lie 0.5–1.5 kcal/mol above the endo-TSs).³ The introduction of an iminium catalyst greatly accelerates the DA reaction as compared to the process involving the parent $\text{X} = \text{NMe}$ imine (the barrier can be reduced by up to ~18 kcal/mol). This barrier lowering is much higher than that caused by strong Lewis acid catalyst AlCl_3 . Interestingly, in this case, the computed HOMO(diene)–LUMO(dienophile) gap ($\Delta\epsilon_{\text{H-L}}$) does follow the same trend as the activation barriers, which is seemingly consistent with the traditional LUMO-lowering concept as the mechanism behind the iminium catalysis.

We applied the ASM approach to unravel the actual physical mechanism governing the iminium catalysis. From the ASDs depicted in Figure 4a, which shows the evolution of the ASM terms for the cycloaddition involving the NMe and NMe_2^+ systems from the separate reactants up to the corresponding TSs, it is clear that the much lower barrier computed for the NMe_2^+ reaction originates mainly from a much stronger interaction between the reactants and a less-destabilizing strain energy. Similar to the LA-catalyzed reactions described above,

Figure 4. (a) Comparative activation strain analyses of the DA reactions between cyclopentadiene and NMe and NMe_2^+ dienophiles projected onto the shorter C...C bond-forming distance. (b) Optimized geometries of the corresponding transition states. Bond distances are given in angstroms.

Figure 5. (a) Comparative energy decomposition analyses of the DA reactions between cyclopentadiene and NMe and NMe₂⁺ dienophiles projected onto the shorter C...C bond-forming distance. (b) Molecular orbital diagram and the most significant occupied orbital overlaps of the cycloadditions computed at a consistent geometry with a C(β)–C(CP) bond length between CP and the dienophile of 2.125 Å.

the latter is the result of the much higher asynchronicity in the NMe₂⁺ reaction (NMe, $\Delta r_{C\cdots C}^{TS} = 0.14$ Å; NMe₂⁺, $\Delta r_{C\cdots C}^{TS} = 0.86$ Å; Figure 4b), which is translated into a much lower degree of distortion of the reactants since the C(β)–C(CP) bond forms before the C(α)–C(CP) bond.

The EDA method was also used to quantitatively understand the factors responsible for the much higher interaction between the deformed reactants computed for the iminium system. Figure 5a graphically shows the evolution of the EDA contributors along the reaction coordinate (from the separate reactants up to the corresponding TSs). We found that, in contrast to the widely accepted key role of orbital interactions, the difference in the ΔE_{Pauli} curves, which is less destabilizing for the NMe₂⁺ cycloaddition, exclusively determines the stronger (i.e., more stabilizing) ΔE_{int} computed for this process. At variance, the ΔV_{elstat} and ΔE_{oi} terms are even more stabilizing for the uncatalyzed (imine) reaction, particularly in the transition-state region. The even stronger total orbital interactions (ΔE_{oi}) computed for the uncatalyzed reaction are therefore not consistent with the more favorable HOMO(CP)–LUMO(dienophile) energy gap and can be, once again, ascribed to the significant weakening of the inverse electron-demand LUMO(CP) $\leftarrow$ π -HOMO(dienophile) interaction occurring in the iminium reaction. This weakened orbital interaction ($\Delta\Delta E(\rho_2) = +8.9$ kcal/mol, at a consistent geometry with a C(β)–C(CP) bond length between CP and the dienophile of 2.125 Å, compensates for the stabilizing normal electron demand HOMO(CP) $\rightarrow$ LUMO(dienophile) interaction ($\Delta\Delta E(\rho_2) = -7.3$ kcal/mol), which is reflected in the weaker total ΔE_{oi} computed for the iminium-catalyzed cycloaddition. These results thus confirm that the Pauli repulsion-lowering and not the LUMO-lowering concept constitutes the ultimate physical mechanism responsible for the iminium ion catalysis. Therefore, our calculations do support the initial resemblance between LA and iminium catalysis suggested by McMillan and co-workers ~20 years ago but in a rather different sense (i.e., a Pauli repulsion-lowering instead of LUMO-lowering mechanism).

