



Iodine-Catalyzed Diels-Alder Reactions

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The Diels-Alder cycloaddition is the most popular pericyclic reaction with numerous applications in synthesis and catalysis. We now demonstrate that we can perform this reaction under mild and metal-free conditions relying on molecular iodine as the catalyst. Cycloadditions with cyclohexadiene, cyclopentadiene, or isoprene with various dienophiles can be performed

Introduction

Over the last years, halogen bonding has grown to become an important concept in various areas of chemistry and particularly in organocatalysis.^[1] Halogen bonding is defined as the attractive interaction of the Lewis-acidic region of a halogen atom with the lone pair of a Lewis base.^[1] The Lewis acidic region of a halogen atom is located in elongation of the R-X bond and the interaction increases from F < CI < Br < I.^[1] One of the first halogen-bond catalyzed reactions, the reduction of quinolines, was published in 2008 by Bolm and colleagues.^[2] In the following years, systematic investigations by Huber and others broadened our understanding of halogen-bond catalysis.^[3] Within the last years, halogen-bond catalysts were employed amongst others in Michael additions,^[4] (hetero)-Diels-Alder reactions,^[5] Nazarov cyclizations,^[6] or in cross-enolate coupling reactions.^[7] Halogen-bond donors can also be used in stereoselective transformations in combination with other modes of activation.^[8] In 2020, Huber and colleagues eventually reported on the application on the first pure chiral halogenbond donor in a Mukaiyama aldol reaction.^[9]

Within the concept of halogen-bond catalysis, molecular iodine reemerged into the focus of organocatalysis. Iodine is inexpensive, benign, and well soluble in organic solvents and reactions can typically be performed under mild conditions.^[10] For a long time, the origin of the catalytic activity was unknown and different explanations (Brønsted-acid, Lewis-acid, or iodonium-ion catalysis) have been proposed in the literature.^[10] We

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typically within minutes in moderate to good yields and high *endo* selectivity. The mechanistic studies including kinetic and DFT investigations clearly indicate a halogen-bond activation and rule out other modes of activation. Furthermore, iodine performs equally well as typical metallic Lewis acids like AICl₃, SnCl₄, or TiCl₄.

were recently able to show that a halogen-bond activation is the most likely explanation for iodine-catalyzed Michael additions^[11] and Nazarov cyclizations (Scheme 1).^[12] In contrast, a iodonium-activation seems to be the origin for carbonyl-olefin metathesis reactions.^[13] As iodine is frequently comparable or even superior in activity compared to traditional metal catalysts like AlCl₃, FeCl₃, or TiCl₄,^[11–13] we wondered whether this simple catalyst can also be employed in other transformations and affords the desired products under mild conditions.

As iodine is particularly effective for the activation of carbonyl groups, we investigated if we could extend the concept of iodine catalysis towards the synthetically important Diels-Alder reaction.^[14] Typically, an electron-rich diene reacts with an electron-deficient dienophile in a concerted [4+2] cycloaddition. While this reaction can occur thermally (frequently at elevated temperatures), catalytic variants are known for a long time. In 1960, Yates and Eaton reported on the strong accelerating effect of AlCl₃ observed for the reaction between anthracene and dimethyl fumarate.^[15] Today, numerous Lewis acids are known to catalyze this transformation (Scheme 2)^[14,16] including carbenium^[17] and silylium ions,^[18] but also organo-catalysts with many different catalyst scaffolds.^[19]

The Diels-Alder reaction was also already investigated in the context of halogen-bonding. Huber and colleagues relied on

Iodine-Catalyzed Michael Addition^[11]

Iodine-Catalyzed Nazarov Cyclization^[12]

$$(X = 0, CH_2^{R^1} \xrightarrow{I_2 (5-10 \text{ mol}\%)} CH_3 CN, 25 °C$$

Iodine-Catalyzed Carbonyl-Olefin Metathesis^[13]

$$H_{3}C \xrightarrow{CH_{3}} H_{2}(10 \text{ mol\%}) \xrightarrow{H_{3}C} H_{3}C \xrightarrow{CH_{3}} H_{3}C \xrightarrow{$$

