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<td>Author(s)</td>
<td>岡本, 専太郎; OKAMOTO, Sentaro; TAKANO, Kouichi; ISHIKAWA, Tomohiro; ISHIGAMI, Satoshi; TSUHAKO, Akiko</td>
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Activity and behavior of imidazolium salts as a phase transfer catalyst for a liquid-liquid phase system

Sentaro Okamoto,* Kouichi Takano, Tomohiro Ishikawa
Satoshi Ishigami and Akiko Tsuhako
Department of Material & Life Chemistry,
Kanagawa University 3-27-1 Rokkakubashi,
Kanagawa-ku, Yokohama 221-8686, Japan

The structure-activity relationship and behavior of N,N-dialkylimidazolium salts as a phase transfer and/or ion exchange catalyst in a liquid-liquid phase system was investigated for various reactions.
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Department of Material & Life Chemistry, Kanagawa University, 3-27-1 Rokkakubashi, Kanagawa-ku, Yokohama 221-8686, Japan

Abstract—The structure-activity relationship and behavior of N,N-dialkylimidazolium salts as a phase transfer and/or ion exchange catalyst in a liquid-liquid phase system was investigated for the reactions such as β-elimination reaction of alkyl halides, nucleophilic epoxidation of α,β-unsaturated carbonyl compounds, alkylation of active methylenes and nucleophilic substitution reaction.

Imidazolium salts 1 are a well-known heterocycle but have recently been recognized as versatile molecules for use as polar organic solvents (ionic liquids, when X is a bulky counter ion) and a precursor of stable heterocyclic carbenes (when R2=H), ligating to metal atoms, and playing itself as a catalyst (Figure 1). Recently, the molecules have assumed a new aspect as a phase transfer or anion exchange catalyst. The use of imidazolium salts 1 as a phase transfer catalyst under solid-liquid biphasic conditions has been reported, which involves alkylation and Michael addition reactions of active methylene compounds and cross-aldol reaction. Meanwhile, use of 1 in organic/aqueous liquid-liquid biphasic systems has recently been reported by Afonso et al. for nucleophilic alkylation and substitution reactions in CH2Cl2/H2O.5a Kim et al. also reported hydrolysis of 1-chloro-2,2,2-trifluoroethane in DMF, DMSO, NMP or γ-butyrolactone/H2O but the solvent system seems homogeneous.5b In these cases, only 1-n-butyl-3-methylimidazolium salt as an imidazolium salt was used. Compared with nitrogen and phosphorus quaternary cations 2 and 3, the salts of which have widely been utilized as phase transfer catalysts,6 the imidazolium cation has been reported to be more stable and is unique because its positive charge is highly delocalized to a five membered heterocyclic ring, the nature of the planar cation of which with variation of substituents might be useful for their design and functionalization as catalysts. However, the structural requirement and relationship to activity and mechanistic behavior as a catalyst have been little explored. Herein reported is the results of investigation on catalytic activity of 1 having various substituents for the several reactions, which clarified the structural requirement for use of 1 as a catalyst and gave their mechanistic aspects.

For the present study, imidazolium salts 1a-g were prepared by sequential alkylation of imidazole or 2-substituted imidazole, respectively, according to the conventional reaction procedure. Thus, 1-substituted or 1,2-disubstituted imidazole prepared from R1X and imidazole or 2-substituted imidazole was alkylated with R3X. The procedure afforded 1a-g in 83-99% yield through two steps.