The remarkable reduction of the Pauli repulsion in the NMe₂⁺ cycloaddition originates from the fact that the key occupied π -orbitals of the dienophile have a larger orbital amplitude on the α - than on the β -carbon, resulting in less occupied–occupied orbital overlap between CP and the β -carbon than the α -carbon of the dienophile (Figure 5b). This asymmetry is also responsible for the observed asynchronicity of the process (see

above), as the formation of the new C(α)–C(CP) bond lags behind the formation of the new C(β)–C(CP) bond to avoid too much Pauli repulsion from occurring in the former. Therefore, the Pauli repulsion-lowering mechanism is behind both: (i) the asynchronicity of the process, which is translated into a less-destabilizing strain energy, and (ii) the stronger interaction between the deformed reactants along the entire process, both factors significantly reducing the barrier of the iminium-catalyzed cycloaddition.

4. BIFUNCTIONAL HYDROGEN BOND DONOR CATALYSIS: THE CASE OF (THIO)UREAS

Once we confirmed that the Pauli repulsion lowering constitutes the mechanism governing the LA and iminium catalyses, where the catalyst establishes a dative or pure covalent bond with the substrate, we wondered whether this concept also operates in transformations where the catalyst is much more weakly attached to the substrate via noncovalent interactions. In this sense, we focused on bifunctional hydrogen bond (HB) donor organocatalysts (i.e., molecules able to bind via two hydrogen bonds because of their broad use in modern organic synthesis).²⁰

In particular, we selected the DA cycloaddition reaction between CP and acrolein (A) catalyzed by different (thio)urea species⁴ analogous to the processes described by Schreiner and co-workers (Scheme 3).²¹ The catalytic activity of these organocatalysts is traditionally ascribed to the bidentate nature of the HB-A complex, which favorably preorganizes and activates, via LUMO lowering, the substrate.²²

Similar to the LA or iminium-catalyzed cycloadditions described above, the (thio)urea-catalyzed DA reactions also proceed in a concerted asynchronous manner through the corresponding six-membered transition states. Strikingly, whereas the former processes and the uncatalyzed reaction preferentially afford the endo-cycloadduct over its exo-counterpart, this selectivity changes when the cycloaddition is catalyzed by a HB (Table 3). The reasons for such a selectivity reversal are not the focus of this Account and can be found in our recent publication.⁴ Moreover, the HB catalyst significantly accelerates the DA reaction by lowering the activation barrier 4–7 kcal/mol. In general, two reactivity trends can be observed: (i) the processes involving thiourea-based HBs proceed with a lower barrier than those promoted by their urea counterparts, which is in line with their experimentally determined stronger acidity

Scheme 3. Uncatalyzed and HB-Catalyzed DA Reactions That Were Considered

Table 3. Computed Activation Barriers ($\Delta E^\ddagger$, in kcal/mol),^a HOMO(Diene)–LUMO(Dienophile) Energy Gaps ($\Delta \epsilon_{H-L}$, in eV),^b and Instantaneous Interaction Energies (ΔE_{int} , in kcal/mol)^c

HB-A	$\Delta E^\ddagger$ ^a	$\Delta \epsilon_{H-L}$ ^b	ΔE_{int} ^c
A	14.3 (14.8)	6.6	
U-A	11.1 (10.4)	5.9	−7.1
TU-A	9.5 (10.0)	5.7	−8.5
UPh-A	8.2 (6.4)	5.6	−9.1
TUPh-A	8.9 (8.0)	5.8	−10.4
UF-A	7.2 (6.0)	5.3	−13.0
TUF-A	7.8 (7.0)	5.3	−13.8

^aComputed as $\Delta E^\ddagger = E(TS) - E(\text{diene}) - E(\text{dienophile})$ at the DLPNO-CCSD(T)/def2-QZVPP//M06-2X/def2-SVPP level. Plain values refer to the endo-approach, whereas values within parentheses refer to the exo-cycloaddition. ^bComputed at the ZORA-M06-2X/TZ2P//M06-2X/def2-SVPP level. ^cComputed as $\Delta E_{int} = E(\text{HB-A}) - E(A) - E(\text{HB})$ using the geometries in the HB-A complex.