Scheme 1. Selected examples for iodine catalysis.[11-13]



different halogen-bond donors for the model reaction between cyclopentadiene (**1b**) and methyl vinyl ketone (**2a**, Scheme 3).^[3d,5a,20] In 2021, they also reported on the use of a bidentate iodine(III) system that can also be used to catalyze a cycloaddition involving cyclohexadiene (**1a**).^[21] Similarly, aza-Diels-Alder reactions can also be catalyzed by related azolium-based catalysts.^[5b,c,22] While these examples proposed the formation of a halogen bond to the heteroatom of the dienophile, Arai and colleagues reported on a [4+2] cyclo-addition between 2-alkenylindoles relying on a C–I… π halogen bond instead.^[5d] Several years before, molecular iodine was already employed as a catalyst in related Povarov reactions, but no mechanistic investigations have been performed so far.^[23]



 $\label{eq:Scheme 2. Selected examples for Lewis-acid-catalyzed Diels-Alder reactions of cyclohexadiene (1a) and methyl vinyl ketone (2a). \end{tabular}$



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We now report on our computational and experimental studies on iodine-catalyzed Diels-Alder reactions and their mechanistic investigation.

Results and Discussion

Computational investigations

We initially investigated the feasibility of an iodine-catalyzed Diels-Alder reaction by DFT calculations. The effect of iodine on different Diels-Alder reactions was already studied in 2011 by Deuri and Phukan^[25] at the B3LYP/6-31G(d) (3-21G(d) for iodine) level of theory and recently by Fernández, Bickelhaupt, and colleagues^[26] amongst others at the DLPNO-CCSD(T)/CBS(3,4/ def2)//ZORA-BP86/TZ2P level.

Both studies suggest that iodine can coordinate to the carbonyl group of the dienophiles replacing traditional Lewis acids, which results in a reduced activation energy. However, both studies did not consider entropic factors and only referred to (zero point-corrected) electronic energies.^[27] Therefore, it is not clear whether the attractive halogen-bond interaction can compensate for the unfavorable entropic contribution. Consequently, we investigated the influence of iodine on several Diels-Alder reactions at the B2PLYP-D3BJ/aug-cc-pVTZ/SMD// M06-2X/6-311 + G(d,p)/SMD level of theory. This method turned out to provide very reliable results for iodine-catalyzed Michael additions^[11a] and Nazarov cyclizations.^[12]

In line with the established mechanism for the Diels-Alder reaction,^[14] all reactions proceed under kinetic control and the *endo* transition states are kinetically preferred.^[28] As exemplary shown in Figure 1, all transition states are slightly asynchronous and both C–C bonds vary significantly in line with the polarized nature of the dienophile. Iodine coordinates to the carbonyl oxygen atom, and the resulting dienophile-iodine complexes **2**-I₂ are almost isoenergetic to the separated reactants (–6 (for **2**e) $<\Delta G < +13$ (for **2**h) kJmol⁻¹). The calculated value for dimethylacrylamide (**2**e) furthermore qualitatively agrees well with experimentally determined values for other amides.^[29] Nonetheless, coordination of iodine to the carbonyl group causes a substantial reduction of the activation free energy ($\Delta\Delta G^+ = 23$ kJmol⁻¹). In all cases, the C=0···I distances are significantly smaller than the sum of the van der Waals radii



Figure 1. Calculated *endo*-transition states with selected bond lengths (in Å) for the uncatalyzed and the iodine-catalyzed Diels-Alder reaction between cyclohexadiene (**1 a**) and methyl vinyl ketone (**2 a**).

