# Computational Study on the Route of Cooperative Organocatalysis Utilizing Thiourea and Halogen Bond Donor Mixture

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A computational analysis of possible routes of cooperative catalysis involving hydrogen bond donating thiourea and halogen bond donating organocatalysts has been carried out at the M06-2X/SDD level of theory using the solvation model based on density (SMD). For the model systems involving thiourea and 2-iodoimidazolium or iodonium salt derivatives, the previously suggested route including sequential electrophilic activation of a reaction electrophile via XB-activated HB donor was ruled out.



## Introduction

Noncovalent organocatalysts providing formation of a hydrogen bonding (HB)1-7 between a catalyst and reaction substrates-in particular, (thio)ureas<sup>8-15</sup> and squaramides<sup>14-18</sup>—have attracted great attention over the last two decades since they typically have low sensitivity to moisture and negligible sensitivity to air under the reaction conditions while demonstrating a lower environmental footprint than metal-complex catalysts. Recently, the field of homogeneous organocatalysis has been significantly expanded due to the intake of catalytically active  $\sigma$ -hole carriers, among which halogen bond (XB)^{19\text{-}21} donors featuring iodine-based  $\sigma\text{-}hole$  carriers exhibited a 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>) exhibit even greater activity than the iodine(I) species.

Recently Prof. Takagi et al. have reported an 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 the increase of electrophilicity of the thiourea's H atoms, thus enhancing the total catalytic activity of the system.

Taking into consideration the fact that cooperative catalysis is an actual and growing trend in homogeneous catalysis,<sup>7,37-39</sup> which is almost unexplored for the XB donating species, and being inspired by the experimentally observed synergetic catalytic effect involving the XB donors, in this work we decided to carry out a computational study on the estimation of the catalytic potential of a mixture of well-proven HB and XB donating organocatalysts.

**Computational details.** The full geometry optimization of all model structures was carried out at the M06-2X/SDD level of theory with the help of the Gaussian-09 program package.<sup>40</sup> The solvent





effects were taken into account implicitly using the SMD (Solvation Model based on Density) continuum solvation model suggested by Truhlar and coworkers<sup>41</sup> for water as a solvent. No symmetry restrictions were applied during the geometry optimization procedure. The Hessian matrices were calculated analytically for all optimized model structures to prove the location of the correct minimum or saddle point (transition state) 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 (version 3.7).<sup>42</sup> The Cartesian atomic coordinates for all model structures are presented in xyz-files (**Supporting Information**).

**Selection of the model reaction and catalysts.** As a model reaction, hydrolysis of methyl chloride has been chosen, since this simple reaction includes the elimination of an anionic species and, thus, is similar to the reaction studied by Prof. Takagi.<sup>22</sup> In addition, this reaction has been studied by us previously for many other noncovalent organocatalysts (**Figure 2**).<sup>29,43,44</sup> As model catalytic species, 2-iodoimidazolium **1** and dibenziodolium **2** have been chosen as iodine(I) and iodine(III)-based XB donating representatives, whereas *N*,*N*'-dimethyl thiourea **3** has been selected as the HB donor.



Figure 2. Model reaction, selected catalysts 1-3, calculated transition state structures and the corresponding Gibbs free energy of activation in kJ mol<sup>-1</sup> given in parentheses.

The optimized structures of associates of 1-3 with the transition state (TS) exhibited nearly perpendicular arrangement of the organocatalytic species and **TS** ( $\angle X$ -Cl-C = 87°-98°; where X is C-I or N-H atoms). The obtained results have indicated that dibenziodolium cation 2 exhibits higher stabilizing effect on the transition state (TS) than 2-iodoimidazolium 1 and thiourea 3 derivatives (145 kJ mol<sup>-1</sup> vs 157 kJ mol<sup>-1</sup> and 152 kJ mol<sup>-1</sup>, respectively; Figure 2). For the triple associates 1.3.TS and 2.3.TS, no synergetic catalytic effect has been observed, since the Gibbs free energy of activation of such associates turned out to be higher by ca. 30 kJ mol<sup>-1</sup> than that for the double associates 1·TS-3·TS (174-185 kJ mol<sup>-1</sup> vs 145–157 kJ mol<sup>-1</sup>, respectively). Considering that increase in the energy of activation for 1.3.TS and 2.3.TS might be caused by negative entropy of association of the species 1 or 2 with 3.TS, we further decided to estimate the possibility of electrophilic activation of thiourea moiety via its intramolecular ligation to the XB-donor's  $\sigma$ -hole, since such type of process is expected to have less entropy loss than intermolecular binding.