($pK_A = 21.1$ and 26.9 for thiourea and urea, respectively)²³ and (ii) the rate enhancement becomes more significant when the hydrogen atom of the parent (thio)urea is replaced by a phenyl group and even more pronounced when the phenyl groups bear the strong electron-withdrawing CF₃ groups. The latter reactivity trend is not only consistent with the experimental findings²¹ but also follows the same trend as the strength of the HB–A bond, measured by the instantaneous interaction energy (ΔE_{int}) between the HB and A fragments (Table 3). Furthermore, there is only a modest linear correlation ($R^2 = 0.88$ and 0.83 , for the endo- and exo-approaches, respectively) between the computed barriers and the HOMO(CP)–LUMO(HB-A) energy gaps ($\Delta \epsilon_{H-L}$), which indicates that the LUMO-lowering mechanism is not controlling the mode of activation of these organocatalysts.

With the help of the ASM method, we analyzed and compared the uncatalyzed exo-cycloaddition with the analogous HB-catalyzed processes involving U-A and UPh-A to quantitatively understand the acceleration induced by these organocatalysts. According to the ASDs shown in Figure 6a, the lower barrier computed for the HB-catalyzed cycloadditions originates again mainly from a much stronger interaction between the deformed reactants along the entire reaction coordinate (ΔE_{int} becomes more stabilizing in the order $A < U-A < UPh-A$) and, to a lesser extent, from a less-destabilizing strain energy. Not surprisingly, the latter directly originates from the degree of asynchronicity,

Figure 6. (a) Comparative activation strain analyses of the exo-DA reactions between cyclopentadiene and acrolein (A) and analogous U-A and UPh-A urea complexes projected onto the shorter C...C bond-forming distance. (b) Optimized geometries of the corresponding transition states. Bond distances are given in angstroms.

which follows the order A ($\Delta r_{C...C}^{TS} = 0.21$ Å) $<$ $U-A$ ($\Delta r_{C...C}^{TS} = 0.34$ Å) $<$ $UPh-A$ ($\Delta r_{C...C}^{TS} = 0.40$ Å, Figure 6b). Please note that when compared to the $\Delta r_{C...C}^{TS}$ values computed for the analogous LA-catalyzed and, in particular, iminium-catalyzed DA reactions, the asynchronicity induced by the HB catalysts is comparatively lower, which is reflected by a smaller difference in the ΔE_{strain} term with respect to that of the uncatalyzed reaction.

The EDA method ascribes the stronger ΔE_{int} computed for the cycloadditions involving U-A and UPh-A solely to a reduction of the ΔE_{Pauli} term (Figure 7a). Indeed, whereas ΔE_{Pauli} becomes less destabilizing from A to U-A and to UPh-A, the attractive ΔV_{elstat} and ΔE_{oi} interactions become more stabilizing for the uncatalyzed reaction. Once again, the NOCV approach confirms that despite the NED HOMO(CP) $\rightarrow$ LUMO(HB-A) interaction becoming slightly more stabilizing in the HB-catalyzed process ($\Delta \Delta E(\rho_1) = -0.8$ kcal/mol), there occurs a significant weakening of the corresponding IED LUMO(CP) $\leftarrow \pi$ -HOMO(dienophile) interaction ($\Delta \Delta E(\rho_2) = +5.8$ kcal/mol), computed at a consistent geometry with a C(β)–C(CP) bond length of 2.14 Å. As a result, the total orbital interactions (ΔE_{oi}) computed for uncatalyzed cycloaddition are more stabilizing than in the analogous HB-catalyzed processes. Similar to the LA and iminium-catalyzed DA reactions, the HB catalyst also polarizes the key reactive π -orbital located on the C=C double bond of the dienophile toward the HB and away from the incoming diene. This polarization is responsible for the computed decrease in the occupied–occupied orbital overlap (Figure 7b) which translates into the computed decrease in the ΔE_{Pauli} term. Therefore, it is confirmed that the rate enhancement provoked by the HB organocatalysts is exclusively caused by a diminished two-orbital, four-electron Pauli repulsion between the key π -orbitals of the reactants. Thus, the Pauli repulsion-lowering concept is a general mechanism operating regardless of the nature of the substrate–catalyst bonding.

5. DIHALOGEN-CATALYZED aza-MICHAEL REACTIONS

After reading the above sections, one might have the impression that the Pauli repulsion-lowering concept is operative only in catalyzed Diels–Alder cycloaddition reactions. However, this is not the case as this concept seems general and fully applicable to different fundamental transformations in organic chemistry.

