Multicomponent Reactions

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Finding Reaction Pathways for Multicomponent Reactions: The Passerini Reaction is a Four-Component Reaction**

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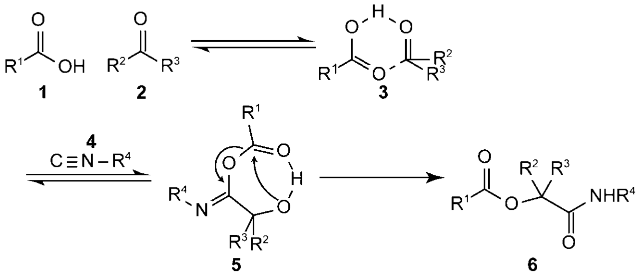
Multicomponent reactions (MCRs), in which three or more molecules react in one pot and generate products containing almost all atoms of the reactant molecules, have been developed extensively as tools to achieve highly atom-, step-, and energy-economic organic syntheses.[1] The Passerini reaction, which is formally a three-component reaction involving a carboxylic acid, an aldehyde (or ketone), and an isocyanide to generate an α-acyloxycarboxamide, is the most fundamental MCR involving isocyanides.[1a,c,2] A conventional mechanism of this reaction is shown in Scheme 1,[1a,2i] where the reaction takes place efficiently at or below room temperature, in apolar solvent, and with high concentration of reactants. Here we present a quantum chemical study of all possible pathways among three reactant molecules of the Passerini reaction using a new theoretical approach for finding transition states (TSs) and propose the most probable pathway without prejudice for presumed pathways or mechanisms.



Scheme 1. A conventional mechanism of the Passerini reaction.[1a,2i]

Advances in quantum chemical calculation methods have enabled accurate and efficient theoretical elucidations of mechanisms, kinetics, and dynamics of many chemical reactions.[3] The intrinsic reaction coordinate (IRC)[4] is an idealized reaction path on quantum chemical potential-energy surfaces (PESs) and has been calculated to elucidate detailed pathways and mechanisms of various chemical reactions. Despite the growing interest in MCRs and the advances in theoretical methods, detailed theoretical studies of full mechanisms of MCRs have been rather scarce. This is in part because of difficulties in guessing structures of TSs that involve extensive bond rearrangements and partly because of the existence of many possible association pathways. Most of previous theoretical studies for MCRs (and also for other complex reactions) have examined only a few of pathways, which are assumed rather arbitrarily on the basis of intuition and experience. Although there have been considerable efforts to develop methods to locate many TSs automatically and systematically,[5] their applications to associative reactions of type $A+B \rightarrow X$ have not been very successful. Lack of systematic methods for reactions of type $A+B \rightarrow X$ has been serious, not only in analysis and prediction of MCRs, but also for many other organic reactions in which often two or more reagents including reactant(s) and catalyst(s) are mixed together and many complex reactions may be taking place simultaneously.

Recently, we proposed a new approach for finding all reaction pathways (with or without TSs) for reactions of type $A+B \rightarrow X$ in an efficient and systematic way,[6] which we call the artificial force induced reaction (AFIR) method. To illustrate this method, let us consider an association reaction between two atoms A and B for which the PES $E(r_{AB})$ as a function of A–B distance r_{AB} looks like Figure 1a and the product structure X is not known. From the reactants, it is usually difficult to guess reasonable structures of TS or X. Now consider a potential curve $F(r_{AB})$ for an AFIR [Eq. (1)]

$$F(r_{AB}) = E(r_{AB}) + \alpha r_{AB} \tag{1}$$

where the last term imposes a artificial constant attractive force ($\alpha \geq 0$) between the two atoms. When α is small, the AFIR potential looks like Figure 1b and gives a tightly interacting AB complex. When α is large, the AFIR potential looks like Figure 1c, downhill from the reactants $A+B$

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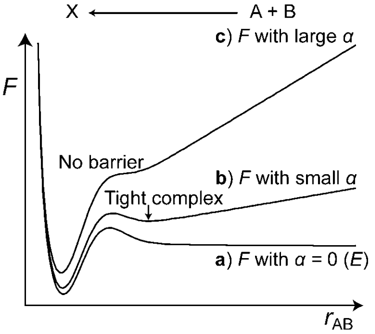


Figure 1. a) $E(r_{AB})$, b) $F(r_{AB})$ with small α, and c) $F(r_{AB})$ with large α.

