Rotaxane Synthesis

Rate Acceleration of the Reaction between Solid Reactants by Premixing in Solution: Application to the Efficient Synthesis of a [2]Rotaxane

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Solventless reactions are currently a subject of extensive interest in both inorganic and organic chemistry.[1] In particular, organic synthesis may benefit from avoiding the use of organic solvents, yet this is valid only if a whole process, including work-up operations, is free from organic solvents. The higher efficiencies and selectivities frequently encountered under solventless conditions are of prime significance in terms of organic synthesis and process chemistry. Many common organic reactions are accelerated under solventless conditions, and we also previously disclosed dramatic rate enhancement for supramolecular self-assembly.[2,3] Most reactions between solid reactants demand mechanical forces such as grinding in a mortar with a pestle or compounding in a ball mill.[4] The reaction generally proceeds through formation of a liquid or melt phase containing an intimate mixture

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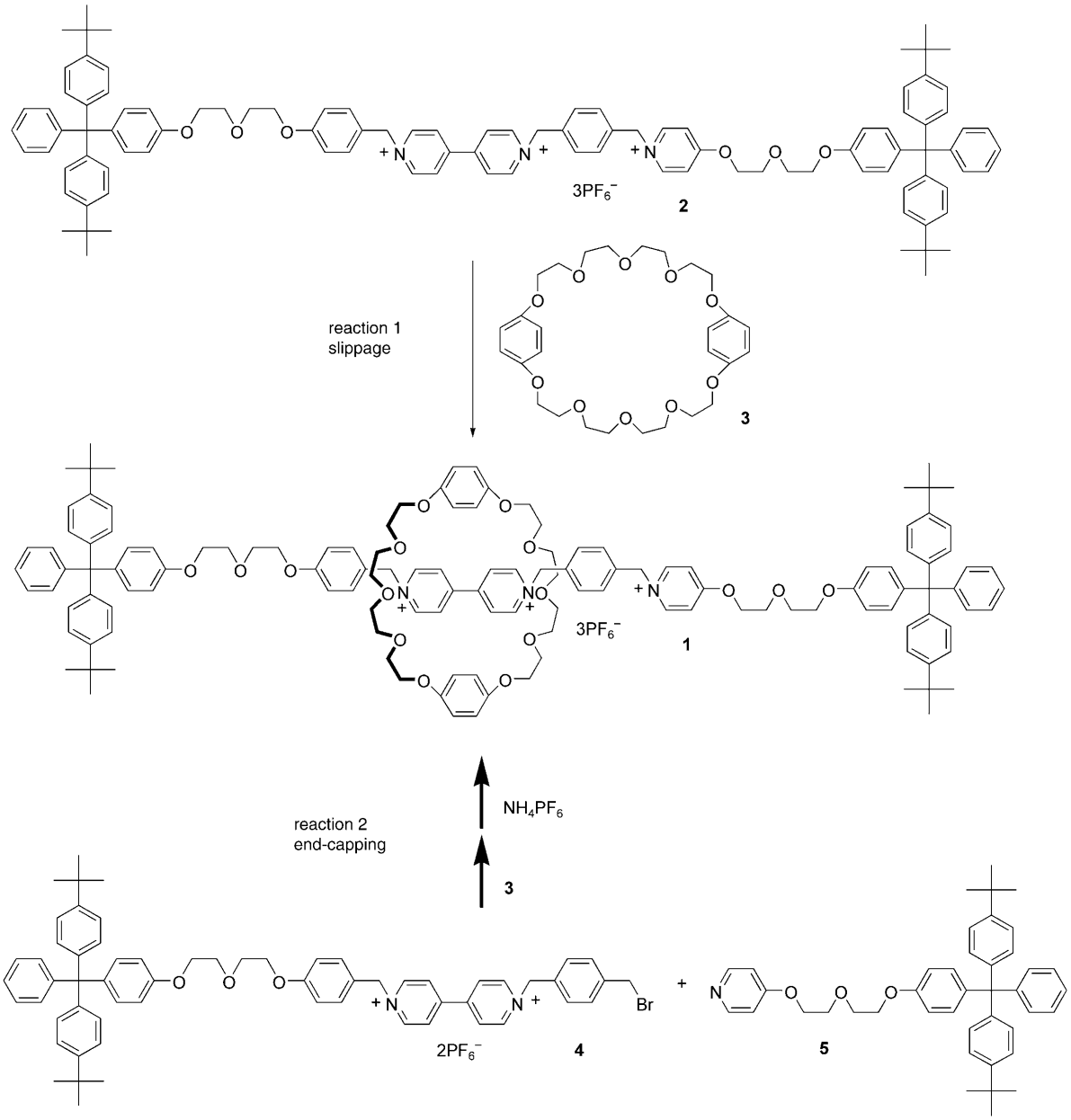
of macroscopic solid reactant particles, so that the molecules of the solid particles are sufficiently mobile for frequent molecular collisions to occur.[5] It was observed in a few cases that solid, powdered reactants liquefy simply on contact with each other. Once the melt has been formed, the reaction occurs very quickly. High mobility was also obtained in the formation of a co-crystal by adding a small amount of an appropriate solvent (2 drops (ca. 0.05 mL) of an organic solvent per ca. 200 mg of the solid mixture).[6]