Figure 7. (a) Comparative energy decomposition analyses of the exo-DA reactions between cyclopentadiene and acrolein (A) and analogous U-A and UPh-A urea complexes projected onto the shorter C...C bond-forming distance. (b) Molecular orbital diagram and the most significant occupied orbital overlaps of the cycloadditions computed at a consistent geometry with a C(β)–C(CP) bond length of 2.14 Å.

Scheme 4. Uncatalyzed (X_2 = None) and Dihalogen-Catalyzed aza-Michael Reactions Involving Pyrrolidine and Methyl Acrylate That Were Considered

For instance, we also analyzed the synthetically useful aza-Michael reaction catalyzed by dihalogen molecules.²⁴ In particular, we focused on the reaction involving pyrrolidine and methyl acrylate catalyzed by X_2 molecules ($X_2 = \text{F}_2, \text{Cl}_2, \text{Br}_2, \text{I}_2$) described by Borah and co-workers²⁵ (Scheme 4). Whereas the uncatalyzed reaction is relatively slow and affords a 60% reaction yield of the corresponding reaction product after 15 h, the I_2 -catalyzed reaction is much faster, providing an 89% yield in only 15 min. Moreover, it is experimentally confirmed that the rate of the process significantly increases with the size of the X_2 catalysis (none $\sim \text{F}_2 < \text{Cl}_2 < \text{Br}_2 < \text{I}_2$).²⁵ Recent density functional theory calculations by Breugst and co-workers²⁶ indicate that (i) the catalyst binds the acrylate through a weak halogen bond involving the ester carbonyl group and (ii) the initial nucleophilic addition of the pyrrolidine nitrogen lone pair to the β -carbon of the X_2 -acrylate complex constitutes the rate-limiting step of the transformation.

With this information in hand, we decided to analyze in detail the processes shown in Scheme 4.¹ Our calculations indicate that the computed activation barrier steadily decreases from the uncatalyzed reaction to the I_2 -catalyzed process (Table 4). This reactivity trend is not only consistent with the available experimental and computational findings but also follows the same trend as the strength of the halogen bond, measured by the instantaneous interaction energy (ΔE_{int}) between the acrylate and X_2 fragments. Moreover, although our EDA calculations support that the nature of the halogen bonding is mainly electrostatic (the ΔV_{elstat} term is twice as strong as the ΔE_{oi} term),¹ the X_2 catalyst resembles a LA in the sense that the LUMO of the corresponding acrylate- X_2 complex becomes increasingly stabilized from F_2 to I_2 . As a result, the HOMO–LUMO gap ($\Delta \epsilon_{\text{H-L}}$), involving the key pyrrolidine nitrogen lone-pair and the π^* -acrylate, also follows the same reactivity

Table 4. Computed Activation Barriers ($\Delta E^\ddagger$, in kcal/mol),^a HOMO(Diene)–LUMO(Dienophile) Energy Gaps ($\Delta \epsilon_{\text{H-L}}$, in eV),^b and Instantaneous Interaction Energies (ΔE_{int} , in kcal/mol)^b

X_2	$\Delta E^\ddagger$	$\Delta \epsilon_{\text{H-L}}$	ΔE_{int}
none	11.2 (12.7)	7.4	
F_2	9.4 (11.7)	7.2	−1.4
Cl_2	7.6 (9.7)	6.6	−3.4
Br_2	6.2 (8.1)	6.0	−5.2
I_2	5.7 (7.1)	5.8	−5.8

^aComputed as $\Delta E^\ddagger = E(\text{TS}) - E(\text{diene}) - E(\text{dienophile})$ at the M06-2X/def2-TZVP level. Energies in parentheses were computed at the DLPNO-CCSD(T)/def2-TZVP//M06-2X/def2-TZVP level.

^bComputed (ZORA-M06-2X/TZ2P//M06-2X/def2-TZVP level) as $\Delta E_{\text{int}} = E(X_2\text{-acrylate}) - E(X_2) - E(\text{acrylate})$ using the geometries in the X_2 -acrylate complex.

trend, and not surprisingly, both parameters ($\Delta E^\ddagger$ and $\Delta \epsilon_{\text{H-L}}$) are nicely correlated (linear correlation coefficient of 0.97). These results are perfectly in line with the traditional LUMO-lowering catalysis concept, which is also used to rationalize related Michael additions.²⁷ We will show next, however, that this is not the case either.