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 $(3.54 \text{ Å})^{[30]}$ and, thus, indicating an attractive interaction between these atoms. A closer analysis of the Wiberg bond order^[31] for the O…I interaction reveal that the reactant and product complexes are very similar (e.g., **2a-I**₂: 0.064, **3aa-I**₂: 0.072), while a larger value of 0.172 was calculated for the corresponding transition state. These values are substantially smaller than those for the triiodide anion (I₃⁻: 0.534) and indicate a noncovalent interaction of molecular iodine during the Diels-Alder cycloaddition.

Table 1 collects the calculated activation free energies for the *endo* transition states for the Diels-Alder reactions of different dienes 1 and dienophiles 2 in the absence and the presence of iodine. More details (e.g., on the *exo* pathways are summarized in the Supporting Information). The computed reactivity trends are generally in line with previous investigations:^[32] Cyclopentadiene (1b) is the most reactive diene followed by isoprene (1c) and cyclohexadiene (1a).^[32c-e] Similarly, the reactivities of the dienophiles qualitatively agree with experimental rate constants for cycloadditions to 9,10dimethylanthracene.^[32a]

For most combinations, the computational investigations predict a significant rate acceleration by iodine. However, in some cases (e.g., **2c**, **2d**, **2i**), similar barriers were calculated which indicates that iodine should not display a strong catalytic effect. Previous investigations of the cycloaddition between **1c** and **2d** at the DLPNO-CCSD(T)/CBS(3,4/def2)//ZORA-BP86/TZ2P level in the gas phase resulted in a transition-state lowering of 5 kJ mol⁻¹ in electronic barrier (ΔE) which nicely agrees with our findings ($\Delta \Delta H^{+} = -7 \text{ kJ mol}^{-1}$). The favorable enthalpic interaction to iodine cannot compensate for the unfavorable entropic contribution and renders the overall barrier in free energy to be comparable to the uncatalyzed process. For maleic anhydride (**2h**), a very reactive dienophile, our calculations predict an even higher activation energy in the presence of iodine (see also below).

To better understand the role of iodine in these reactions, we performed additional calculations. An NCIPLOT analysis^[33] (see the Supporting Information) indicates medium to strong attractive interactions between the dienophile part and the catalyst. A closer investigation with natural population analyses^[34] of iodine complexes confirmed a significant interaction between the oxygen lone pairs and the anti-bonding σ^* orbital of the I–I bond (e.g.: for 2a-I₂: 56, TS-I₂: 168, and 3aa-I₂: 61 kJ mol⁻¹). While the interactions in the reactant and complexes are typically similar, much larger values were calculated for the transition states. This again indicates that the transition states are rather asynchronous resulting in a substantial charge transfer between diene and dienophile. To obtain a more quantitative picture into the interaction between the organic fragments and iodine, we additionally relied on symmetryadapted perturbation theory (SAPT).^[35] Figure 2 summarizes the results of the SAPT2+3(CCD) analysis for the reaction between cyclohexadiene (1 a) and methyl vinyl ketone (2 a),^[36] while the results of the corresponding SAPTO analysis^[37] are shown in the Supporting Information.

As already observed in the DFT calculations described above, the SAPT interaction energies (red bars in Figure 2) in

Table 1. Calculated Activation Free Energies ΔG^{+} (in kJ mol⁻¹) for the Uncatalyzed and Iodine-Catalyzed Diels-Alder Reactions of Cyclohexadiene (1 a), Cyclopentadiene (1 b), and Isoprene (1 c) with Different Dienophiles 2.^[a]