Bearing in mind the importance of the mixing effect on the reaction between the solid reactants, we postulated that the mixing of reactants in solution followed by evaporation should give rise to a more favorable amalgam for a solventless reaction because the reactant molecules in the solid thus formed should be brought into contact. We demonstrate here that such a molecular-level mixing is, in fact, much more effective than the mixing of solid particles, as shown by the example of the efficient synthesis of [2]rotaxane **1**.

The present study stemmed from the synthesis of **1** (Scheme 1, reaction 1) by the incomplete slippage method.[7] A poor yield (38%) was obtained after heating the thread **2** with four equivalents of crown ether **3** in CH_3CN at 55°C for three days. Consequently, we utilized an end-capping method (reaction 2),[8] which involves reaction between *p*-substituted benzyl bromide **4** and *p*-substituted pyridine **5** as a key step to provide **2** [Eq. (1)]. The simple solventless protocol was not so effective: When solid **4** and **5** were ground at ambient temperature in a mortar with a pestle for 1.5 h **2** was produced in 60% yield and a substantial amount of the starting materials remained. The reactant mixture stayed powdery



Scheme 1. Synthesis of the [2]rotaxane **1**.

and no melt was formed on grinding. However, a remarkable improvement was made by using the premixing method. Both reactants were dissolved in acetone in a mortar, and then the solvent was evaporated in vacuo for 5 min. The film that had formed on the surface of the mortar was then ground. The starting materials disappeared within 50 min, as evident from thin-layer chromatography, and an 85% yield of **2**[9] was obtained even though no melt was formed during the manipulation. More interestingly, when the film was merely kept on the mortar or more conveniently on an inner surface of a flask without grinding, the reaction also proceeded to afford **2** in 80% yield after 2 h. No change was observed in the appearance of the film, except a slight deepening of the yellow color.

$$\mathbf{4} + \mathbf{5} \rightarrow \overset{NH_4PF_6}{\rightarrow} \mathbf{2} \qquad (1)$$

An NMR investigation was then carried out on the shorter thread **8** synthesized in an analogous manner to confirm that the reaction actually proceeded in the solid film without grinding (Table 1, entry 1). Grinding of the film composed of **6** and **7** for 30 minutes afforded **8** in 79% yield, while standing for 2 h afforded **8** in 85% yield. The reaction was monitored by ^{1}H NMR spectroscopy (Figure 1). The reaction proceeded to some extent in a fresh film which was obtained by mixing **6** and **7** in solution and subsequent evaporation (5 min after the start of mixing) as shown by the 75% recovery of **6** (Figure 1a).[10] The reaction then progressed to leave 2% of **6** after 2 h (Figure 1c). The reaction could apparently be driven without external mechanical forces, probably because of the effective contacts between the reactants molecules. For comparison, the same reaction was conducted in solution. The high concentration method was recently found to be useful for the end-capping synthesis of rotaxanes.[11] This protocol furnished **2** in 85% yield (by NMR) after standing a solution (0.2 mL) of **4** (0.03 mmol) and **5** (0.06 mmol)[12] in acetone at ambient temperature. Unfortunately, however, it took two days to reach the maximum yield. Similarly, **8** was obtained in 83% yield after two days.