Figure 8a shows the computed ASDs for the different aza-Michael reactions from the initial reactant complexes up to the corresponding TSs projected onto the key $C_\beta \cdots N$ bond-forming distance. Our ASM analyses indicate that the strain energy (ΔE_{strain}), that is, the energy penalty associated with the deformation of the reactants to adopt the TS geometry, is nearly identical in all cases and therefore it is not at all responsible for the observed reactivity trend. In contrast, the interaction energy becomes increasingly more stabilizing from the uncatalyzed to the I_2 -catalyzed process. This is exactly the

Figure 8. (a) Comparative activation strain analyses of the uncatalyzed (X_2 = none) and X_2 -catalyzed aza-Michael reactions involving pyrrolidine and methyl acrylate projected onto the $N\cdots C$ bond-forming distance. (b) Corresponding energy decomposition analyses for the processes involving X_2 = none and I₂.

Figure 9. Molecular orbital diagram and the most significant occupied orbital overlaps of the considered aza-Michael additions computed at a consistent geometry with a C=C bond length stretch of 0.062 Å. (a) HOMO(pyrrolidine)- π (acrylate) and (b) HOMO(pyrrolidine)- π^* (acrylate).

same trend as the activation barriers, so it can be concluded that the accelerated reactivity of the X_2 -catalyzed reactions originates almost exclusively from a stronger interaction between the deformed reactants along the entire reaction coordinate. EDA analyses show that the stronger interaction computed for the catalyzed processes results exclusively from a substantial reduction of the Pauli repulsion term (the difference in the attractive ΔV_{elstat} and ΔE_{oi} interactions for both processes is nearly negligible), as illustrated in Figure 8b by the two extreme situations represented by the uncatalyzed and I₂-catalyzed reactions. Therefore, the Pauli repulsion lowering constitutes once again the physical mechanism governing the catalytic role of the Lewis acid dihalogen molecules in these aza-Michael addition reactions.

The origin of both the reduction of the Pauli repulsion and the negligible change of the orbital interactions induced by the X_2 catalyst can be understood once again in terms of Kohn-Sham molecular orbital analyses. The HOMO(pyrrolidine) and the π -molecular orbital involving the reactive C=C double bond of the acrylate are identified as the main sources of Pauli repulsion. The orbital overlap between these molecular orbitals is largest and most destabilizing for the uncatalyzed reaction ($S = 0.17$) and smallest and least destabilizing for the I₂-catalyzed reaction

($S = 0.10$) (Figure 9a). The reason is that the X_2 catalyst induces a significant polarization of the π -MO, away from the C=C double bond of the acrylate reactant, leading to a reduction of its electron density which lowers the destabilizing four-electron Pauli repulsion. This polarization is also responsible for the computed negligible change in the stabilizing orbital interactions. As shown in Figure 9b, the HOMO(pyrrolidine)-LUMO(π^* -acrylate) overlap steadily decreases from the uncatalyzed to the I₂-catalyzed reaction. This polarization-induced weakening of the HOMO-LUMO overlaps effectively counteracts the more favorable (smaller) energy gaps commented on above and results in the nearly identical orbital interactions computed for both processes.

6. CONCLUSIONS AND OUTLOOK

Through representative examples, herein we have shown that the traditional LUMO-lowering catalysis concept, based on qualitative frontier molecular orbital (FMO) theory, is rather incomplete and cannot be used to rationalize the mode of activation of catalysts in fundamental transformations in organic chemistry. Instead, we propose the concept of Pauli repulsion lowering which constitutes the actual electronic mechanism behind the catalysis. Regardless of the way the catalyst binds to

one of the reactants (i.e., from pure covalent or dative bonds to hydrogen or halogen bonds), it induces a significant polarization of π -orbitals away from the atoms that form bonds with the other reactant and, in this way, reduces two-orbital, four-electron Pauli repulsion. This is the ultimate physical factor responsible for the acceleration of the process as compared to the analogous uncatalyzed reaction. This concept seems general and applicable to rather different transformations, spanning from nucleophilic additions to cycloaddition reactions.²⁸ For this reason, we envisage that the insights emerging from the ASM-EDA method will guide future experimental developments toward the design of more efficient catalytic transformations.