		$\left \right\rangle$	Ĺ			
	1a	1b	1c			
2a	+ 114 (no l ₂) + 91 (with l ₂)	+ 102 (no l ₂) + 86 (with l ₂)	+ 106 (no I_2) + 86 (with I_2)			
о Н 2b	+ 111 (no l₂) + 89 (with l₂)	$+$ 98 (no $I_2)$ $+$ 81 (with $I_2)$	$+ 105 (no I_2) + 84 (with I_2)$			
O OH 2c	$+ 111 \text{ (no } I_2) + 109 \text{ (with } I_2)$	$+$ 95 (no $I_2)$ $+$ 94 (with $I_2)$	+106 (no I ₂) +104 (with I ₂)			
OMe 2d	+ 93 (no l ₂) + 88 (with l ₂)	$+77$ (no $\rm l_2)$ $+73$ (with $\rm l_2)$	$+86$ (no $I_2)$ $+87$ (with $I_2)$			
NMe ₂	$+$ 122 (no $I_2)$ $+$ 113 (with $I_2)$	$+106$ (no $I_2)$ $+95$ (with $I_2)$	+116 (no I ₂) +103 (with I ₂)			
Ph 2f	$+124$ (no I_2) $+105$ (with I_2)	$+$ 105 (no $I_2)$ $+$ 87 (with $I_2)$	$+ 114 (no l_2) + 96 (with l_2)$			
Ph 2g	$+$ 132 (no $l_2)$ $+$ 113 (with $l_2)$	+ 116 (no l₂) + 99 (with l₂)	$+ 123 (no I_2) + 103 (with I_2)$			
2h	+ 83 (no l ₂) + 89 (with l ₂)	+ 71 (no l₂) + 76 (with l₂)	+85 (no l₂) +91 (with l₂)			
CN 2i	+ 115 (no l ₂) + 115 (with l ₂)	+ 98 (no l ₂) + 97 (with l ₂)	+ 111 (no l ₂) + 110 (with l ₂)			
[a] B2PLYP-D3BJ/au (CH ₃ CN).	[a] B2PLYP-D3BJ/aug-cc-pVTZ/SMD(CH ₃ CN)//M06-2X/6-311 + G(d,p)/SMD (CH ₂ CN)					

the reactant and product complexes (2 a-I₂ and 3 aa-I₂) are very similar (-22 and -26 kJmol⁻¹) and a stronger interaction is observed in the transition state (-46 kJmol⁻¹). In line with this,





Figure 2. Analysis of the interaction energies by symmetry-adapted perturbation theory (SAPT2 + 3(CCD)/def2-TZVPP, in kJ mol⁻¹).

almost identical energy decompositions were calculated for 2a-I₂ and **3aa-I₂**, while significant differences can be observed for the corresponding transition state TS-I₂. The exchange contribution (black bars) significantly increases which indicates that there is a substantial Pauli repulsion between the lone pairs on the oxygen and iodine atoms. This unfavorable interaction is compensated by a substantial increase in the electrostatic and induction (green and orange bars) contributions and by a moderate increase in dispersive interactions (blue bars). These results lead to the conclusion that there is a substantial charge transfer from the dienophile onto the catalyst, which is in line with the typical picture of a Lewis-acid or halogen-bond catalysis. While these results focus on the nature of the O⁻⁻⁻I interaction, different results can be expected for the dienedienophile interaction. The latter was recently studied by Hamlin, Fernández, Bickelhaupt, and colleagues and highlighted the reduction of Pauli repulsion as an important feature.^[26,38]

In summary, the computational investigations clearly indicated that iodine-catalyzed cycloadditions should be feasible and encouraged us to study the catalytic effect also experimentally.

Solvent screening

To probe the concept of iodine-catalyzed Diels-Alder reactions, we initially selected the cycloaddition between cyclohexadiene (**1a**) and methyl vinyl ketone (**2a**). This reaction typically does not proceed in the absence of a catalyst, and, therefore, allows for a reliable reaction monitoring. In addition, we also looked at the analogous reaction of cyclopentadiene (**1b**), which is known to proceed slowly even in the absence of a catalyst. Iodine (**15** mol%) was added to an equimolar mixture (**1.2** equiv. for **1b**) of the reactants in different solvents. After 30 min, the reaction mixtures were deactivated by filtration through a mixture of Na₂CO₃ and Na₂S₂O₃, and the yields were determined by GC.