First, we investigated nucleophilic epoxidation of α,β-unsaturated ketone 4 to 5 in the presence of a catalytic amount (3 mol%) of imidazolium salts 1 in the two-phase system of aqueous NaOCl solution and an organic solvent.
and evaluated the efficiency of various 1 having different substituents. The results are summarized in Table 1, in which the relative efficiency value was calculated based on the yields of 5 observed after an appropriate reaction time as indicated. In the actual experiments, the reactions were highly dependent on the stirring efficiency. Therefore, to avoid errors arising from stirring efficiency, the reactions were performed using the same type and size of vessels and magnetic stirring bars with the same stirring rate and the reaction with 1c was always carried out as the standard when the reactions with other catalysts were performed. Values for efficiency shown in Table 1 were calculated as a ratio of yield of 5 with each catalyst toward that with 1c in toluene under the same reaction conditions. As can be seen from the table, imidazolium salts, except for 2-unsubstituted 1a, exhibited catalytic activity for the transformation. The systematic structure-activity relationship was observed among compounds 1d-1g which have a phenyl group at the 2- position of imidazolium ring and N-substituents with different chain length at the 1- and 3-positions: Increase of the total carbon number of chains at the 1- and 3-positions increased catalytic activity, presumably due to enhanced solubility of (imidazolium)+ X and/or (imidazolium)−OCl in the organic solvent utilized. Actually, 1d which is nearly insoluble in toluene could not catalyze the reaction in a toluene-water system. As illustrated in Figure 2, 1 may act as an ion-exchanging agent in the reaction media, i.e., an (imidazolium)+−OCl generated catalytically from (imidazolium)+−X might be an active species.

Table 1. Relative efficiency of catalysts for the nucleophilic epoxidation of 4 to 5 with aqueous NaOCl.

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Total C-number</th>
<th>Relative Efficiency</th>
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<tbody>
<tr>
<td>no</td>
<td>no reaction</td>
<td>no reaction</td>
</tr>
<tr>
<td>TBAB</td>
<td>16</td>
<td>0.56</td>
</tr>
<tr>
<td>1a</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>1b</td>
<td>16</td>
<td>0.98</td>
</tr>
<tr>
<td>1c</td>
<td>16</td>
<td>1.00 (standard)</td>
</tr>
<tr>
<td>1d</td>
<td>5</td>
<td>0.86</td>
</tr>
<tr>
<td>1e</td>
<td>8</td>
<td>0.77</td>
</tr>
<tr>
<td>1f</td>
<td>12</td>
<td>0.96</td>
</tr>
<tr>
<td>1g</td>
<td>16</td>
<td>1.12</td>
</tr>
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</table>

*Total carbon-number of the substituents at the 1- and 3- positions of the imidazolium ring. The value is shown as the ratio of yield of 5 with each catalyst toward that with 1c in toluene under the same reaction conditions. 5 was obtained in 92% isolated yield by the reaction with 3 mol% of 1c for 24 h at room temperature.

To clarify the reason why 2-unsubstituted imidazolium salt 1a could not catalyze the reaction of 4 to 5, 1a was treated with aqueous NaOCl/CH2Cl2 and it was found that under the oxidative conditions 1a was decomposed to give the corresponding urea derivative and unknown compounds (Equation 1).

Next, we studied behavior of imidazolium salts as a catalyst under the basic conditions required for basic β-elimination reaction of alkyl halide to alkene (Equation 3) and nucleophilic alkylation of the compounds having a acidic proton (Equation 4). The β-elimination reaction of alkyl halide was performed as follows: A mixture of aqueous 50% NaOH (1 mL), toluene (1 mL) and PhCH3CH2Br (1.5 mmol) was stirred at room temperature (22–24 °C) in the absence or presence of imidazolium salt 1 or n-Bu4NBr (TBAB) (5 mol%). It was found that imidazolium salts 1a and 1c could effectively catalyze the reaction as well as TBAB. It was noted that unsubstituted imidazolium 1a as well as substituted 1c could equally exhibit catalytic activity, while 1a could not catalyze nucleophilic epoxidation of 4 to 5 and decomposed under the oxidative conditions. The time course of the reactions with 1c and TBAB was traced by GC analyses and is shown in Figure 3. A control experiment without catalyst did not afford the product styrene at all. Time vs. log (1-x) plots (x = conversion, 0 ≤ x ≤ 1) for both reactions catalyzed by 1c and TBAB fit well to simple lines when the conversion was less than 80% (<~10 h), where the reaction could be considered as an expected pseudo-first order under the conditions in

![Figure 2. Possible mechanism of epoxidation of 4 to 5.](image)

Since an imidazolium salt 1c solved in toluene and acted as an ion-exchange catalyst for the reaction of Table 1, a 1c/toluene/H2O system was utilized to nucleophilic substitution reaction (Equation 2). As expected, conversion of alkyl bromide to the iodide proceeded in the presence of an imidazolium salt 1e, and 1e was a better catalyst than TBAB under the conditions given.