Study of bifunctional XB-HB donating species. To further study the possibility of realization of a synergetic effect during the catalysis, we decided to operate with thiourea-functionalized benziodolium salts 5–7 featuring both the XB and HB donating functionalities in one species (Figure 3). In this case, methylbenziodolium cation 4 has been chosen as a referent XB donor. Although these complex species are yet unknown, the involvement of both types of catalytically active centers in one molecule should minimize the influence of entropy factor during the calculations, which is important for the study of "clear" electrophilic activation of the HB donating moiety by the ligation to the  $\sigma$ -hole. Open-chain species 5–7 featuring non-interacting XB and HB moieties, as well as their cyclic forms 5\*–7\* including interacting XB

**Table 1.** Catalyst…transition state binding parameters. The lengths of N–H…Cl, I…Cl, and I…S noncovalent contacts, ratio between the Lagrangian kinetic energy  $G(\mathbf{r})$  and potential energy density  $V(\mathbf{r})$  (a.u.) at the bond critical points (BCPs) from the QTAIM analysis of the N–H…Cl, I…Cl, and I…S noncovalent contacts in the model species, and calculated by natural bond orbitals (NBO) analysis charge transfer from transition state to catalyst.

Model structure	Distance, Å	% of Bondi's vdW sum	-G( <b>r</b> )/V( <b>r</b> )	TS to catalyst charge transfer,
	N–H…Cl			KJ MOI-'
<b>5</b> HB	2.484	84	1.10	61
	2.395	81	1.00	
<b>5</b> HB*	2.326	79	0.93	99
	2.339	79	0.93	
<b>6</b> HB	2.367	80	1.00	97
	2.332	79	1.00	
<b>6</b> HB*	2.341	79	0.93	99
	2.341	79	0.93	
<b>7</b> HB	2.370	80	1.00	86
	2.374	80	1.00	
<b>7</b> HB*	2.363	80	1.00	101
	2.310	78	0.94	
	I····Cl			
<b>5</b> XB	3.179	85	1.08	52
<b>5</b> XB*	3.182	85	1.00	56
<b>6</b> XB	3.164	85	1.08	56
<b>6</b> XB*	3.172	85	1.08	55
<b>7</b> XB	3.172	85	1.08	56
<b>7</b> XB*	3.192	86	1.00	55
	I…S			
<b>5</b> HB*	3.199	85	1.09	
<b>5</b> XB*	3.246	86	1.10	
6HB*	3.270	87	1.11	
<b>6</b> XB*	3.341	88	1.11	
7HB*	2.280	60	1.00	
<b>7</b> XB*	3.340	88	1.13	

and HB donating groups, can form two types of associates with TS, namely thiourea-bound and iodonium-bound species (5HB–7HB and 5HB\*–7HB\*, as well as 5XB–7XB and 5XB\*–7XB\*, respectively; Figure 3). The obtained results indicate that 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 4–12 kJ mol<sup>-1</sup> in  $\Delta G$  scale, which lays in expected energy interval.<sup>45</sup>

The QTAIM analysis<sup>46</sup> of the catalyst---transition state associates demonstrated the presence of appropriate bond critical points (BCPs) for the optimized model structures (Table 1). The low magnitude of the electron density, positive values of the Laplacian of electron density, and near-zero energy density in these BCPs are typical for non-covalent interactions. The balance between the Lagrangian kinetic energy  $G(\mathbf{r})$  and potential energy density  $V(\mathbf{r})$  at the BCPs reveals the nature of these interactions; if the ratio - $G(\mathbf{r})/V(\mathbf{r}) > 1$ , the nature of the interaction is purely noncovalent, whereas  $-G(\mathbf{r})/V(\mathbf{r}) < 1$  indicates some covalent component.<sup>47</sup> Based on this criterion, we can conclude that the covalent contribution is almost absent in the studied interatomic interactions, although minor increase in covalent contribution to the bonding, as well as transition state-to-catalyst charge transfer values are observed for cyclic forms 5HB\*-7HB\* compared to their acyclic forms 5HB-7HB, respectively.

Cyclic species **5**<sup>\*</sup>–**7**<sup>\*</sup> include interacting XB and HB donating groups, which might be able to 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,



Figure 3. The calculated structures of bifunctional catalyst…transition state associates and the corresponding Gibbs free energy of activation in kJ mol<sup>-1</sup> given in parentheses.