In line with the low reactivity of 1a, no cycloaddition was observed in the absence of iodine in any solvent. In contrast, background reactions could be detected as expected in all solvents for the reaction of the more reactive diene 1b (see the Supporting Information for details). Nonetheless, a significant acceleration was observed in acetonitrile for both dienes and the cycloadducts were formed in fast reactions (73 and 94%, Table 2). Isolated product yields were almost identical to those determined by GC (see the Supporting Information for details), and no alternate reaction products could be detected during the solvent screening. In line with the expectations from our computational investigations and from previous experimental studies,^[14] the endo-cycloadduct 3 aa could be observed as the only product (endo: exo > 50:1) for the combination of 1 a and 2a. A slightly smaller selectivity (ca 9:1) was determined for the cycloadditions involving cyclopentadiene (1b) and the combined yield of both cycloadducts is given in Table 2 for this system (see the Supporting Information for more details).

	or $rac{1}{2}$ (15 mol%) solvent, 30 min, 25 °C or $rac{1}{2}$ or $rac{1}{2}$						
		1a 1b 2a	3aa	3ba			
Solvent	3 aa [%]	3 ba [%]	Solvent	3aa [%]	3 ba [%]		
CH₃CN	73	94 (13) ^[b]	THF	<1	98 (28) ^[b]		
CI(CH ₂) ₂ CI	39	99 (23) ^[b]	MTBE	<1	98 (8) ^[b]		
CH ₂ Cl ₂	38	93 (10) ^[b]	benzene	<1	87 (16) ^[b]		
PhNO ₂	79	_[c]	toluene	<1	87 (10) ^[b]		
H ₃ CNO ₂ ^[d]	67	86 (18) ^[b]	<i>p</i> -xylene	<1	80 (18) ^[b]		
PhCN	33	98 (8) ^[b]	pentane	<1	83 (21) ^[b]		
acetone	11	90 (18) ^[b]	DMF	<1	41 (57) ^[b]		
CHCl ₃ ^[e]	<1	73 (28) ^[b]	DMSO	<1	79 (56) ^[b]		
CCl₄	<1	98 (59) ^[b]	HFIP	<1	61 (8) ^[b]		
EtOAc	<1	94 (14) ^[b]	MeOH	<1	55 (21) ^[b]		
Et ₂ O	<1	97 (26) ^[b]					

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While iodine-catalyzed Nazarov cyclizations^[12] and Michael additions^[11b] tolerated many different solvents, iodine-catalyzed Diels-Alder reactions seem to be more solvent-dependent. While cycloadditions with the highly reactive cyclopentadiene (1 b) again proceed in almost all solvents (also in the absence of iodine), reactions of cyclohexadiene (1 a) only take place in polar solvents. For the latter, nitromethane (67%) and nitrobenzene (79%) resulted in comparable GC yields than acetonitrile (73%). Remarkably, only 5 mol% iodine could be used in nitromethane, indicating that lower catalyst loadings should also be feasible in some solvents. A moderate yield (38%) was also observed for dichloromethane in contrast to previous reports in the literature.[21] While very Lewis-basic solvents like DMF or DMSO are known to interact with iodine and deactivate it for further reactions,^[29] apolar solvents like toluene or pentane are also unsuitable for the iodine-catalyzed Diels-Alder reaction of 1a. Interestingly, with the exception of DMSO and DMF, cycloadditions with 1b proceed in almost all solvents and high yields were typically observed after 30 min. Although there is no general correlation with e.g., Reichardt's $E_{\rm N}^{\rm T}$ parameter,^[39] a certain solvent polarity (approx. 0.3) seems to be required for a successful reaction of cyclohexadiene (1 a). A similar observation has also been reported for iodinecatalyzed Povarov reactions^[23a] and was also observed in other Diels-Alder reactions.^[40]

Mode of activation

Although the computational investigations described above support the picture of a halogen-bond catalysis by molecular iodine, we wanted to elucidate the role of the catalyst in these reactions as well. Besides the activation as a Lewis acid, Brønsted-acid catalysis by HI (generated via decomposition of iodine) and an iodonium-ion activation are frequently proposed as alternate explanations.^[10] For the mechanistic analysis, we again selected the reaction between cyclohexadiene (**1 a**) and methyl vinyl ketone (**2 a**) in acetonitrile (Table 3). As the



