# Cooperative Catalysis Involving Hydrogen and Halogen Bond Donors: A Computational Study on the Thiourea–Iodonium System

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**ABSTRACT:** A computational analysis of possible routes of cooperative catalysis involving hydrogen bond (HB) and halogen bond (XB) donating organocatalysts has been carried out. Previously suggested route including electrophilic activation of HB donor by XB donor was ruled out but a path involving double activation of a reaction electrophile by its simultaneous association with the HB and XB donating species was confirmed by DFT calculations.



Noncovalent organocatalysts providing formation of a hydrogen bonding (HB)<sup>1-7</sup> between a catalyst and reaction substrates—in particular, (thio)ureas<sup>8-15</sup> and squaramides<sup>14-18</sup>—has gained a great attention over the last two decades, because they typically have low sensitivity to moisture and negligible sensitivity to air under the reaction conditions, as well as demonstrate a lower environmental footprint than metal-complex catalysts. Recently, the field of homogeneous organocatalysis has been significantly expanded due to intake of catalytically active  $\sigma$ -hole carriers, among which halogen bond  $(XB)^{19-21}$  donors featuring iodine-based  $\sigma$ -hole carriers exhibited higher catalytic activity than that of well-proven (thio)urea-based organocatalysts (Figure 1, A).<sup>22,23</sup> Thus, cationic iodine(I)-containing species—in particular, iodoazoliums B<sup>22,24-29</sup> effectively catalyze many organic transformations, whereas cationic hypervalent iodine(III) derivatives C (i.e., diaryliodonium salts<sup>30-36</sup>) exhibited even greater activity than the iodine(I) species.

Recently Takagi et al. reported experimental observation of synergetic catalytic effect for the mixture of Schreiner's thiourea (**A**) and 2-iodoimidazolium salt (**B**) in the reaction of cationic polymerization of isobutyl vinyl ether.<sup>22</sup> The authors<sup>22</sup> suggested that this effect might be realized via ligation of the thiourea to the XB donor via the S atom (**D**), which results in increase of electrophilicity of the thiourea's H atoms thus enhancing the total catalytic activity of the system. Considering that cooperative catalysis, <sup>6,37-39</sup> which is almost unexplored for the XB donating species, in this work we decided to carry out a computational study on estimation of the catalytic potential of a mixture of well-proven HB and XB donating organocatalysts.

As a model reaction, hydrolysis of methyl chloride has been chosen, since this simple reaction includes elimination of an anionic species and thus is similar to the reaction studied by Takagi.<sup>22</sup> In addition, this reaction has been studied by us previously for many other noncovalent organocatalysts (**Figure 2**).<sup>29,40,41</sup>



**Figure 1.** Representative examples of HB and XB donating organocatalysts, their modes of association with reaction substrates, and the suggested<sup>22</sup> associate providing synergetic catalytic effect.

As model catalytic species, methylbenziodolium  $\mathbf{1}$  has been chosen as XB donating representative, whereas N,N'-dimethyl derivatives of urea  $\mathbf{2}$ , thiourea  $\mathbf{3}$ , and squaramide  $\mathbf{4}$  has been selected as the HB donors.

The obtained computational results clearly indicated that all the species provide significant catalytic effect reducing the Gibbs free energy of activation from 296 kJ mol<sup>-1</sup> (for the non-catalyzed reaction) to 144–196 kJ mol<sup>-1</sup> (for the **1–4** catalyzed processes). The XB donor **1** expectedly represents the lowest Gibbs free energy of activation compared with HB donors **2–4** and binds the transition state (**TS**) via I···Cl and H···Cl noncovalent bonds with nearly linear arrangement of the I···Cl···C···O atoms. The least catalytically active urea derivative **2** led to the **2·TS** associate featuring one H···Cl and one H···N bonds, whereas more active derivatives **3** and **4** associated with **TS** via two H···Cl and one H···S or H···O bonds, respectively. Thus, all the chosen HB donors additionally served as Lewis bases binding the water molecule via hydrogen bond and leading to the associates with parallel arrangement of any of **2–4** and **TS** (**Figure 2**).



Figure 2. Model reaction, selected primary catalysts 1–4, calculated transition state structures and corresponding Gibbs free energy of activation.

