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# An NMR study on a pseudo-intramolecular transacylation reaction of an α-aryl-β-keto ester†

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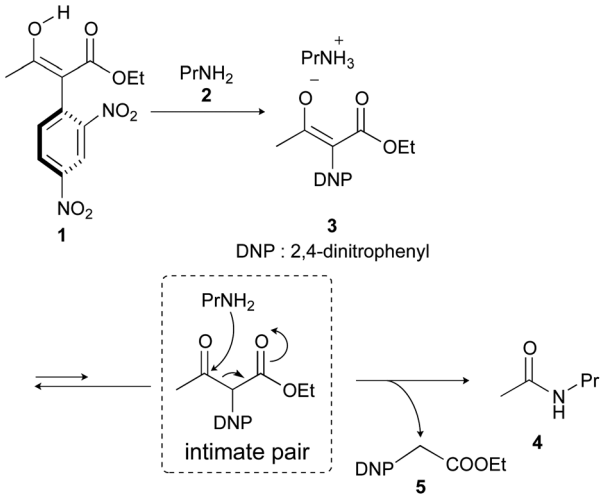
The pseudo-intramolecular transacylation reaction efficiently proceeds like an intramolecular reaction, even though it is actually an intermolecular reaction. We have obtained valuable insights by monitoring the reaction by $^1$H NMR spectroscopy.

The development of a highly efficient reaction which diminishes both resource waste and energy, is highly desirable from the viewpoint of green chemistry. In general, an intramolecular reaction proceeds more efficiently than an intermolecular reaction because of a higher collision frequency between reaction sites. In other words, an increase in the collision frequency of reactants results in the improvement of the reaction efficiency, even in an intermolecular process. Indeed, the use of reaction fields such as micelles and microcapsules, enables reactions to proceed easily by increasing the opportunity of reactants to encounter each other.[1] Such great success implies that efficient intermolecular reactions can be achieved if the collision frequency of the reactants can be increased, even in the absence of a reaction field.

Recently, we demonstrated a highly effective method called pseudo-intramolecular reactions.[2,3] The reactions proceed under mild conditions without any reaction fields, additives and troublesome manipulations. Using this method vicinally functionalized 1,4-dihydropyridines, 1,2-diazepines, and diazabicyclic compounds have been readily synthesized.[2]

The transacylation reaction is another example of the pseudo-intramolecular process (Scheme 1).[3a] The α-arylation of a β-keto ester increases the acidity of the hydrogen atom of the active methylene[4] because the aryl group stabilizes its enol form.[5] As a result, the ammonium salt **3** is easily formed upon treatment with the amine **2**. When a small amount of the amine is liberated under equilibrium, the nucleophilic amine and the electrophilic keto ester locate close to each other. This is referred to as an intimate pair. The spatial proximity of the reagents enables an efficient nucleophilic substitution reaction to proceed, transferring the acyl group from the keto ester **1** to the amine **2** under mild conditions. The steric congestion around the reaction site also prevents the approach of other molecules, which consequently depresses any side reactions.[3] Indeed, the efficient progress of the reaction could be easily monitored by $^1$H NMR spectroscopy. Just after the addition of an equimolar amount of the amine **2** to a solution of the α-aryl-β-keto ester **1** in $CDCl_3$, the formation of the ammonium enolate **3** could be confirmed by the immediate disappearance of the signal assigned to the enol hydrogen atom. With the decrease in the signals for the salt, the signals for the transacylated products **4** and **5** increased, without any detectable formation of by-products, to achieve quantitative conversion.




Scheme 1 A mechanism for the pseudo-intramolecular transacylation reaction.

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† Electronic supplementary information (ESI) available: Monitoring the transacylation reaction by $^1$H NMR spectroscopy using benzene-$d_6$ as the solvent and NMR data of compounds **1**, **4**, and **5**. An NMR study of the reaction of propylamine **2** and an equimolar amount of acetone in benzene-$d_6$. See DOI: 10.1039/c3ra45568h

The above features of the pseudo-intramolecular process enable the chemoselective and regioselective acylation reaction to proceed without any modification of the substrate, such as the protection of another functionality. Furthermore, this reaction also enables us to facilely synthesize unsymmetrical malonic acid derivatives by using an α-arylated acetonedicarboxylate.[3] Hence, the present transacylation reaction is a promising method for synthesising polyfunctionalized compounds. However, for applying the method to more elaborate syntheses, it is necessary to obtain further insights into the concept of "the pseudo-intramolecular process". If the reaction proceeds in a pseudo-intramolecular process, the reaction order is considered to be close to first order because the reactants have already encountered each other in the intimate pair. From this viewpoint, we have studied the correlation between the reaction rate and the polarity of the reaction medium/the concentration of the substrates by monitoring the progress of the reaction using $^1$H NMR spectroscopy. In addition, we have evaluated the reaction order on the basis of the results.