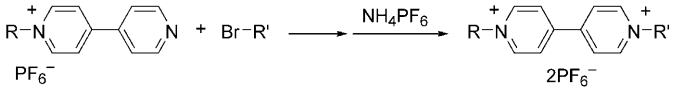
Similar but more enhanced reactivity was observed with a simpler case (Table 1, entry 2). Grinding a solid mixture of neat **9** and **10** for 1.5 h resulted in the *N*-alkylation product **11**[9] in 63% yield (by NMR). However, grinding a film produced from a solution of **9** and **10** in acetone afforded an 82% yield (by NMR) of **11** after 15 minutes, while an 80% yield (by NMR) was obtained after the film had stood for 40 minutes. The freshly prepared film was extracted with $CDCl_3$ and the ^{1}H NMR spectrum recorded to ascertain if the acetone solvent remained in the film. No signal attributable to the acetone was observed in this solution, which implied the acetone played no role in the interactions between the reactant molecules in the film. In contrast, two days were necessary for the high concentration solution method to provide an 86% yield (by NMR) of **11**.

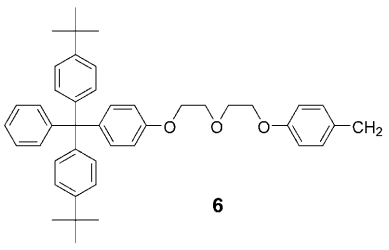
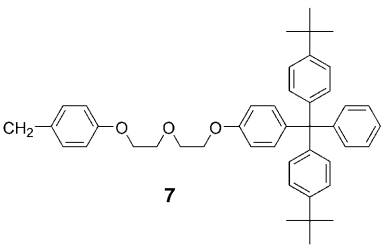
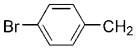
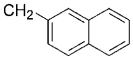
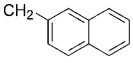
The use of *N*-methyl derivative **12** instead of **9** led to unsatisfactory results (Table 1, entry 3). Evaporation of a solution of **12** and **10** in acetone did not give a film, but instead gave a white solid. No reaction occurred upon grinding or on standing of this solid, while the reaction gave a quantitative yield of the *N*-alkylation product[9] in two days in acetone. This result implies that formation of the film is crucial for the smooth reaction in the solid state.

The importance of the molecular-level mixing was proved as follows. A well-shaken powdery mixture composed of **3**/**4**, **6**/**7**, or **9**/**10** was pressed (40 kg cm^{-2}) for 1 h. No reaction occurred in all cases, thus indicating that molecule-to-molecule contacts are crucial for the reaction to occur: mixing in solution is the best while mechanical forces are somewhat useful. The grinding helps to change relatively compatible solid reactants into a molten state. The formation of voids and cracks[13] may be facilitated by mechanical forces in the cases of the solid reactants where no molten mixtures are formed.

Finally, the premixing protocol also proved to be effective for the synthesis of [2]rotaxane **1**[9] (Scheme 1, reaction 2).

Table 1: Solventless N-alkylation by the premixing method.



Entry	R	R′	Product	Yield [%]/*t* [min] grinding	standing
1	 **6**	 **7**	**8**	79/30	85/120
2	 **9**	 **10**	**11**	82/15	80/40
3	**12**	 **10**		no reaction	

