

# A solvent-free organic synthesis from solid-state reactants through autogenous fusion due to formation of molecular complexes and increasing alcohol nucleophilicity

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**Abstract**—Crystalline imidazole (IM, mp 361–364 K) fuses autogenously immediately after making contact at room temperature with menthol (MT, mp 316 K) as a consequence of the hydrogen bond. Autogenous fusion is triggered by the recombination of the hydrogen bonds from the homogeneous ones (MT–MT) stabilizing MT crystals to the heterogeneous ones between OH of MT and N of IM to form an intermediate molecular complex at a eutectic composition. Formation of molecular complex parallels the increase in the nucleophilic affinity of MT by the intermolecular hydrogen bonds, as confirmed by the peak shift of  $^1\text{H}$  NMR as well as by DFT computation.

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## 1. Introduction

Solvent-free organic syntheses are gathering increasing interest from the viewpoints of green chemistry.<sup>1</sup> In any solvent-free reactions, interaction between dissimilar species becomes sensitive since solvation and associated shielding by solvent molecules are absent. Specific interactions between dissimilar solid organic species, among other hydrogen bonding and/or  $\pi$  interaction may, therefore, play a more significant role than those in a solution state, provided that the distance between the solid particles is shorter than the critical distance, through which electrons or protons can move across.<sup>2,3</sup> We here discuss mechanisms of a representative solid state organic synthesis via an intermediate molecular complex, inspired by the report of Hagiwara and co-workers with solid state alcoholysis of 1,1'-thiocarbonyl-diimidazole.<sup>4</sup>

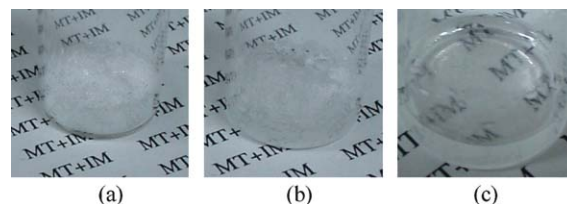
## 2. Experimental

We used (–)-menthol (MT, mp 316 K, Tokyo Kasei) and imidazole (IM, mp 361–364 K, Kanto Kagaku) as

purchased.  $^1\text{H}$  NMR spectra were observed with Varian Mercury-300 in 300 MHz. For the samples in a fused state, we used a special sample holder, that is, a coaxial inserts (Wilmad, Aldrich). We performed solvent free FT-IR spectroscopy either by a KBr disc method (IR, FTS-175, BIORAD) or by using React-IR (ReactIR 4000™, Mettler, Toledo) for fused specimens.

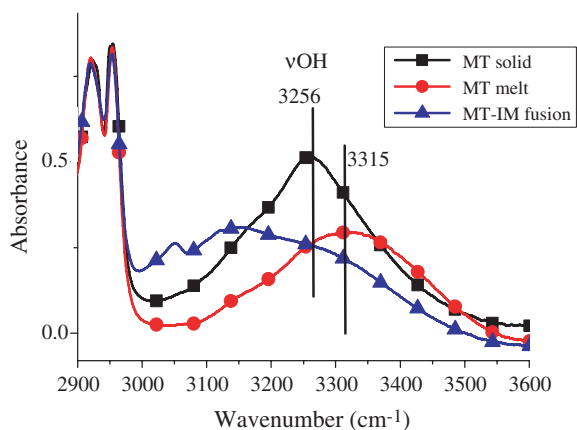
## 3. Results and discussion

Optical microscopic observation at room temperature allowed us to observe incipient fusion at the contact point immediately after their physical encounter. As shown in Figure 1, we observed significant bulk fusion by the bare eye, 10 min after contacting IM with MT



**Figure 1.** Process of autogenous fusion between IM and MT: (a) before contact; (b) 10 min after contact. Substrates near contact points are getting wet; (c) 30 min after contact. Entire substrates were fused.

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**Figure 2.** Change in the IR spectra by heating and autogenic fusion.

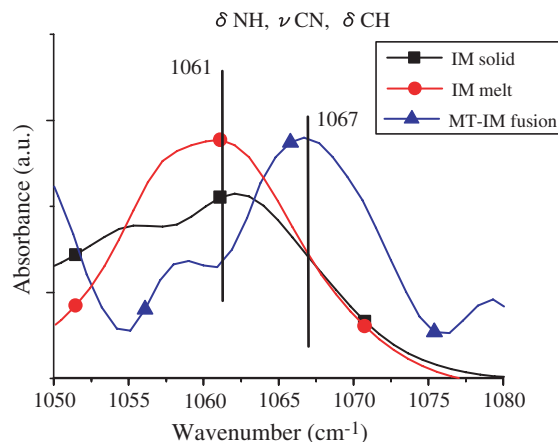
without any external stimuli. Autogenous fusion was completed 30 min after the initial contact.

