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H-Bonding Additives Act Like Lewis Acid Catalysts

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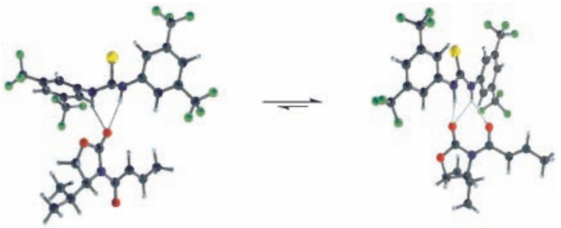
ABSTRACT

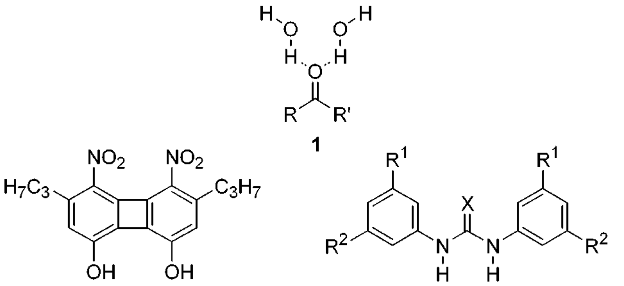


A combination of NMR, IR, and ab initio techniques reveals the striking structural similarities of an exemplary H-bonded complex of an *N*-acyloxazolidinone with an *N,N′*-disubstituted electron-poor thiourea and the corresponding Lewis acid complex. Although the H-bond association constant is lower than for the Lewis acid adduct, Diels–Alder reactions are accelerated and stereochemically altered in a fashion similar to weak Lewis acids.

Although the use of Lewis acids is ubiquitous in organic synthesis,[1] the utilization of hydrogen-bond donor additives in place of Lewis acids for the complexation of basic heteroatoms is rather underdeveloped.[2] This kind of interaction is important not only in synthesis but also in supramolecular chemistry,[3] molecular recognition,[4] and crystal engineering.[5] The hydrogen-bonding properties of ureas play an important role in their functions as herbicides, inclusion compounds and as HIV-protease inhibitors.[6] Recent efforts led to a few promising hydrogen-bond donor additives based on bisphenols (**2**)[7] and ureas (**3a**−**c**).[2a,8] Although some ureas cocrystallize with oxygen-containing compounds,[4−5,9] many form oils and make structural analyses difficult.[10]

Computational studies suggested that hydrogen bond donors are able to provide two or more hydrogen bonds to

Scheme 1



1

2

3a X = O, $R^1 = NO_2$, R^2 = H
3b X = O, $R^1 = CF_3$, $R^2 = CO_2C_8H_{17}$
3c X = S, $R^1 = CF_3$, $R^2 = CO_2C_8H_{17}$
3d X = O, $R^1 = CF_3$, R^2 = H
3e X = S, $R^1 = CF_3$, R^2 = H
3f X = S, $R^1 = CF_3$, $R^2 = CF_3$

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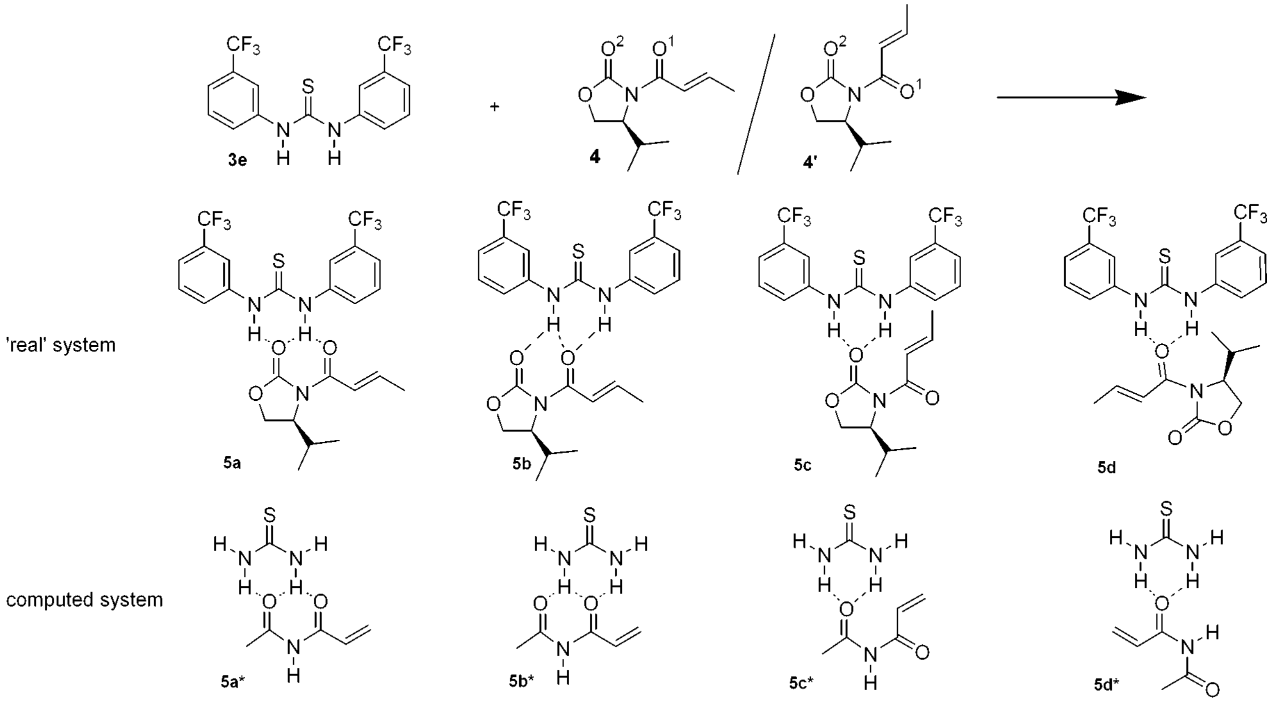
Scheme 2