For further study of possibility of realization of a synergetic effect during the catalysis, we decided to operate with thioureafunctionalized benziodolium salts 5-7 featuring both the XB and HB donating functionalities in one species (Figure 3). The cyclic form of cations (5\*-7\*) stabilized by intramolecular XB between the I and S atoms is more stable than the corresponding open-chain form (5–7) by 30–37 kJ mol<sup>-1</sup> in  $\Delta G$  scale in the absence of the solvent, but the energy gap is expected to be significantly lower in the case of consideration of ligated solvent molecules taken in explicit form.<sup>42</sup> Taking into account significant inaccuracy in the relative energy between two forms of the catalysts in real systems, further they are discussed separately. For binding of 5-7 and 5\*-7\* with TS, no solvent molecules have been discussed since the general idea of this work is to compare *relative* energy between the associates and the solvation effects were expected to be very similar for the same functionalities in the selected species.

Open-chain species 5–7 featuring non-interacting XB and HB moieties form two types of associates with TS, namely thioureabound and iodonium-bound species (5A–7A and 5C–7C, respectively). The Gibbs free energy of activation for the thioureabound associates 5B and 6B is very similar with that of 3B (3·TS on Figure 2), whereas the energy of 7B is remarkably higher (Figure 3). For the iodonium-bound associates 5D–7D, the activation energy turned out to be slightly higher but comparable with that of 1B (1·TS on Figure 2). Thus, the obtained results gave expectable values of the activation energy, since non-interacting XB and HB donating functionalities in 5–7 provide similar stabilization of TS compared with that of separately taken XB and HB donating species 1 and 3, respectively.

Cyclic forms of the selected catalysts ( $5^*-7^*$ ) include interacting XB and HB donating groups, which might be able to significantly affect the catalytic activity of each other. Considering that ligation of the thiourea moiety to one of the iodine  $\sigma$ -hole should provide electrophilic activation of the former, one may expect the increase of the catalytic activity of the HB donating functionality when they bind the **TS**. And vice versa, occupation of one of the  $\sigma$ -holes by the

electron-donating species should result in decrease of the catalytic activity of the iodonium moiety.<sup>29,42</sup> These suggestions are coherent with our estimation of the values of maximum electrostatic potentials [V<sub>s</sub>(max)] on the corresponding atoms: 480–515 kJ mol<sup>-1</sup> on the  $\sigma$ -holes of the I atom in **5–7** vs 445–465 kJ mol<sup>-1</sup> on that of 5\*-7\*, and 475-525 kJ mol<sup>-1</sup> on the amide H atoms of 5-7 vs 515-535 kJ mol<sup>-1</sup> for  $5^*-7^*$ . In addition, the I---S interactions in  $5^*-7^*$  are accompanied by a charge transfer from the lone pair of the S atom to the antibonding I–C orbitals equal to 56–81 kJ mol<sup>-1</sup> (namely 81 kJ mol<sup>-1</sup> for 5\*, 60 kJ mol<sup>-1</sup> for 6\*, 56 kJ mol<sup>-1</sup> for 7\*, according to second order perturbation theory analysis of Fock matrix in natural bond orbitals basis), which has moderate<sup>41,43</sup> value for such type interactions. A comparison with the primary species 1 (530 kJ mol<sup>-1</sup> on the iodine  $\sigma$ -holes) and **3** (220 kJ mol<sup>-1</sup> on the amide H atoms) indicate slight reduction of the V<sub>s</sub>(max) value for the I atom and its significant increase on the amide H atoms.

The obtained results clearly indicated remarkably lower stabilization of TS then it is ligated to the I atom of cyclic 5\*-7\* species compared with non-functionalized benziodolium cation  ${\bf 1}$ (162–172 kJ mol<sup>-1</sup> vs 144 kJ mol<sup>-1</sup> for **5**C\*–**7**C\* and **1**B, respectively). But then TS is ligated to the amide H atoms of the thiourea moiety in cyclic 5\*–7\*, it surprisingly does not provide higher stabilization than that of N,N'-dimethylthiourea **3** (158–172 kJ mol<sup>-1</sup> vs 158 kJ mol<sup>-1</sup> for 5B\*-7B\* and 3B, respectively) and these data contradict with the suggestion of enhance of catalytic activity of thiourea…XB donor associate compared with that of thiourea and XB donor taken separately. Moreover, this observation also contradicts with the previously observed dependence of the catalytic activity on the V<sub>s</sub>(max) value.<sup>29</sup> The latter problem most likely should be explained in terms of overlap of electrostatic fields from the cationic iodonium species and the thiourea moiety. Thus, considering that the 2.5-fold increase in the electrostatic potential on the amide H atoms is not provided by the potential located on these atoms but the longranging external field of the cationic iodolium species, the iodoliumbound thiourea does not provide significantly higher catalytic effect on the ligated transition state.



Figure 3. The calculated structures of bifunctional catalyst...transition state associates and relative Gibbs free energies for all model systems.