![Image](image)
the presence of large excess of a base and a relatively small amount of catalyst to the substrate halide. The results indicate that catalyst 1c was stable and did not change the structure of its cation counterpart during the reaction.

Figure 3. Reaction time course (a) and time vs. log (1-x) plots (b) of elimination reaction of PhCH$_2$CH$_2$Br in aqueous NaOH-toluene. (x = conversion (0 ≤ x ≤ 1))

Deprotonation and alkylation reaction of the compounds having an acidic proton illustrated in Equation 4 was investigated. Thus, 1c as well as TBAB were effective for alkylation of indene in an aqueous KOH-toluene system to give selectively mono-alkylated compound in good yield (Equation 4).

To clarify an active species as a base and the structural stability of 1 under the basic conditions, we carried out the following experiments: The $^1$H NMR spectra of the residue obtained by the reaction of 1c with an excess amount of KOH in toluene/H$_2$O and the following concentration of the organic phase indicated an imidazolium ring structure similar to 1c, peaks of which had somewhat different chemical shifts from those of 1c. As revealed from Equation 5, protons at the 4- and 5-positions could be exchanged with protons of solvent(s) by a deprotonation/protonation pathway under the basic conditions. Meanwhile, as shown in Equation 6, it was found that the reaction of deuteronated indene (totally 76% D at 1- and 3-positions) and $n$-BuBr in toluene-50% KOH in H$_2$O with 50 mol% of 1c which gave the corresponding alkylated indene in good yield recovered 1c with 10% of deuterium incorporation at the C4 (or C5) position. The deuterium incorporation thus observed was apparently larger than the total D/H ratio included in the mixture of the substrates, reagents (1c and KOH) and solvent (H$_2$O). It is pointed out that the reaction under basic conditions at least involves the C4- (or C5-) anion of 1c, which can act as a base for deprotonation of indene.

Based on these results, a possible mechanism for the elimination reaction of alkyl halides and alkylation of indene is illustrated in Figure 4. The imidazolium bromide 1 can react with MOH (M = K or Na) on the surface between the organic and aqueous phases to give imidazol-4-ylidene A, which may deprotonate an acidic proton of the substrate to occur the elimination or alkylation reaction and generate (imidazolium)$^-$ again. In addition, a catalytic cycle involving an (imidazolium)$^-$OH (B), derived from 1 by an ion-exchange reaction, as an active base cannot be ruled out. An anion A may also be generated through formation of B.

Figure 4. Possible mechanism of elimination reaction and proton-exchange reaction of the imidazolium.

In contrast to imidazolium 1a-g, the benzo derivative of imidazolium salt 1h could not catalyze the β-elimination reaction shown in Equation 2. It was found that the reaction of 1h with KOH gave the corresponding ring-opening product (Equation 7).
In summary, we have reported the structural requirement and structure-activity relationship of 1,3-disubstituted and 1,2,3-trisubstituted imidazolium as a phase transfer catalyst in a liquid-liquid phase system under various reaction conditions. In addition to a similar ion-exchanging mechanism to that for usual phase transfer catalysts such as quaternary ammonium salts, it was suggested that the reaction under the basic conditions may involve an imidazol-4-yllide compound as an active species. These results might be useful for further application and design of imidazolium salts as a phase transfer catalyst.

Acknowledgment

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References and notes


8. 3-Butyl-1H-indene might be produced by alkene-isomerization of initially produced 1-buty1-1H-indene.

9. Ring deuteriation of imidazolium cations in D₂O under basic conditions has been reported: Gierroth, R.; Bankmann, D. Tetrahedron Lett. 2006, 47, 4293.

10. Prepared from indene by the reaction with 10% KOH in D₂O in the presence of n-Bu₄NB₄ (5 mol%).