without a barrier to product X. The structure of this product on $F(r_{AB})$ optimized from the reactants is an excellent starting point for optimization of the true product on $E(r_{AB})$. Moreover, the structure of the highest point of $E(r_{AB})$ along the AFIR path turned out to be a reasonable starting guess for optimization of the true TS on $E(r_{AB})$.[6] When A and B consist of many atoms, one can adopt some reasonable AFIR potential. In the present application, we adopted $F(\mathbf{Q})$ in the form of Equation (2)

$$F(\mathbf{Q}) = E(\mathbf{Q}) + \alpha \frac{\sum_{i\in A}\sum_{j\in B}\left[(R_i+R_j)/r_{ij}\right]^p r_{ij}}{\sum_{i\in A}\sum_{j\in B}\left[(R_i+R_j)/r_{ij}\right]^p} \quad (2),$$

where $\mathbf{Q}$ are the atomic coordinates $\{Q_i\}$, $E(\mathbf{Q})$ is the PES, R_i and R_j are covalent radii of the ith and jth atoms, respectively, r_{ij} is a distance between the ith and jth atoms, p is an arbitrary integer (set to 6) of a weight function, and summations are taken over all pairs of atoms in the reactants A and B. In this function, the r_{ij} term imposes an artificial force between the ith and jth atoms. The r_{ij} terms are multiplied by the weight function of the modified Shepard interpolation[7] so that the force is large only between atoms at close distance. If at the beginning the reacting multiple components are placed in a particular relative orientation, the attractive forces acting preferentially between closer atoms mostly retain this orientation and force the optimization to converge to a local minimum with a similar orientation. In practice, as one increases the value of α, at first a tight reactant complex is found (Figure 1b) and then, above a threshold α, the TS on the AFIR PES disappears and "the reaction" reaches the product without TS (Figure 1c). Of course one has to take into account that the reactants can come together in all different relative orientations. In triatomic reactions A + B + C, Equation (1) is rewritten as Equation (3).

$$F(r_{AB},r_{AC},r_{BC}) = E(r_{AB},r_{AC},r_{BC}) + \alpha_1 r_{AB} + \alpha_2 r_{AC} + \alpha_3 r_{BC} \quad (3)$$

In general trimolecular reactions, two extra terms for attractions between A and C and between B and C are added to Equation (2). Extensions to reactions involving four or more components can be done likewise. The method to compute the artificial forces from Equation (2) and the present treatment of the parameter α are described in detail in the Supporting Information.

Therefore, the overall proposed procedure is as follows. 1) Start from all possible orientations of the reactants (using some grid or random sampling). 2) For each orientation optimize the AFIR structure for a few values of α. 3) For the AFIR path without barrier, find the meta-IRC[8] (mass-weighted steepest descent path) starting from the AFIR tight pre-reaction complex structure. 4) Start with the highest point of $E(\mathbf{Q})$ along the AFIR path, and perform a standard TS optimization without artificial force to obtain the true TS structure. 5) Use the AFIR structure of the product and perform a standard optimization without artificial force to obtain the true product structure. We may add that paths of AFIR can also be calculated for intramolecular reactions of type A→X by imposing the forces between pairs of atoms related to bond formations. In this study, some such reaction steps leading to the product and byproducts were calculated by this usage of the AFIR method.

We adopted HCOOH, HCHO, and CH_3NC as the simplest set of reactants of the Passerini reaction. First, the AFIR method was applied to the trimolecular system and the three bi-molecular systems (i.e., HCOOH + HCHO, HCOOH + CH_3NC, and HCHO + CH_3NC. Figure 2 shows all obtained association pathways with TSs lower than 150 kJ mol^{-1} at the M06[9]/6-31 + G** level including corrections for zero-point energy (ZPE). Although the reaction **28**→**30** (and some other reactions shown below) has a metastable intermediate, it is omitted for clarity and is shown in the Supporting Information. Among all bi- and trimolecular association pathways, reaction **19**→**21** is the most favorable in terms of the energy of the transition state. The structure of **21** is very similar to that of the proposed intermediate **5** (see Scheme 1).[1a,2i] Further support for this pathway and later reaction steps is described below. We emphasize that no arbitrary assumption or a priori input (except for the set of reactant molecules) was needed to obtain the present results. Moreover, the method gave not only the lowest pathway but also many higher ones; determination of such pathways strengthens the reliability of a proposed mechanism.