Solvation is one of the crucial factors affecting the reactivity of an intermolecular process, because two solvated substrates diminish the collision frequency.[6] As a result, the rate of an intermolecular process changes depending on the polarity of the reaction medium. On the other hand, for an intramolecular process reaction sites close to each other should be less influenced by the polarity of the solvent.[7] With the characteristics of intermolecular and intramolecular processes in mind, we hypothesized that the rate of the pseudo-intramolecular process should not be influenced by the polarity of the solvent even though it is actually an intermolecular process. In order to confirm this hypothesis, we monitored the transacylation reaction by $^1$H NMR spectroscopy using six different deuterated solvents (acetonitrile-$d_3$, THF-$d_8$, benzene-$d_6$, chloroform-$d$, methanol-$d_4$, and acetone-$d_6$) (Fig. 1). The dielectric constants ($\varepsilon_r$) and dipole moments ($\mu$) of these solvents are shown in Table 1.[8]

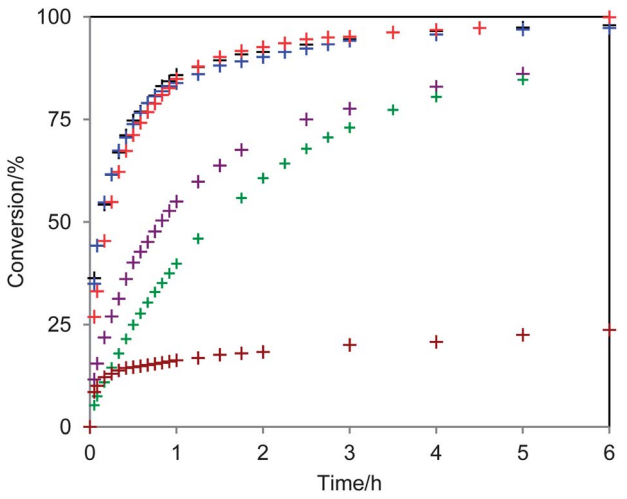


Fig. 1 Time/conversion curves for **3** in different solvents: acetonitrile (black), THF (blue), benzene (red), chloroform (purple), methanol (green), and acetone (brown). The reactions were conducted at 30 °C using a 0.06 M solution.

The progress of the transacylation reaction was monitored by $^1$H NMR spectroscopy at intervals of several minutes (hours). Since no signals were observed other than those for the ammonium salt **3**, the transacylated product **4** and 2,4-dinitrophenylacetate **5**, the reaction rate can be discussed on the basis of the conversion of **3**. When acetone-$d_6$, methanol-$d_4$, and chloroform-$d$ were used, the reactivities were different from each other. This is probably due to the interaction of the solvent with the amine **2**, which would arise from an electrophilic moiety[9,10] or a hydroxy group to form a hydrogen bond. Contrary to this, when benzene-$d_6$, THF-$d_8$, and acetonitrile-$d_3$ were used as the solvent, the transacylation reactions proceeded with the same reaction rate. It is noteworthy that the reaction rates in the latter three solvents were almost the same despite their extremely different polarities. This result strongly indicates that the transacylation reaction was not affected by the polarity of the solvent, as we hypothesized.

Next, the effect of the concentration of the reaction mixture was studied in a similar way by changing the concentration in the range from 0.24 to 0.015 M (Fig. 2 and Table 2). Although the reaction rate varied depending on the concentration, it became almost the same in highly diluted solutions. In the case of an intermolecular process, the reaction rate would become considerably slower with the dilution of the reaction mixture. Thus, the results support the fact that the reaction is a pseudo-intramolecular process.