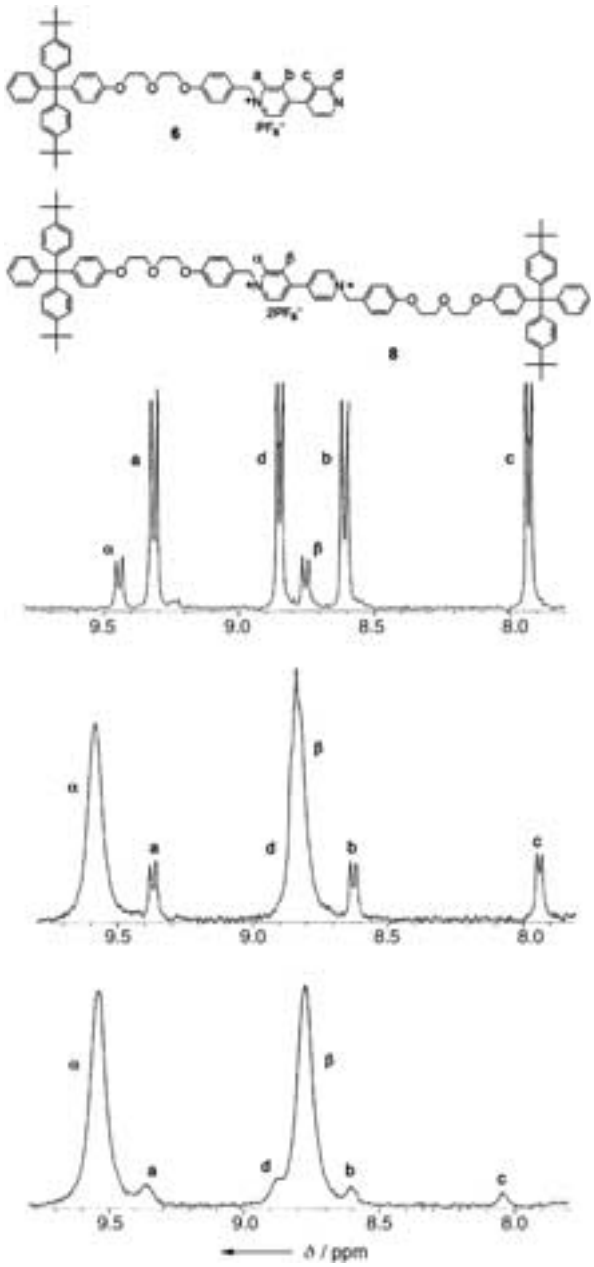


Figure 1. NMR spectra of a portion of the film consisting of **6** and **7** in $CDCl_3$: a) after 5 min (see text): 75% of **6** remaining; b) after 1 h: 43% of **6** remaining; c) after 2 h: 2% of **6** remaining.

The film was obtained by mixing **3** (0.06 mmol), **4** (0.03 mmol), and **5** (0.06 mmol) in a binary solvent of acetone (0.1 mL) and dichloromethane (0.1 mL) followed by evaporation. The mixed solvent was used because crown ether **3** is not soluble in acetone. Rotaxane **1** was formed in 85% yield along with 8% of **2** after the film had stood for four hours at ambient temperature. It should be noted that the yield of **1** was only 11%, with 12% of **2** and 57% of **4**, when a powdery mixture of **3**, **4**, and **5** was ground directly. The high concentration solution method required three days in anisole at 25°C to afford **1** and **2** in yields of 78% and 11%, respectively.

In conclusion, the reaction between solid reactants is accelerated by premixing the reactants in solution. The acceleration is accessible only when a film is formed after evaporation. It seems that the reactants must be compatibile for the formation of the film, which results in molecular-level amalgamation. The longer reaction time in solution offsets the essential features of the solventless reaction, in particular, of the molecule-to-molecule contacts. The reaction is accelerated by the high concentration effect under solventless conditions and, more importantly, the de-solvation energy, which is inevitable in a solution reaction, is saved.

This protocol might not be categorized as a solventless reaction in a strict sense if the premixing step is counted, yet the reaction itself proceeds under solventless conditions. In a practical sense, however, reactants can be charged into a reactor much more conveniently in solution than can solid reactants. We have so far demonstrated the validity of the new protocol with simple N-alkylation. Further applications to other reactions are now in progress.