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Notes

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Israel Fernández (Madrid, ES, 1977) studied chemistry at the Universidad Complutense de Madrid (UCM). After obtaining his Ph.D. degree (with honors) under the supervision of Prof. M. A. Sierra, he joined the theoretical and computational chemistry group of Prof. G. Frenking at the Philipps-Universität Marburg as a postdoctoral researcher. He has received several awards, including the Barluenga's Medal and the Julián Sanz del Río award. At present, he is an associate professor at the UCM. His current research is focused on both the bonding situation of organic and organometallic compounds and their reactivity.

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REFERENCES

- (1) Hamlin, T.; Fernández, I.; Bickelhaupt, F. M. How dihalogens catalyze Michael addition reactions. *Angew. Chem., Int. Ed.* **2019**, *58*, 8922–8926.
- (2) Vermeeren, P.; Hamlin, T.; Fernández, I.; Bickelhaupt, F. M. How Lewis acids catalyze Diels-Alder reactions. *Angew. Chem., Int. Ed.* **2020**, *59*, 6201–6206; *Angew. Chem.* **2020**, *132*, 6260–6265.
- (3) Vermeeren, P.; Hamlin, T.; Fernández, I.; Bickelhaupt, F. M. Origin of rate enhancement and asynchronicity in iminium catalyzed Diels-Alder reactions. *Chem. Sci.* **2020**, *11*, 8105–8112.
- (4) Vermeeren, P.; Hamlin, T.; Bickelhaupt, F. M.; Fernández, I. Bifunctional hydrogen bond donor-catalyzed Diels-Alder reactions: origin of stereoselectivity and rate enhancement. *Chem. - Eur. J.* **2021**, *27*, 5180.
- (5) Fukui, K. The role of frontier orbitals in chemical reactions. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 801–809 and references therein.
- (6) Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Verlag, Chemie, GmbH: Weinheim, 1970.
- (7) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley: New York, 1976. New ed.: Fleming, I. *Molecular Orbitals and Organic Chemical Reactions*, Wiley, New Jersey, 2009. Fleming, I. *Molecular Orbitals and Organic Chemical Reactions*; Wiley: New York, 2009.
- (8) For representative examples, see (a) Ge, M.; Stoltz, B. M.; Corey, E. J. Mechanistic insights into the factors determining exo-endo Selectivity in the Lewis acid-catalyzed Diels-Alder reaction of 1,3-dienes with 2-cycloalkenones. *Org. Lett.* **2000**, *2*, 1927–1929. (b) Fernández, I.; Sierra, M. A.; Cossío, F. P. DFT study on the Diels-Alder cycloaddition between alkenyl-M(0) (M = Cr, W) carbene complexes and neutral 1,3-dienes. *J. Org. Chem.* **2008**, *73*, 2083–2089. (c) Yu, P.; Li, W.; Houk, K. N. Mechanisms and origins of selectivities of the Lewis acid-catalyzed Diels-Alder reactions between arylallenes and acrylates. *J. Org. Chem.* **2017**, *82*, 6398–6402. (d) Yepes, D.; Pérez, P.; Jaque, P.; Fernández, I. Effect of Lewis acid bulkiness on the stereoselectivity of Diels-Alder reactions between acyclic dienes and α,β -enals. *Org. Chem. Front.* **2017**, *4*, 1390–1399.
- (9) See, for instance, Clayden, J.; Greeves, N.; Warren, S. *Organic Chemistry*, 2nd ed.; Oxford University Press: Oxford, 2012.
- (10) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. New strategies for organic catalysis: the first highly enantioselective organocatalytic Diels-Alder reaction. *J. Am. Chem. Soc.* **2000**, *122*, 4243–4244.
- (11) See, for instance, (a) Kahn, S. D.; Pau, C. F.; Overman, L. E.; Hehre, W. J. Modeling chemical reactivity. 1. Regioselectivity of Diels-Alder cycloadditions of electron-rich dienes with electron-deficient