bind to oxygen atoms in ethers or carbonyl groups (**1**, Scheme 1).[11] Thus, **3b,c** have been used effectively as additives in dipolar Claisen rearrangements[12] and in allylation reactions of α-sulfinyl radicals.[2a] However, the hydrogen-bonding motifs for, e.g., 1,3-diketo compounds (well established for their complexes with Lewis acids[13]), and the conformational preferences in the H-bond acceptor have largely been left unexplored.[3,14] Since the structure of, e.g., a Michael-type dienophile with an oxazolidinone auxiliary determines the stereoselectivity of radical additions[15] or Diels−Alder reactions,[16] we set out to study the complexation between thiourea **3e** and *N*-acyloxazolidinone **4** by a combination of dynamic NMR, low-temperature IR, and high-level computational methods (density functional theory, DFT). The portability of the Lewis acid concept of H-bond donors as catalysts in Diels−Alder reactions is probed here. For computational feasibility we used the model complexes **5a*−5d***, which only involve the essential structural features (Scheme 2).

A straightforward way of analyzing the complexation of **3e** or a Lewis acid, such as $AlCl_3$, with **4** would be an NMR polarization transfer experiment (NOE) of the free and complexed species (Figure 1). As there is a through-space interaction of the α-proton (H^E) with the methyl groups (H^A and $H^{A'}$) of the isopropyl moiety, the minor isomer **4** is present in all spectra, unfortunately even in A. Therefore, this analysis does not aid in assigning structural preferences of the oxazolidinone in the complexes. Nevertheless, the thiourea phenyl groups show interactions with all oxazolidinone protons (C). These proton probes on the hydrogen-bonding additive, naturally absent in $AlCl_3$, reveal the association of **3e** and **4**. The resulting structural details and the binding energy, however, are not disclosed.

The strength of the interaction was determined by an NMR titration.[17] In 1:1 mixtures of **3e** and **4** in CD_2Cl_2, the ^1H NMR shows only one N−H signal at 291 K but three (corresponding to **3e**, **3e·3e**, and **3e·4**) signals at 193 K; coalescence occurs at $T_c = 208$ K.[18] The following thermochemical parameters were determined: For **3e·3e**, $\Delta G_{298} = -0.6 \pm 0.2$ kcal mol^{-1}, $\Delta H = -11.2 \pm 1.1$ kcal mol^{-1}, $\Delta S = -35.6 \pm 3.8$ cal mol^{-1} K^{-1}. For **3e·4**, $\Delta G_{298} = -3.4 \pm 0.2$ kcal mol^{-1}, $\Delta H = -6.5 \pm 1.3$ kcal mol^{-1}, $\Delta S = -9.6 \pm 2.6$ kcal mol^{-1} K^{-1}. These values are well below the barriers for internal rotation of the thiourea ($\Delta G_{298} = 13.5 \pm 0.1$ kcal mol^{-1}).[18] As a consequence of the large dimerization entropy, **3e·3e** can only form at very low