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observed yields were identical under normal lab lighting and in the dark as well as in the presence of a radical scavenger (entries 1–3 in Table 3), radical pathways are unlikely. *N*lodosuccinimide, a typical source for iodonium ions, was completely inactive under the reaction conditions and the starting materials remained unchanged as indicated by GC analysis. Similarly, Brønsted acids (entries 6–9) perform poorly and only afford small quantities of the cycloadduct **3 aa**. As the low catalytic activity of aqueous HI in acetonitrile can be suppressed by the addition of Nal (entry 8), it is likely that this effect is caused by trace impurities of iodine (obtained through an oxidation of HI). Based on the results of Table 3, both a Brønsted-acid as well as an iodonium activation are unlikely to account for the catalytic effect of iodine.

To further support our hypothesis of a halogen-bondcatalyzed cycloaddition, we also determined the reaction order in iodine kinetically. We measured the initial rates for different iodine concentrations (7–14 mol%) under otherwise identical conditions by IR spectroscopy. The resulting double-logarithmic plot between the initial rates and the iodine concentrations resulted in a linear correlation with a slope of one (Figure 3), indicating that only one iodine molecule is involved in the ratedetermining transition state. This reaction order also renders an activation via the iodonium ion (I^+) very unlikely. Both I^+ and $I^$ readily react with iodine to form higher iodine species which in turn should result in a higher reaction order.^[13]

We additionally aimed to determine the activation parameters for the iodine-catalyzed cycloaddition of **1a** and **2a**. Therefore, we measured the initial rates for these reactions at different temperatures (15–40 °C) in CH₃CN using 8 mol% iodine (Figure 4). An Eyring analysis revealed a relatively small activation enthalpy (ΔH^{\pm}) of 31 kJ mol⁻¹ that perfectly agrees with the calculated ΔH^{\pm} of 32 kJ mol⁻¹. The formal termolecular reaction is also reflected in a considerable activation entropy



Figure 3. Determination of the reaction order in iodine for the cycloaddition between cyclohexadiene (1 a) and methyl vinyl ketone (2 a) ([1 a] = [2 a] = 90 mmol L⁻¹, CH₃CN, 25 °C).





Figure 4. Determination of the activation parameters for the iodinecatalyzed Diels-Alder reaction between cyclohexadiene (**1** a) and methyl vinyl ketone (**2** a) ([**1** a] = [**2** a] = 90 mmol L⁻¹, [I₂] = 7.4 mmol L⁻¹, CH₃CN).

 $(\Delta S^{+} = -181 \text{ JK}^{-1} \text{ mol}^{-1})$. From these values, the activation free energy at 298 K can be calculated to 85 kJmol⁻¹. This value is also in excellent agreement with the calculated barrier of 91 kJmol⁻¹ (Table 1) and further supports a halogen-bond pathway.

Substrate scope

After establishing the mode of activation, we next investigated the substrate scope of this reaction (Scheme 4). All reactions were performed in acetonitrile using 15 mol% of the catalyst. These conditions should allow for reasonable reaction rates and the kinetics discussed above indicate that lower catalyst loadings should be feasible for most cases. The reaction mixtures were deactivated when TLC analyses indicated the complete consumption of the dienophile.

With the exception of acrylic (2c) and maleic acid (2k) as well as maleic anhydride (2h), no background reaction was observed without a catalyst. While the carboxylic acids only afforded relatively small amounts of the corresponding cyclo-adduct, reactions involving maleic anhydride proceeded very quickly in the absence of iodine and were typically completed within minutes. Consequently, no iodine catalysis was attempted for 2h.