one may expect the increase of the catalytic activity of the HB donating functionality when it binds the TS. And vice versa, occupation of one of the  $\sigma\text{-holes}$  by the electron-donating species should result in the decrease of the catalytic activity of the iodonium moiety.<sup>29,45</sup> For the iodine atom, this suggestion is coherent with our estimation of the values of maximum electrostatic potential  $[V_s(max)]$ : 615–672 kJ mol<sup>-1</sup> on the  $\sigma$ -holes of the I atom in 5–7 vs 525–549 kJ mol<sup>-1</sup> on that of  $5^*-7^*$ , whereas V<sub>s</sub>(max) values on the amide H atoms lay in similar intervals: 527-650 kJ mol-1 for 5-7 vs 568–622 kJ mol<sup>-1</sup> for  $5^*-7^*$ . The comparison with the primary species 4 (619–633 kJ mol<sup>-1</sup> on the iodine  $\sigma$ -holes) and 3 (332 kJ mol<sup>-1</sup> <sup>1</sup> on the amide H atoms) indicates a slight reduction of the V<sub>s</sub>(max) value for the I atom for the cyclic forms 5\*-7\* and its significant increase on the amide H atoms irrespectively to configuration of the bifunctional species. Most likely, the latter observation should be explained in terms of overlap of electrostatic fields from the cationic iodonium species and the thiourea moiety. Thus, the 2-fold increase in the electrostatic potential on the amide H atoms is not provided by the potential located on these atoms but the long-ranging external field of the cationic iodolium species. Binding of the transition state by the HBs results in higher charge transfer values than ligation to the iodine  $\sigma$ -hole (61–101 kJ mol^-1 vs 52–56 kJ mol^-<sup>1</sup>, respectively; **Table 1**), which may cause higher stabilization of the transition state by the ligation to thiourea moiety compared to binding to the iodine center. In addition, for associates involving cyclic form of the catalysts 5HB\*-7HB\* charge transfer values are higher than the corresponding values for the associates involving open-chain species (5HB-7HB), which also can indirectly evidence that ligation of the thiourea group to the iodine  $\sigma$ -hole can increase electrophilicity of the former.

Despite all of the above, the calculations indicate that although the Gibbs free energy of activation for the thiourea-bound associates  $5HB^*-7HB^*$  is lower than that for 5HB-7HB (140–141 kJ mol<sup>-1</sup> vs 143–147 kJ mol<sup>-1</sup>, respectively; **Figure 3**), the obtained values are similar within accuracy of the computational method. Moreover, for the iodonium-bound associates 5XB-7XB and  $5XB^*-7XB^*$ , the activation energy turned out to lay in the same energy intervals irrespectively to the substrate configuration (143–147 kJ mol<sup>-1</sup> and 142–154 kJ mol<sup>-1</sup>, respectively) and these values are similar to that of primary iodolium salt **4** (141 kJ mol<sup>-1</sup>). Preassociation of the substrates does not affect the activation barriers because it has the positive Gibbs free energy values (26–37 kJ mol<sup>-1</sup> for **5–7** and **5\*–7\***) and thus does not lead the systems to the local energy minimum.

Considering that the key factor determining the possibility of the synergistic catalytic effect between the XB and HB donors via the suggested electrophilic activation of the latter is reduction of the Gibbs free energy of activation after coordination of the thiourea to the iodine  $\sigma$ -hole, analysis of the obtained data does not confirm the feasibility of such cooperative catalytic effect. Taking into account that no synergetic catalytic effect has been determined for the *intramolecular* binding of the catalytic centers in **5–7**, realization of this effect via *intermolecular* cooperation of two catalytically active species seems even less possible due to the entropy penalty, which has been confirmed by the results represented on **Figure 2**. Nevertheless, the obtained results indicate that the catalytic activity of iodonium salts can be increased by involving of their structure auxiliary groups able to bind a transition state jointly with halogen bonding (**7**XB-S; **Figure 3**).

In summary, in this note we have presented the computational study which indicates that cooperative catalysis by XB and HB donors is unlikely proceed via a sequential activation of the electrophile by the XB-donor-activated HB donor. Several indirect routes leading to the increased catalytic activity are discussible for these systems. On the one hand, the thiourea can stabilize the catalytically active XB donor (potentially unstable under the reaction conditions), thus prolonging its action during the reaction. This route has been briefly mentioned in reference 22, recently observed by us<sup>48</sup> for the case of silver(I) triflate–iodolium triflate mixture, and suggested<sup>49</sup> for iodopyridinium-based XB-donating catalysts. On the other hand, the HB donor can bind the counter-ion of the XB donating species leading to a 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, which certainly deserves a deeper study.

#### **Associated Content**

#### **Data Availability Statement**

The data underlying this study are available in the published article and its Supporting Information.

#### **Supporting Information**

**Table S1**. Calculated Gibbs free energies (G, in Hartree) for optimized equilibrium model structures; **Table S2**. Values of the density of all electrons –  $\rho(\mathbf{r})$ , Laplacian of electron density –  $\nabla^2 \rho(\mathbf{r})$ , energy density – H<sub>b</sub>, potential energy density – V( $\mathbf{r}$ ), and Lagrangian kinetic energy – G( $\mathbf{r}$ ) (a.u.) at the bond critical points (3, –1), corresponding to N–H…Cl, I…Cl, and I…S noncovalent contacts in the model species (PDF)

Optimized Structures (XYZ)

#### **Conflicts of Interest**

The authors declare no conflict of interest.

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