As IR spectra changed with autogenous fusion, we compared them with those of molten reactants. As shown in **Figure 2**, the intensity of  $\nu\text{OH}$  absorption band at around  $3200\text{--}3300\text{ cm}^{-1}$  decreased by autogenous fusion ('MT-IM fusion'). A similar decrease in the absorption intensity was observed by melting IM alone upon heating up to 523 K. A columnar array of hydrogen bonds along the  $c$ -axis in MT is reported by Bombicz et al.<sup>5</sup> For the decrease of  $\nu\text{OH}$  band intensity, we find no other reasons than the breakage of hydrogen bonds between the MT molecules stabilizing its crystalline state. We therefore conclude that the autogenous fusion is triggered by the destruction of the long-range order of MT molecules due to the loss of stabilizing homogenous (MT-MT) hydrogen bonds. This, in turn, intensifies the OH bond strength of MT to induce a blueshift of the  $\nu\text{OH}$  band.

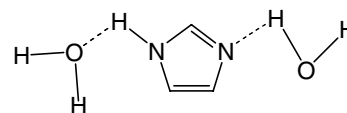
After gentle heating to melt MT ('MT melt'), we observed a blueshift of  $\nu\text{OH}$  band from  $3256$  to  $3315\text{ cm}^{-1}$ . In the case of autogenous fusion, we recognize different states of new bondings from the diversity of the bands between  $3111$  and  $3121\text{ cm}^{-1}$ , assigned to  $\nu\text{CH}$  band, without appreciable  $\nu\text{OH}$  bands.<sup>3</sup> By the same token,  $\nu\text{OH}$  bands appeared at smaller wavenumbers for MT-IM fusion than for MT-melt, just because of the formation of intermolecular H-bonds. We emphasize that these changes do not occur in a solution, for example, in  $\text{CHCl}_3$ , as we confirmed by React-IR,  $^1\text{H}$  NMR and UV-vis spectra.

On the other hand,  $\nu\text{CN}$ ,  $\delta\text{NH}$ ,  $\delta\text{CH}$  bands from IM blueshifted from  $1061$  to  $1067\text{ cm}^{-1}$ , as shown in **Figure 3**, as a consequence of molecular complex (MC) formation. It is well known that IM acquires proton easily by the lone pair electrons of nitrogen from environmental  $\text{H}_2\text{O}$ , while carrying out an inter-molecular proton transfer from NH to oxygen. These processes result in the formation of a 2:1 complex with  $\text{H}_2\text{O}$  (see **Scheme 1**).<sup>3,6</sup>

From the observed shifts of the IR bands, being nearly the same as those interpreted by the interaction mechanism of **Scheme 1**, we reasonably conclude that the same



**Figure 3.** Shift of the IR spectra assigned IM by heating and autogenous fusion.



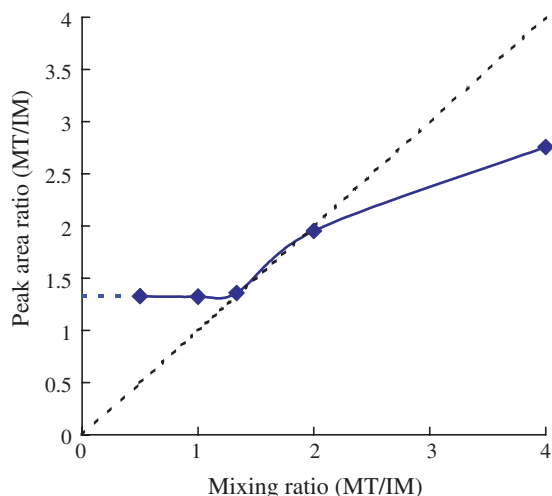
**Scheme 1.**

change occurs on IM during MC formation in the present study. Initiation of autogenous fusion is, therefore, described by the recombination of H-bonds, as a consequence of charge transfer, that is, delocalization and redistribution of the electrons from the lone pair of N or NH in IM to oxygen of intra-crystalline H-bond in MT.