Experimental Section

2: Compounds **4** (37 mg, 0.03 mmol) and **5** (36 mg, 0.06 mmol) were dissolved in acetone (0.2 mL) in a mortar. The acetone solution turned into a yellow film after 5 min on standing in open air followed by evaporation in vacuo. The film was ground with a pestle for 50 min. The mixture was dissolved in a mixture of acetone (5 mL), $CHCl_3$ (2 mL), and H_2O (1 mL). NH_4PF_6 (146 mg, 0.9 mmol) was then added to the resulting solution. The acetone was evaporated from this solution, and the resulting H_2O suspension was filtered. The solid product thus obtained was dried in vacuo. The ^{1}H NMR spectrum of this crude mixture indicated formation of **2** in 85% yield. Column chromatography of this mixture on silica gel (70:16:11:3 CH_3OH/CH_2Cl_2/CH_3NO_2/NH_4Cl(2N)) furnished **2** (42 mg, 76%): ^{1}H NMR (300 MHz, CD_3COCD_3): $\delta = 9.46$ (d, $J = 5.1$ Hz, 4H), 8.93 (d, $J = 7.2$ Hz, 2H), 8.80–8.75 (m, 4H), 7.79–7.61 (m, 8H), 7.34–7.05, (m, 34H), 6.87–6.80 (m, 4H), 6.20 (s, 2H), 6.10 (s, 2H), 5.88 (s, 2H), 4.64–4.62 (m, 2H), 4.20–4.12 (m, 6H), 4.01–3.99 (m, 2H), 3.90–3.88 (m, 6H) 1.30 ppm (s, 36H); ^{13}C NMR (75.5 MHz, CD_3COCD_3) $\delta = 172.0$, 161.1, 157.8, 157.7, 151.4, 151.1, 149.2, 149.1, 148.2, 146.8, 146.7, 146.4, 145.0, 140.1, 140.0, 136.6, 135.3, 132.8, 132.7, 132.1, 131.6, 131.3, 131.1, 130.7, 128.5, 128.3, 128.2, 128.1, 126.6, 126.5, 125.8, 125.1, 125.0, 116.2, 115.2, 114.1, 114.0, 71.5, 70.4, 70.2, 69.4, 68.5, 68.1, 68.0, 65.3, 65.0, 64.2, 62.7, 34.8, 31.6 ppm; MS (MALDI-TOF) found: *m/z* 1643.76 $[M-2PF_6]^+$, calcd for $C_{104}H_{112}F_6N_3O_6P$: *m/z* 1643.82.

The film prepared as above in a mortar or in a flask was kept standing in open air at ambient temperature for 2 h to provide **2** in 80% yield based on ^{1}H NMR spectroscopy and isolated in 72% yield.

1: A mixture of **3** (32 mg, 0.06 mmol), **4** (37 mg, 0.03 mmol), and **5** (36 mg, 0.06 mmol) were dissolved in acetone (0.1 mL) and dichloromethane (0.1 mL) in a 50-mL flask. The resulting red solution was evaporated in vacuo, whereupon a film developed on the surface of the flask. After 5 min, the evaporation was stopped and the film was left standing in the open air at ambient temperature for 4 h. The mixture was dissolved in acetone (10 mL) and H_2O (2 mL). NH_4PF_6 (98 mg, 0.6 mmol) was added to the resulting solution. The acetone was evaporated from this solution, and the resulting H_2O suspension was filtered. The solid product thus obtained was dried in vacuo. The ^{1}H NMR spectrum of this crude product indicated formation of **1** in 85% yield together with **2** in 8% yield. Column chromatography of this mixture on silica gel (70:16:11:3 CH_3OH/CH_2Cl_2/CH_3NO_2/NH_4Cl(2N)) furnished **1** (56 mg, 79%): ^{1}H NMR (300 MHz, CD_3COCD_3): $\delta = 9.23$ (d, $J = 6.6$ Hz, 2H), 9.18 (d, $J = 6.6$ Hz, 2H), 8.93 (d, $J = 7.3$ Hz, 2H), 8.30–8.25 (m, 4H), 7.89 (d, $J = 8.4$ Hz, 2H),

7.79–7.72 (m, 4H), 7.61 (d, $J = 7.5$ Hz, 2H), 7.33–7.06 (m, 34H), 6.85–6.80 (m, 4H), 6.17 (s, 2H), 6.05 (s, 8H), 5.90 (s, 2H), 4.54–4.52 (m, 2H), 4.22–4.20 (m, 2H), 4.14–4.08 (m, 4H), 3.96–3.65 (m, 40H), 1.29 ppm (s, 36H); ^{13}C NMR (75.5 MHz, CD_3COCD_3): $\delta = 171.9$, 161.1, 157.8, 157.7, 152.9, 149.2, 149.1, 148.2, 146.8, 146.7, 146.4, 145.0, 140.2, 140.1, 136.6, 135.3, 132.9, 132.8, 132.3, 131.6, 131.5, 131.4, 130.7, 128.2, 128.1, 126.6, 126.5, 126.3, 126.1, 125.1, 125.0, 116.1, 115.5, 115.1, 114.1, 114.0, 71.5, 71.3, 71.0, 70.7, 70.5, 70.4, 70.3, 69.4, 68.6, 68.3, 68.1, 68.0, 65.3, 65.0, 64.2, 62.7, 34.8, 31.6 ppm; MS (MALDI-TOF) found: m/z 2180.78 $[M-2PF_6]^+$, calcd for $C_{132}H_{152}F_6N_3O_{16}P$: m/z 2180.08.

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