In order to obtain further insight, the reaction orders $n$ of the reactions carried out at different concentrations were calculated using eqn (1), where $k$ is the rate constant, $A$ is the concentration of the ammonium enolate **3**, and $t$ is the reaction time.[11] The calculated value $n$ of each reaction was between first and second order (Table 3). Since the quantitative formation of the ammonium salt **3** was confirmed just after the addition of the amine **2** to a solution of the keto ester **1**, the higher reaction order is caused by the intermolecular reaction between two intimate pairs, as shown in Fig. 3.

$$\frac{1}{n-1}\left(\frac{1}{[A]^{n-1}} - \frac{1}{[A]_0{}^{n-1}}\right) = kt \qquad (1)$$

These results imply that a first order reaction and a second order reaction proceed in the present system. Consequently, the pseudo-intramolecular process is concluded to be fundamentally a first order reaction.

In summary, the present transacylation reaction was monitored by $^1$H NMR spectroscopy to give the following

Table 1 Rate constants $k$ and relative rate constants $k_{rel}$ with the solvent parameters

| Solvent | $\varepsilon_r$ | $\mu$/D | $k$/mol$^{-1}$ | $k_{rel}$ |
|---|---|---|---|---|
| Acetonitrile | 37.5 | 3.4 | $5.57 \times 10^{-4}$ | 1.0 |
| THF | 7.6 | 1.7 | $5.46 \times 10^{-4}$ | 0.99 |
| Benzene | 2.3 | 0 | $5.50 \times 10^{-4}$ | 1.0 |
| Chloroform | 4.8 | 1.2 | $1.77 \times 10^{-4}$ | 0.32 |
| Methanol | 32.6 | 1.7 | $1.18 \times 10^{-4}$ | 0.21 |
| Acetone | 20.7 | 2.7 | $5.60 \times 10^{-6}$ | 0.010 |

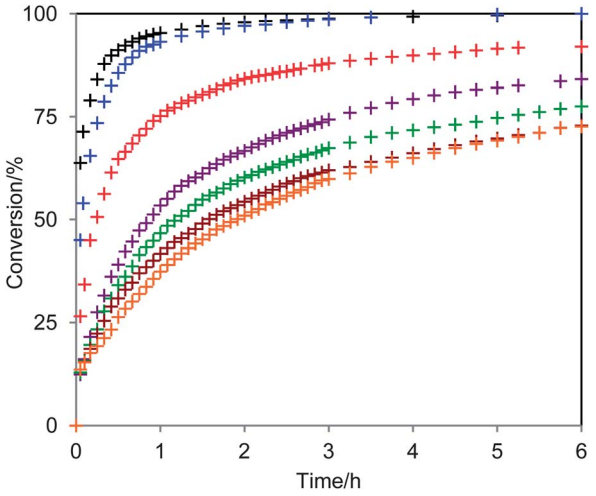


Fig. 2 Time/conversion curves for **3** at various concentrations: 0.24 (black), 0.12 (clue), 0.06 (red), 0.03 (purple), 0.025 (green), 0.02 (brown), and 0.015 (orange) M. The reactions were conducted at 30 °C using benzene-$d_6$ as the solvent.

Table 2 % Conversions of **3** monitored at hourly intervals at 30 °C using benzene-$d_6$, at differing concentrations of **3**

| | Conversion/% | | | |
|---|---|---|---|---|
| Concentration/M | 1 h | 2 h | 3 h | 4 h |
| 0.24 | 96 | 98 | 99 | 100 |
| 0.12 | 94 | 98 | 99 | 100 |
| 0.06 | 76 | 85 | 88 | 90 |
| 0.03 | 54 | 67 | 75 | 80 |
| 0.025 | 47 | 61 | 68 | 72 |
| 0.02 | 42 | 55 | 62 | 67 |
| 0.015 | 38 | 51 | 60 | 65 |

Table 3 Reaction orders measured for the reactions in benzene-$d_6$

| Concentration/M | Reaction order |
|---|---|
| 0.24 | 1.8 |
| 0.12 | 1.6 |
| 0.06 | 1.6 |
| 0.03 | 1.6 |
| 0.015 | 1.4 |

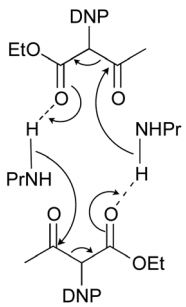


Fig. 3 A plausible reaction mechanism between two intimate pairs.

insights: (1) the reaction rate was not affected by the polarity of the solvent; (2) the reaction proceeded efficiently even in highly diluted solvents; and (3) the reaction order was lower than second order. These results reveal that the transacylation reaction proceeds like an intramolecular process rather than an intermolecular process. This information will be helpful for designing highly efficient and environmentally benign synthetic protocols for polyfunctionalized compounds.