When we mixed IM and MT in an equal molar ratio, we frequently observed suspended small crystals in molten MC. IM is known to form charge transfer complexes in a solid state with aromatic hydrocarbons (i.e., naphthalene, anthracene, biphenyl and phenanthrene) in various molar ratios.<sup>7</sup> To determine the molar ratio, MT/IM, in a molten state, we used conventional  $^1\text{H}$  NMR after we completely separated the specimen from a solvent at 293 K by a neat NMR technique.<sup>8</sup> (The raw NMR spectra data are shown in **Supplementary data**.)

As shown in **Figure 4**, the peak area ratio of NMR in the melt remains unchanged at 1.33 when the MT/IM mixing ratio is smaller than 1.33. This strongly suggests that the composition,  $\text{MT/IM} = 4/3$  (1.33), corresponds to that of the eutectic. Formation of the eutectic explains the observation of instantaneous fusion.<sup>9</sup> When the nominal molar ratio exceeds 1.33, the content of MT in the molten phase increases with the nominal ratio along the broken straight line representing the proportionality. This means that MC in a molten state can dissolve MT to a significant extent.

Propagation of the autogenous fusion is, therefore, explained by the repetition of partial dissolution of MT into MC, and consequent continuation of MC formation, in an autocatalytic manner. We also recognize the apparent saturation of MT into MC from the ob-

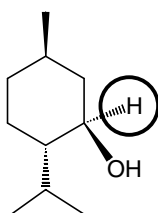


**Figure 4.** Change in the molar ratio of the molten phase at 293 K with the mixing ratio, MT/IM.

served level off, recognized as a deviation from the broken straight line in Figure 4.

We further examined the electronic states in the fused MC by  $^1\text{H}$  NMR and compared with those in the molten states by conventional heating up to 523 K. We observed the shift of the NMR signal from the proton (see the Scheme 2) to exhibit the shift toward the higher frequency side, indicating the less shielded state than that of the simple molten state. It is caused by a decrease in the electron density around the carbon atom next to the proton. This corresponds to the increase in the electron density around the oxygen atom of OH group, leading to an increase in the nucleophilic affinity of oxygen in MT by the formation of MC.

To confirm the above-mentioned mechanism, we carried out DFT computation by using B3LYP method on a basis set of 6-31+G\* (6-31+Gd) for the structural optimization with the aid of Gaussian'03. Fang et al.<sup>10</sup> carried out a computational study on the complex formed from phenol and amine including IM, with the type of interaction same as OH–N hydrogen bond in the present study, by using 6-31+G\* basis set. We therefore selected 6-31+G\* basis set for MC from IM and MT in this study. As we compared the electron densities around the oxygen in OH and the proton in its backbone CH bond, we found that the absolute value of the former increased from 0.646 to 0.703, while that for the latter decreased from 0.179 to 0.168. This implies an increase in the charge density around oxygen as a consequence



**Scheme 2.**

of MC formation to increase the nucleophilic affinity of MT. This supports the observed shift of the  $^1\text{H}$  NMR signal mentioned above.

A rapid solid-state alcoholysis of 1,1'-thiocarbonyl-diimidazole (TCDI) with solid state alcohols including MT, reported by Hagiwara et al.<sup>4</sup> is, then, explained reasonably by the MC formation between a solid alcohol like MT, and IM, the latter being the decomposition product of TCDI. The benefit of starting from a solid mixture is also clear since the formation of MC is only possible when the charge transfer, as an incipient step of hydrogen bond recombination, is not disturbed by the presence of solvents. We actually observed the increase in the yield of the product, thiocarbonylimidazolide, and the rate of reaction by adding TCDI to MC after their establishment. We also emphasize that the hydrogen bond between solid particles easily occurs at ambient temperatures whenever the distance between the donor and the acceptor is short enough for charge transfer.<sup>2</sup>

#### 4. Summary

Imidazole (IM) forms a eutectic autogenously with menthol (MT) at the molar ratio MT/IM = 4/3 (1.33) as a result of hydrogen bond across the boundary between dissimilar particles. Autogenous fusion is triggered by the recombination of the hydrogen bonds from the homogeneous ones (MT–MT) stabilizing MT crystals to the heterogeneous ones between OH of MT and N of IM to form an intermediate molecular complex at a eutectic composition. Melting front is driven by the developing concentration gradient of the molecular complex (MC) by repeating recombination of hydrogen bonds and local fusion until the whole mass turns into MC in an autocatalytic manner. The process was promoted by the increase in the nucleophilic affinity of MT, as confirmed by the peak shift of  $^1\text{H}$  NMR as well as by DFT computation.

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#### Supplementary data

We indicated the NMR spectra in neat condition for supporting data. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.02.143.

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