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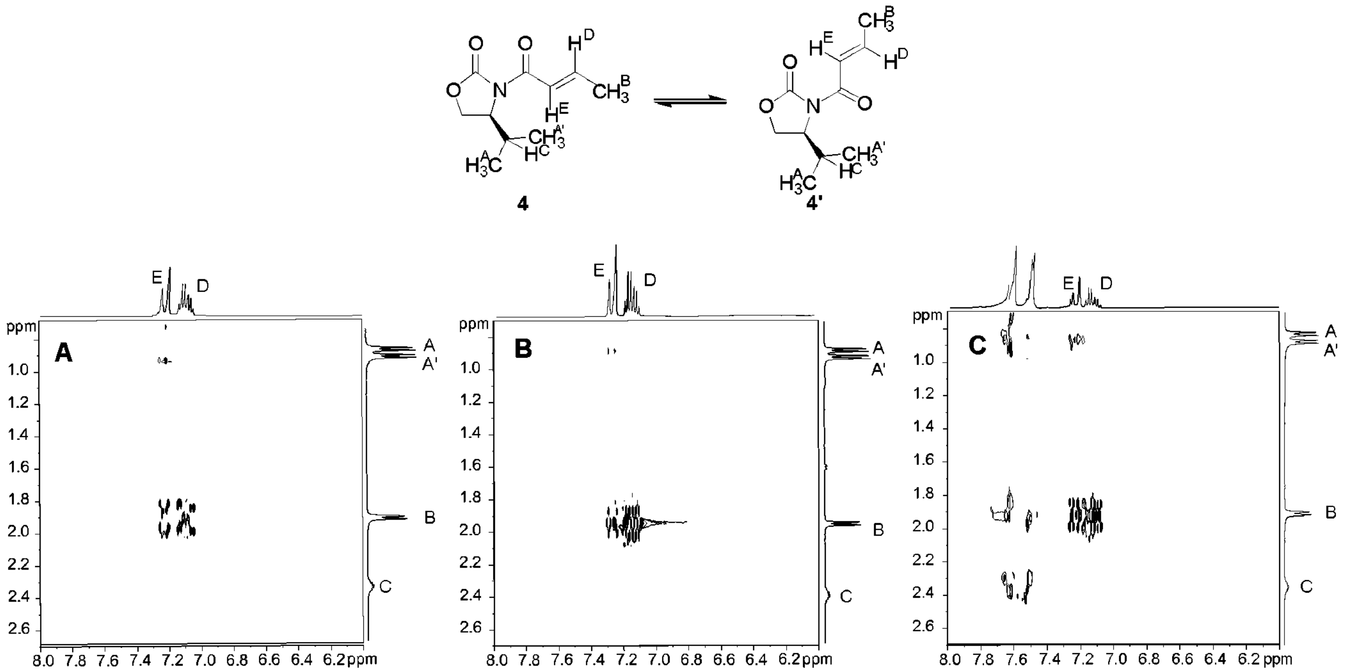

Figure 1. ^{1}H NOE spectra of pure **4** (A), a 1:1 mixture of **4** and $AlCl_3$ (B), and a 1:1 mixture of **4** and **3e** (C).

temperatures; the formation of **3e·4**, on the other hand, is favored at room temperature.

To differentiate the relative conformation of **3e·4** we compared the *shifts* ($\Delta\nu$) of the C═O IR absorptions of the two carbonyl functions with computed[19] $\Delta\nu$'s of model complexes **5a*−5d***. This reveals the site of complexation (Scheme 2) and the preferred conformation of the **4** moiety in **3e·4**. All computations were carried out at the DFT level utilizing the Becke-3-Lee-Yang-Parr (B3LYP)[20] method with the cc-pVTZ (on C, H, O, and N) and 3-21G(*) (S) basis sets[21] for optimizations and IR frequency computations; a 6-311+G** basis on all atoms gave the final energies.

Although the dissociation energies (D_0) are qualitatively well reproduced, clearly favoring **5a*** and **5b*** (Table 1), a distinction between these two cannot be made on the basis of the computations alone. Since the 77 K IR spectra show that thiourea **3e** does interact with *both* carbonyl groups, which are shifted by +24.4 cm^{-1} (O^2) and +7.2 cm^{-1} (O^1) relative to uncomplexed **4**, *only* **5a*** and **5b*** are possible candidates. Hence, the oxazolidinone conformation is clearly that of **4** in the **3e·4** complex, i.e., **5a**. The differences in $\Delta\nu$ indicate that O^2 interacts more strongly with the H-bond donor than O^1. If one assumes a constant error (ca. 7 cm^{-1}) in the $\Delta\nu$'s, the agreement between **3e·4** (therefore **5a**) with model structure **5a*** is evident (Table 1).