Figure 3 shows reaction profiles leading to product **6** from the reactants via **21**. In Scheme 1 a complex **3** is assumed, and **3** should correspond to H-bonded complex **7** in the present results, whereby the kinetic stability of **7** (standard-state free energy of activation $\Delta G^{\neq,0}$ at 0 °C) is discussed in the Supporting Information not only for formaldehyde but also for acetone and acetaldehyde. Reaction of **7** with CH_3NC generates **21** via TS **20**. Compound **21** can rearrange into **6** in three steps via **27** and **30** with high barriers at TSs **43**, **44**, and **45**. (Although direct, more concerted pathways exist (**21**→**6**, **21**→**30**, and **27**→**6**), they all have even higher barriers.) Compound **21** has never been observed in the Passerini reaction, and is considered to be a short-lived species which rearranges to **6** immediately.[2i] Calculated barriers for these pathways are too high to explain the rate of the Passerini reaction and the lack of observation of **21**. In Figure 4 another route to **6** via **18** is shown. Application of the present method to **18** + HCOOH gave **57** as the lowest TS, which directly produces **6**. This pathway is more feasible than the route via **21**. However, its barrier is still too high to explain the efficient

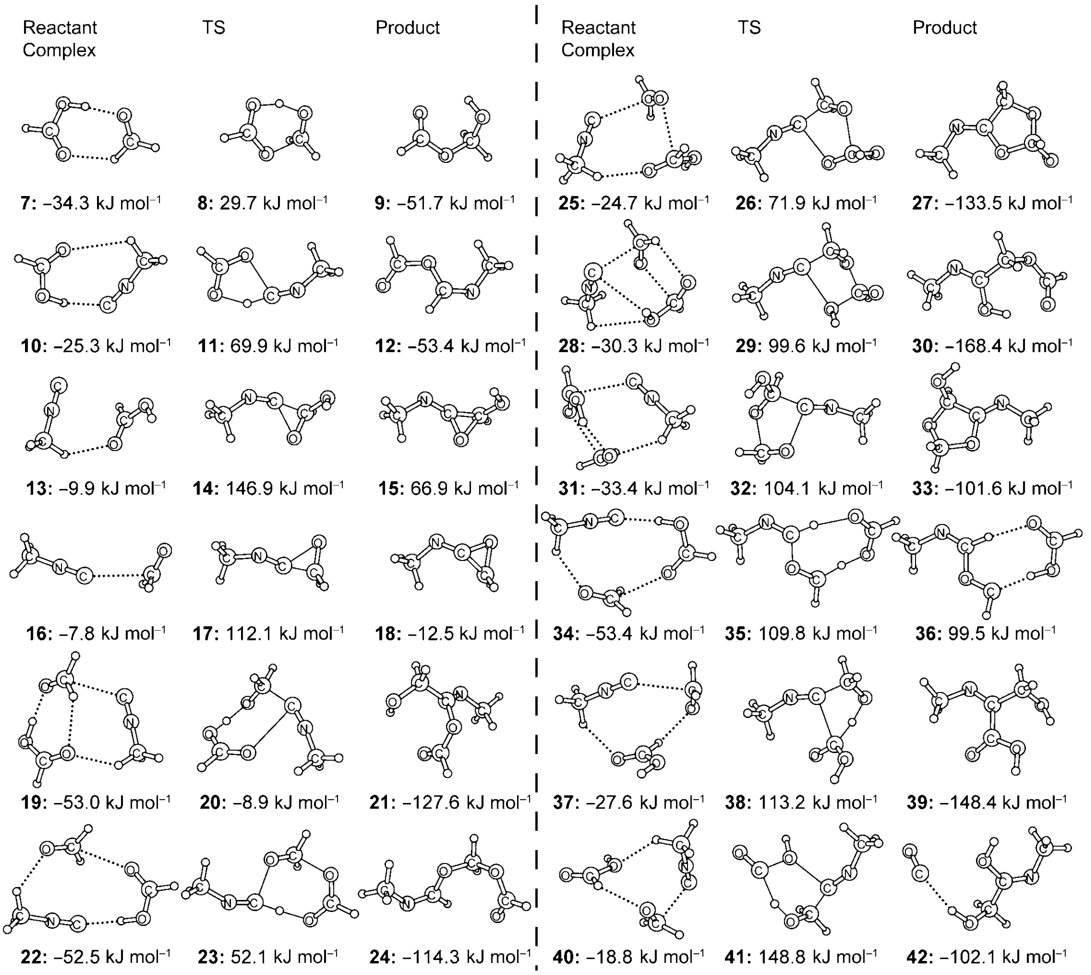


Figure 2. All obtained initial association pathways at the M06/6-31+G** level. Energies (including ZPE corrections) are relative to the separated three reactant molecules.

production of **6** because generation of a byproduct is preferable, as shown below. No pathway with three-component reaction was satisfactory.