As expected from their reactivities, $^{[32a-c]}$ cyclohexadiene (1 a) and isoprene (1 c) reacted only with aldehydes and ketones as dienophiles. Cycloadditions occurred more readily with cyclopentadiene (1 b) and different functional groups including acids, amides, and nitriles were tolerated in the dienophile. In most cases, cycloadditions were obtained within minutes and with high *endo* selectivities. For methacrolein (2 j), a partial decom-



Scheme 4. Substrate scope (Conditions: [1 a,c] = [2] = 0.5 M, [1 b] = 0.6 M, $[l_2] = 7.5 \text{ mM}$, CH_3CN , 25 °C) for the iodine-catalyzed Diels-Alder reaction; [a]; 37% without l_2).

position of the dienophile was observed under the reaction conditions, which is most likely caused by polymerization.

Several dienophiles did not result in the desired products: Cinnamaldehyde (**2g**), acrylic acid (**2c**), and several esters (e.g., **2d,m,n**) did not afford the corresponding cycloadducts even with the most reactive diene **1b**. While the DFT calculations already indicated high barriers for **2g** (presumably due to the better conjugation of the π -system), reasonable activation free energies have been calculated for the ester **2d**. Although similar observation has also been made for tritylium ions,^[17] no obvious reaction could be identified that accounts for that finding.



Comparison with other catalysts

As our mechanistic analysis clearly support the assumption of a halogen-bond activation by iodine, we eventually wanted to compare the catalytic activity of iodine to that of other typical catalysts. We, therefore, performed the reaction between cyclohexadiene (1 a) and methyl vinyl ketone (2 a) in acetonitrile with different catalysts (10 mol%) that are frequently employed in Diels-Alder reactions (Table 4).^[14] It should be noted that the optimal reaction conditions vary from catalyst to catalyst, but for the sake of simplicity, we selected acetonitrile as the solvent of choice for this comparison. As discussed above, many catalysts are highly active in this cycloaddition and BF₃·OEt₂ performs best under the reaction conditions affording almost quantitative conversion after 5 minutes. Remarkably, iodine can compete with strong Lewis acids such as AICI₃, TiCl₄, SnCl₄ or also tritylium ions. In all cases, an endo-exo equilibration was observed after the cycloaddition was complete, but again, it seems that this isomerization is slower for iodine compared to AlCl₃ or TiCl₄.

Although a direct comparison with other halogen-bond donors used in Diels-Alder reactions is somewhat difficult due to the different reaction conditions,^[3d,5a,20,21] our investigations



clearly demonstrate that iodine is superior to most of them and can also compete with bidentate iodine(III) systems. Interestingly, molecular bromine, which can occasionally be used to replace iodine as a catalyst,^[41] is inactive under the reaction conditions. On the one hand, bromine is generally a weaker halogen-bond donor compared to iodine.^[1] On the other hand, addition reactions of bromine are thermodynamically more favorable and could result in catalyst consumption.^[42] Furthermore, typical organocatalysts including Schreiner's thiourea $4a^{[19a]}$ and secondary amines $4b,c^{[19b,c,e,g,i]}$ were found to be completely inactive under these reaction conditions.

The different reactivity observed for various Lewis acids in our experimental investigation seems to contradict previous high-level calculations (see above).^[26] This investigation predicted an increasing catalytic effect within the series $I_2 < SnCl_4 <$ $TiCl_4 < ZnCl_2 < BF_3 < AlCl_3$ for the reaction between isoprene (1c) and methyl acrylate (2d).^[26] One explanation for this deviation could result from acetonitrile as the solvent chosen for this comparison. Acetonitrile is weakly Lewis basic itself and could, therefore, interact with the stronger Lewis acids and reduce their activities. Furthermore, it should be noted again that we were unable to observe any iodine-catalyzed cycloaddition involving esters that were used for the computational investigation (see above). However, as iodine is usually considered to be environmentally more favorable compared to metallic Lewis acids and furthermore tolerates also weakly Lewis-basic solvents, these findings once again underline the practical importance of iodine catalysis.