Absence of the increase of catalytic activity also might be raised from different binding modes of TS to the thiourea moiety in 3 and  $5^*-7^*$ , namely parallel arrangement between 3 and TS with two Cl...H and one H...S bonds and linear arrangement between  $5^*-7^*$ and TS without the H...S bond. In order to check the importance of binding with the S atom serving as a Lewis base in the stabilization of the model transition state, the energy of corresponding binding modes **5**E–**7**E were calculated (**Figure 3**). The obtained values indicated higher stabilization of **TS** by **7**E compared to **3**B and **5**B\*–**7**B\* (146 kJ mol<sup>-1</sup> vs 158–172 kJ mol<sup>-1</sup>, respectively) but even in this case the catalytic activity was not higher than that of primary iodolium cation **1** (146 kJ mol<sup>-1</sup> vs 144 kJ mol<sup>-1</sup>). Based upon this

observation, it can be concluded that the H $\cdots$ S bonding does not have a crucial role in the stabilization of **TS**.

Finally, possibility of double activation of methyl chloride by **1** and **3** independently binding with the former to give trimolecular associate  $1 \cdot TS \cdot 3$  after nucleophilic attack of H<sub>2</sub>O has been checked (Figure 4). It was found that the model reaction has significantly lower activation energy when proceeds via this transition state. Thus, independent activation of the substrate seems to be more plausible explanation for the synergetic catalytic effect for the iodolium and thiourea mixture than iodolium-provided electrophilic activation of the thiourea.

In summary, in this short note we carried out the computational study which indicates that experimentally observed<sup>22</sup> cooperative catalysis by XB and HB donors is likely provided by double activation of the electrophile by XB and HB donors rather than sequential activation of the electrophile by the XB-donor-activated HB donor (Figure 5). Worthwhile to mention that several indirect routes leading to the increased catalytic activity are discussible for these systems. On the one hand, HB donor can stabilize the catalytically active XB donor (potentially unstable under the reaction conditions) thus prolonging its action during the reaction. This route has been casually mentioned in ref.<sup>22</sup> and recently observed by us<sup>44</sup> for the case of silver(I)-iodolium triflate mixture. On the other hand, HB donor can bind the counter-ion of the XB donating species leading to higher concentration of the dissociated (and catalytically active) form of the latter. We sincerely hope that this work will stimulate further development of the field of cooperative organocatalysis involving  $\sigma$ -hole carriers.



Figure 4. Structures of 1·TS, 3·TS, and 1·TS·3 and corresponding Gibbs free energies of activation.



**Figure 5.** Confirmed and unconfirmed cooperative catalytic modes of the XB and HB donor mixture.

### **Computational Details**

Finally, possibility of double activation of methyl chloride by 1 and **3** independently binding with the former to give trimolecular The full geometry optimizations of all model structures was carried out at the DFT level of theory using the M06-2X functional<sup>45</sup> with the help of the Gaussian-09 program package.<sup>46</sup> The M06-2X functional was specifically developed and parameterized for a correct description of noncovalent interactions and thermochemistry (especially in the case of main group chemical elements)<sup>45</sup> and was also validated for these purposes in several benchmark studies.<sup>47-49</sup> We have chosen this functional according to our previous experience and its successful performance in a number of halogen and chalcogen bonds studies in various similar supramolecular systems and organocatalysis processes.<sup>40,42</sup> The quasi-relativistic MWB46 pseudopotentials,<sup>50</sup> which described 46 core electrons, and the appropriate contracted basis sets were used for iodine atoms, while the standard 6-31G\* basis sets were used for other atoms. No symmetry restrictions were applied during the geometry optimizations. The Hessian matrices were calculated analytically for all optimized model structures to prove the location of the correct minimum or saddle point on the potential energy surface (no imaginary frequencies or only one imaginary frequency, respectively). The calculation of molecular surface electrostatic potentials was performed using the Multiwfn program<sup>51</sup> (version 3.7). The Cartesian atomic coordinates for all model structures are presented in attached xyz-file (Supporting Information).

#### **Supporting Information**

**Table S1.** Calculated total electronic energies (E, in Hartree), enthalpies (H, in Hartree), Gibbs free energies (G, in Hartree), and entropies (S, cal/mol•K) for optimized equilibrium model structures; **Table S2.** Calculated values of maximal and minimal molecular surface electrostatic potentials located on the heteroatoms and/or H atoms for optimized equilibrium model structures (V<sub>s</sub>(max) and V<sub>s</sub>(min), in kJ/mol) (**PDF**)

Optimized Structures (XYZ)

#### **Conflicts of Interest**

The authors declare no conflict of interest.

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