dienophiles. *J. Am. Chem. Soc.* **1986**, *108*, 7381–7396. (b) Spino, C.; Rezaei, H.; Dory, Y. L. Characteristics of the two frontier orbital interactions in the Diels-Alder cycloaddition. *J. Org. Chem.* **2004**, *69*, 757–764. (c) Ussing, B. R.; Hang, C.; Singleton, D. A. Dynamic effects on the periselectivity, rate, isotope effects, and mechanism of cycloadditions of ketenes with cyclopentadiene. *J. Am. Chem. Soc.* **2006**, *128*, 7594–7607. (d) García-Rodeja, Y.; Solá, M.; Bickelhaupt, F. M.; Fernández, I. Reactivity and selectivity of bowl-shaped polycyclic aromatic hydrocarbons: relationship to C_{60} . *Chem. - Eur. J.* **2016**, *22*, 1368–1378. (e) Fernández, I.; Fernking, G. The Diels-Alder reaction from the EDA-NOCV perspective: a re-examination of the Frontier Molecular Orbital model. *Eur. J. Org. Chem.* **2019**, *2019*, 478–485.

(12) For reviews, see (a) Pindur, U.; Lutz, G.; Otto, C. Acceleration and selectivity enhancement of Diels-Alder reactions by special and catalytic methods. *Chem. Rev.* **1993**, *93*, 741–761. (b) Fringuelli, F.; Piermatti, O.; Pizzo, F.; Vaccaro, L. Recent advances in Lewis acid catalyzed Diels-Alder reactions in aqueous media. *Eur. J. Org. Chem.* **2001**, *2001*, 439–455.

(13) (a) Inukai, T.; Kojima, T. Catalytic actions of aluminum chloride on the isoprene-methyl acrylate Diels-Alder reaction. *J. Org. Chem.* **1966**, *31*, 1121–1123. See also (b) Wulff, W. D.; Bauta, W. E.; Kaesler, R. W.; Lankford, P. J.; Miller, R. S.; Murray, C. K.; Yang, C. Chromium and tungsten pentacarbonyl groups as reactivity auxiliaries in the Diels-Alder reactions of alkenyl carbene complexes with 1,3-dienes. *J. Am. Chem. Soc.* **1990**, *112*, 3642–3659.

(14) Childs, R. F.; Mulholland, D. L.; Nixon, A. The Lewis acid complexes of α,β -unsaturated carbonyl and nitrile compounds. A nuclear magnetic resonance study. *Can. J. Chem.* **1982**, *60*, 801–808.

(15) For reviews, see (a) Fernández, I.; Bickelhaupt, F. M. The activation strain model and molecular orbital theory: understanding and designing chemical reactions. *Chem. Soc. Rev.* **2014**, *43*, 4953–4967. (b) Bickelhaupt, F. M.; Houk, K. N. Analyzing reaction rates with the Distortion/Interaction-Activation Strain Model. *Angew. Chem., Int. Ed.* **2017**, *56*, 10070–10086; Das Distortion/Interaction-Activation-Strain-Modell zur Analyse von Reaktionsgeschwindigkeiten. *Angew. Chem.* **2017**, *129*, 10204–10221. (c) Fernández, I. Understanding the reactivity of polycyclic aromatic hydrocarbons and related compounds. *Chem. Sci.* **2020**, *11*, 3769–3770 For a step-by-step protocol, see also. (d) Vermeeren, P.; van der Lubbe, S. C. C.; Fonseca Guerra, C.; Bickelhaupt, F. M.; Hamlin, T. A. Understanding chemical reactivity using the Activation Strain Model. *Nat. Protoc.* **2020**, *15*, 649–667.

(16) (a) Bickelhaupt, F. M.; Baerends, E. J. In *Reviews in Computational Chemistry*; Lipkowitz, K. B., Boyd, D. B., Eds.; Wiley-VCH: Weinheim, 2000; Vol. 15, pp 1–86. (b) Zhao, L.; von Hopffgarten, M.; Andradá, D. M.; Frenking, G. Energy decomposition analysis. *WIREs Comput. Mol. Sci.* **2018**, *8*, e1345 and references therein.

(17) Mitoraj, M. P.; Michalak, A.; Ziegler, T. A. A combined charge and energy decomposition scheme for bond analysis. *J. Chem. Theory Comput.* **2009**, *5*, 962–975.