Table 1. Measured (**3e·4**) and Computed (**5a*−5d***) Shifts ($\Delta\nu$, cm^{-1}) of the C═O IR Absorptions for **4** versus Complex **5**[a]

species	$\Delta\nu$ (C═O$^{2)}$)	$\Delta\nu$ (C═O$^{1)}$)	D_0
5a*	+30.8	+13.7	10.6
5b*	+35.3	+11.3	11.1
5c*	−10.7	−22.8	8.6
5d*	−30.9	+5.8	7.0
3e·4 (exp)	+24.4	+7.2	6.5 ± 1.3

[a] Note that we do not expect to reproduce the experimental binding energy ($-D_0$) with the model system; the agreement in the frequency shifts $\Delta\nu$ determines the complexation site.

These findings are well in line with studies on the complexation of **4** with strong Lewis acids such as Et_2AlCl where the high facial selectivities in catalyzed reactions are due to the interaction of the Lewis acid (as $AlEt_2^+$) with both carbonyl groups.[13] Hence, despite large differences in the interaction energies, hydrogen-bond donors and metal-containing Lewis acids can lead to isostructural complexes with 1,3-diketo compounds.

Our conclusions from the NMR, IR, and computational studies are further supported by a Diels−Alder reaction of **4** with cyclopentadiene (Table 2).[22] This reaction is ideally suited to examine the effect of catalysts because oxazolidi-

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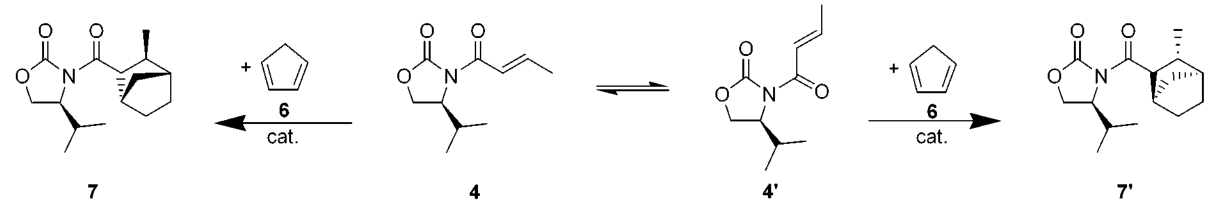
Table 2. Experimental Data for the Diels−Alder Reactions between **4** and Cyclopentadiene (**6**)[a]



entry	catalyst	catalyst concn (rel to **4**)/solvent	*T* [°C]	*t* [h]	yield [%]	**7**:**7′**
1		0/benzene	130	96	55	36:64
2	$AlCl_3$	25 mol %/$CHCl_3$	−78	1	95	92:8
3	$TiCl_4$	25 mol %/$CHCl_3$	−78	1	92	89:11
4	**3e**	25 mol %/$CHCl_3$	23	48	74	77:23
5	**3f**	25 mol %/$CHCl_3$	23	48	78	81:19

[a] Yields and product ratios were determined by NMR integration of the reaction mixtures.[16]

nones generally do not react with simple dienophiles at room temperature; prolonged heating is required (entry 1). In marked contrast, Lewis acids such as $AlCl_3$ and $TiCl_4$ accelerate these reactions enormously (entries 2 and 3). Our hydrogen-bonding additive **3e** and even more so the more electron-deficient **3f** (Scheme 1) catalyze (at 25 mol %) the chosen reaction well enough so that it can be carried out at 23 °C with appreciable yields (entries 4 and 5). In the catalyzed reactions the de's are also enhanced, and these values translate directly back into the preferred conformation of the starting materials. As the major product requires that the oxazolidinone adopts conformation **4** (note that the ground-state preference of the uncomplexed species is **4′**), this must also be the preferred structure in the Lewis acid and H-bonded complexes, in perfect agreement with our proceeding analysis.

Hence, the combined approaches exploited here reveal detailed structural information on the apparent similarities of Lewis acid and hydrogen-bonded complexes for a model system. The final reactivity study emphasizes the validity of this three-pronged (NMR, IR, computations) ansatz.

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(22) **Experimental Procedure.** All Diels−Alder reactions were carried out in sealed glass tubes containing 5 mL of a solution of 0.05 M dienophile **4**, 0.5 M cyclopentadiene (**6**), and the respective amount of catalyst (relative to the dienophile concentration) in the chosen solvent. After the period of time given in Table 2, 1 mL of water was added. The organic layer was separated and dried with Na_2SO_4. The solvent was removed under reduced pressure. The crude reaction mixture was dissolved in $CDCl_3$ and analyzed on a Bruker AMX 400 NMR spectrometer.