## Notes and references

1 Reviews: (*a*) M. Hatano and K. Ishihara, *Chem. Commun.*, 2012, **48**, 4273–4283; (*b*) V. Ramamurthy and A. Parthasarathy, *Isr. J. Chem.*, 2011, **51**, 817–829; (*c*) T. Murase and M. Fujita, *Chem. Rec.*, 2010, **10**, 342–347; (*d*) M. Yoshizawa, J. K. Klosterman and M. Fujita, *Angew. Chem., Int. Ed.*, 2009, **48**, 3418–3438; (*e*) T. S. Koblenz, J. Wassenaar and J. N. Reek, *Chem. Soc. Rev.*, 2008, **37**, 247–262; (*f*) S. Liu and B. C. Gibb, *Chem. Commun.*, 2008, 3709–3716; (*g*) T. Dwars, E. Paetzold and G. Oehme, *Angew. Chem., Int. Ed.*, 2005, **44**, 7174–7199; (*h*) M. D. Pluth, R. G. Bergman and K. N. Raymond, *Acc. Chem. Res.*, 2009, **42**, 1650–1659.

2 (*a*) N. Nishiwaki, *Heterocycles*, 2013, **87**, 967–990; (*b*) S. Hirao, K. Kobiro, J. Sawayama, K. Saigo and N. Nishiwaki, *Tetrahedron Lett.*, 2012, **53**, 1424–1430; (*c*) N. Nishiwaki, S. Hirao, J. Sawayama, K. Saigo and K. Kobiro, *Chem. Commun.*, 2011, **47**, 4938–4940; (*d*) N. Nishiwaki, K. Kakutani, M. Tamura and M. Ariga, *Chem. Lett.*, 2009, **38**, 680–681.

3 (*a*) N. Nishiwaki, D. Nishida, T. Ohnishi, F. Hidaka, S. Shimizu, M. Tamura, K. Hori, Y. Tohda and M. Ariga, *J. Org. Chem.*, 2003, **68**, 8650–8656; (*b*) Y. Nakaike, N. Taba, S. Itoh, Y. Tobe, N. Nishiwaki and M. Ariga, *Bull. Chem. Soc. Jpn.*, 2007, **80**, 2413–2417.

4 (*a*) M. P. Egorov, V. K. Bel'skii, É. S. Petrov, M. I. Terekhova and I. P. Beletskaya, *Journal of Organic Chemistry of the USSR*, 1985, 1855–1862; (*b*) Z. Bánkowska, I. Zadrzna and D. Stopa, *Pol. J. Chem.*, 1979, **53**, 1563–1569.

5 (*a*) H. Yamataka and Z. Rappoport, *J. Am. Chem. Soc.*, 2000, **122**, 9818–9828; (*b*) A. Miller, *J. Org. Chem.*, 1976, **41**, 3599–3602.

6 K. C. Westaway and Z. Lai, *Can. J. Chem.*, 1989, **67**, 345–349.

7 (*a*) M. E. Jung and J. Gervay, *J. Am. Chem. Soc.*, 1989, **111**, 5469–5470; (*b*) V. Thavasi, R. Philip, A. Bettens and L. P. Leong, *J. Phys. Chem. A*, 2009, **113**, 3068–3077.

8 (*a*) A. R. Hirst and D. K. Smith, *Langmuir*, 2004, **20**, 10851–10857; (*b*) P. J. Kinlen, J. Liu, Y. Ding, C. R. Graham and E. E. Remsen, *Macromolecules*, 1998, **31**, 1735–1744; (*c*) K. Clays and A. Persoons, *Phys. Rev. Lett.*, 1991, **66**, 2980–2983.

9 Chloroform is known to form a hydrogen bond with an amine: (*a*) G. Pathak and S. Pradhan, *Proc. - Indian Acad. Sci., Chem. Sci.*, 1987, **99**, 413–417; (*b*) S. Ng, *J. Chem. Soc., Faraday Trans. 1*, 1976, **72**, 1101–1104; (*c*) H. Suhr, *J. Mol. Struct.*, 1968, **1**, 295–303.

10 When equimolar amount of acetone was added to a solution of the propylamine **2** in benzene-$d_6$, small signals were observed in the lower field, which were assigned to the propylammonium group derived from the addition of **2** to the carbonyl group (see ESI†). In acetone solution, larger amount of the adduct should be formed.
11 *The Third Series of Experimental Chemistry*, ed. T. Tachibana, Maruzen, Tokyo, 1975, vol. 14, pp. 2580–2587.