(18) (a) MacMillan, D. W. C.; Watson, A. J. B. In *Science of Synthesis*; List, B., Ed.; Thieme: Stuttgart, Germany, 2012. (b) Erkkilä, A.; Majander, I.; Pihko, P. M. Iminium Catalysis. *Chem. Rev.* **2007**, *107*, 5416–5470.

(19) For a recent review, see Wang, Z. Advances in the asymmetric total synthesis of natural products using chiral secondary amine catalyzed reactions of α,β -unsaturated aldehydes. *Molecules* **2019**, *24*, 3412–3450 and references therein.

(20) For recent reviews, see (a) Gimeno, M. C.; Herrera, R. P. Hydrogen bonding and internal or external Lewis or Brønsted acid assisted (thio)urea catalysts. *Eur. J. Org. Chem.* **2020**, *2020*, 1057–1068. (b) Skrzynska, A.; Frankowski, S.; Albrecht, L. Cyclic 1-azadienes in the organocatalytic inverse-electron-demand aza-Diels-Alder cycloaddition. *Asian J. Org. Chem.* **2020**, *9*, 1688–1700 and references therein.

(21) (a) Wittkopp, A.; Schreiner, P. R. Metal-free, noncovalent catalysis of Diels-Alder reactions by neutral hydrogen bond donors in organic solvents and in water. *Chem. - Eur. J.* **2003**, *9*, 407–414. (b) Schreiner, P. R. Metal-free organocatalysis through explicit hydrogen bonding interactions. *Chem. Soc. Rev.* **2003**, *32*, 289–296.

See also (c) Zhang, Z.; Schreiner, P. R. (Thio)urea organocatalysis - What can be learnt from anion recognition? *Chem. Soc. Rev.* **2009**, *38*, 1187–1198.

(22) Madarász, Á.; Dósa, Z.; Varga, S.; Soós, T.; Csámpai, A.; Pápai, I. Thiourea derivatives as Brønsted acid organocatalysts. *ACS Catal.* **2016**, *6*, 4379–4387.

(23) Jakab, G.; Tancon, C.; Zhang, Z.; Lippert, K. M.; Schreiner, P. R. (Thio)urea organocatalyst equilibrium acidities in DMSO. *Org. Lett.* **2012**, *14*, 1724–1727.

(24) Representative examples: (a) Chu, C.-M.; Gao, S.; Sastry, M. N. V.; Yao, C.-F. *Tetrahedron Lett.* **2005**, *46*, 4971–4974. (b) Lin, C.; Hsu, J.; Sastry, M. N. V.; Fang, H.; Tu, Z.; Liu, J.-T.; Ching-Fa, Y. I_2 -catalyzed Michael addition of indole and pyrrole to nitroolefins. *Tetrahedron* **2005**, *61*, 11751–11757. (c) Breugst, M.; von der Heiden, D. Mechanisms in iodine catalysis. *Chem. - Eur. J.* **2018**, *24*, 9187–9188. (d) Breugst, M.; Koenig, J. σ -Hole interactions in catalysis. *Eur. J. Org. Chem.* **2020**, *2020*, 5473–5487.

(25) Borah, K. J.; Phukan, M.; Borah, R. Aza-Michael addition of amines to α,β -unsaturated compounds using molecular iodine as catalyst. *Synth. Commun.* **2010**, *40*, 2830–2836.

(26) Breugst, M.; Detmar, E.; von der Heiden, D. Origin of the catalytic effects of molecular iodine: a computational analysis. *ACS Catal.* **2016**, *6*, 3203–3212. See also reference 24c.

(27) Giraldo, C.; Gómez, S.; Weinhold, F.; Restrepo, A. Insight into the mechanism of the Michael reaction. *ChemPhysChem* **2016**, *17*, 2022–2034.

(28) For other recent examples from our team involving the Pauli repulsion-lowering concept, see (a) Vermeeren, P.; Brinkhuis, F.; Hamlin, T. A.; Bickelhaupt, F. M. How alkali cations catalyze aromatic Diels-Alder reactions. *Chem. - Asian J.* **2020**, *15*, 1167–1174. (b) Hansen, T.; Vermeeren, P.; Yoshisada, R.; Filippov, D. V.; van der Marel, G. A.; Codée, J. D. C.; Hamlin, T. A. How Lewis Acids Catalyze Ring-Openings of Cyclohexene Oxide. *J. Org. Chem.* **2021**, *86*, 3565–3573.