We further applied the present method to key four-component pathways: **19**+HCOOH, **21**+HCOOH, **27**+HCOOH, and **30**+HCOOH (Figure 3). Among these, the second and third calculations gave HCOOH-involving reaction pathways that lowered barriers dramatically.

In the initial associative step from **19** to **21**, the extra HCOOH is not very important as it has only a role like a solvent. Its coordination lowers the barrier by 30.2 kJ mol^{-1}, because the binding energy of the extra HCOOH is larger at **20** than at **19**. However, coordination is not preferred under certain conditions because of entropy effects. Calculations of $\Delta G^{\neq,0}$ (at 0 °C) suggested that both pathways with and without extra HCOOH may be important depending on the concentrations of the reactants and temperature (see Supporting Information). Furthermore, in both pathways, the mechanism of bond rearrangement is identical. We note that this small acceleration effect may enhance enantioselectivity under certain conditions when a chiral Brønsted acid is used as catalyst instead of HCOOH.[2h]

The fourth component, an extra HCOOH molecule, plays a critical role in the later bond rearrangement steps; it is directly involved in the reactions as a proton donor and proton acceptor. As clearly seen in Figure 3, its participation lowers the barrier by as much as 108.3 kJ mol^{-1} in the first bond rearrangement step **49**→**51**, in comparison with **21**→**27**. Moreover, in the second bond rearrangement step the four-component intermediate **52** directly generates the product **6** in one step, in which the extra HCOOH also participates in the reaction to replace the two original very high barriers (147.4 and 124.2 kJ mol^{-1}) by a single small one (33.2 kJ mol^{-1}). During these two bond rearrangement steps, proton exchange involving the extra HCOOH molecule occurs twice.

Without these HCOOH-involving pathways, direct association channels **25**→**27** and **28**→**30** (see Figure 2) and the channel via **18** in Figure 4, as well as production of a byproduct (shown in Figure 5), are more favorable than the route via **21**. As seen in Figure 3, the extra HCOOH changes the sawtoothlike bond rearrangement profile into a staircase-like one along which the system can reach **6** easily. This is in good agreement with the experimental fact that no inter-