Conclusion

We have developed a new and mild protocol for Diels-Alder reactions relying on molecular iodine as a catalyst. The cycloadditions can be performed under mild and metal-free conditions with a cheap and environmentally benign catalyst. Mechanistic investigations indicate that iodine activates the dienophile via a halogen bond and other pathways like a hidden Brønsted-acid catalysis or an iodonium activation seem unlikely.

Experimental Section

Experimental details

General procedure for iodine-catalyzed Diels-Alder reactions. The diene 1 (1.0 eq. for 1 a and 1 c, 1.2 eq. for freshly cracked 1 b) and the dienophile 2 (1.0 eq.) were dissolved in CH₃CN (0.5 mL) under argon. The same volume of an iodine solution in CH₃CN was immediately added resulting in a catalyst loading of 15 mol%. The reaction mixture was stirred at 25 °C until TLC analysis indicated full consumption of the dienophile. The reaction mixture was directly subjected to column chromatography on silica gel to give the desired cycloadduct.



Computational details

The conformational space for all intermediates was explored using the OPLS3 force field^[43] and a modified Monte Carlo search routine implemented in MacroModel.^[44] An energy cutoff of 100 kJ molwas chosen for the conformational analysis, and structures with heavy-atom root-mean-square deviations (RMSD) less than 0.5 Å after the initial force field optimizations were considered to be the same conformer. The remaining structures were subsequently optimized with the meta-hybrid M06-2X functional,^[45] the triple- ζ basis set 6-311 + G(d,p) for all atoms except I, and the aug-cc-pVTZ basis set with the corresponding pseudopotential (commonly called aug-cc-pVTZ-PP) for iodine.^[46] Solvation by acetonitrile was accounted for by the SMD solvation model^[47] with refined SMD parameters for iodine.^[48] Vibrational analysis verified that each structure was a minimum or transition state. Following the intrinsic reaction coordinates (IRC) confirmed that all transition states connected the corresponding minima on the potential energy surface. Thermal corrections were calculated from unscaled harmonic vibrational frequencies at the same level of theory and refer to a standard state of 298.15 K and 1 mol L⁻¹. Entropic contributions to free energies were obtained from partition functions evaluated with Grimme's quasi-harmonic approximation.[49] This method employs the free-rotor approximation for all frequencies below 100 cm⁻¹, the rigid-rotor-harmonic-oscillator (RRHO) approximation for all frequencies above 100 cm^{-1} , and a damping function to interpolate between the two expressions. Similar results were obtained from partition functions evaluated with Cramer's and Truhlar's guasiharmonic approximation.^[50] This method uses the same approximations as the usual harmonic oscillator approximation, except that all vibrational frequencies lower than 100 cm⁻¹ are set equal to 100 cm⁻¹. Energies were subsequently calculated with single-point calculations employing the double-hybrid B2PLYP functional,^[51] Grimme's D3 correction with Becke-Johnson damping,^[52] the large triple- ζ basis set aug-cc-pVTZ for all atoms, the aug-cc-pVTZ-PP pseudopotential for I,^[46] and, the modified SMD solvation model for acetonitrile.[47,48] An integration grid corresponding to 99 radial shells and 974 angular points was used throughout this investigation for the numerical integration of the density. All DFT calculations were performed with Gaussian 16,^[53] natural population analysis and Wiberg bond analysis used the NBO 6.0 program^[34] in combination with Gaussian 16.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Catalysis · Cycloadditions · DFT Calculations · Halogen Bonding · Reaction Mechanisms

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Mild but Effective. Molecular iodine can be used to catalyze Diels-Alder reactions of different dienes in good yield and with high *endo*-selectivity under very mild conditions. Mechanistic studies indicate that iodine acts as a halogen-bond donor in these reactions. A comparison with typical metal-based catalysts further indicates that iodine is comparable to Lewis acids such as AICI₃. T. Arndt, P. K. Wagner, Dr. J. J. Koenig, Priv.-Doz. Dr. M. Breugst*

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