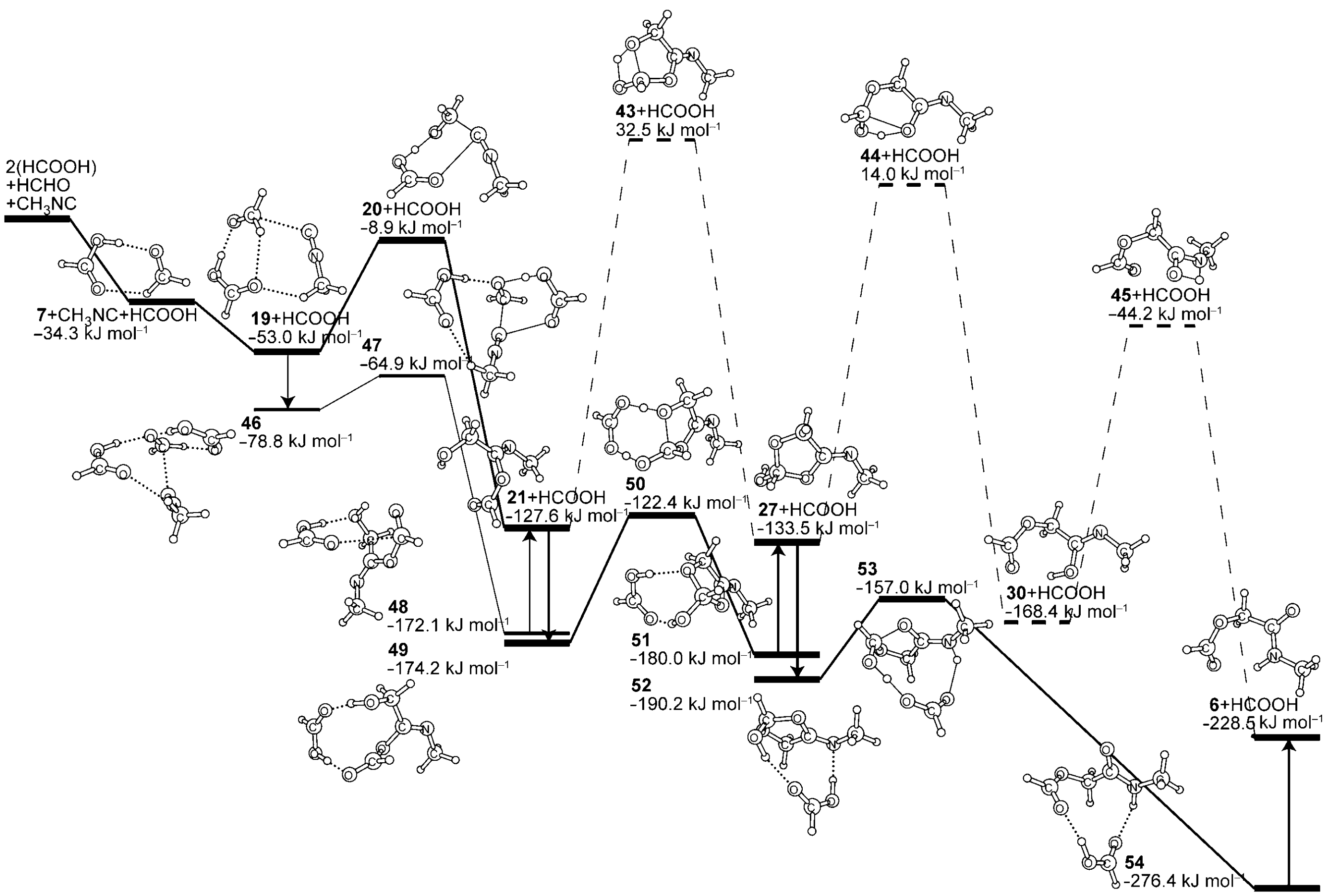


Figure 3. Potential profile of the most preferable pathway (solid line) leading to product **6** at the M06/6-31 + G** level. This pathway involves four components. A minor three-component pathway is also shown (dashed line) for comparison. Energies (including ZPE corrections) are relative to the separated four reactant molecules. The most favorable route is emphasized with thick lines.

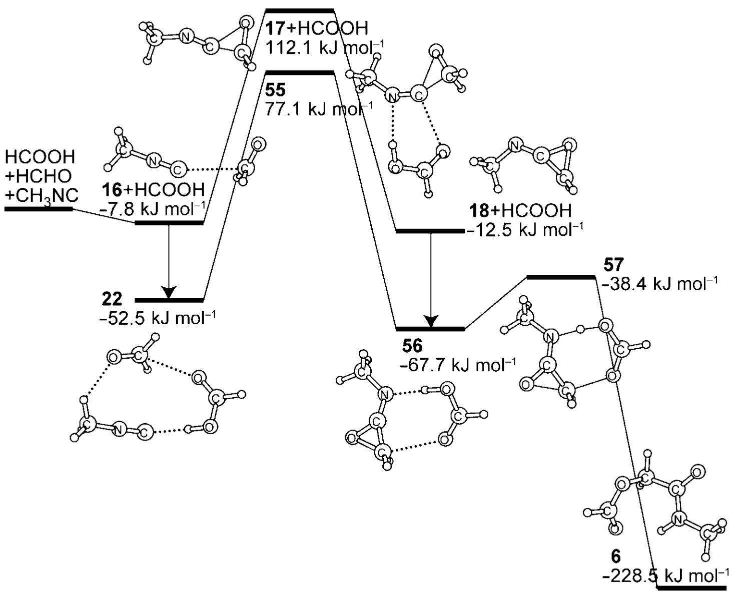


Figure 4. A minor route to produce **6** at the M06/6-31 + G** level. Energies (including ZPE corrections) are relative to the separated three reactant molecules.

mediate has been observed in this reaction. Thus, we conclude that participation of an extra HCOOH molecule is essential in the mechanism of the Passerini reaction.

Production of byproduct **12**[2e] is also discussed in Figure 5 on the basis of some channels in Figure 2. It can be produced directly by the reaction **10**→**12**. The lowest TS for the reaction **12** + HCHO is **59**. This reaction requires high E_a, and consequently **12** remains as a byproduct. Although the lowest TS for the reaction **9** + CH_3NC is also **59**, it is much higher than **8**. Note that there is no direct pathway from **9** + CH_3NC to **21**. The second lowest TS for the reaction **12** + HCHO is **61**, which generates the product of the reaction **22**→**24**. Although **24** is kinetically stable, its generation is highly unlikely because of high barriers.

The mechanism of the Passerini reaction we propose on the basis of the present calculations is summarized in Scheme 2. The E_a values for the present set of reactants in the gas phase at the M06/6-31 + G** level and in dichloromethane solvent (shown in parentheses) at the PCM[10]-M06/6-31 + G** level are shown as references. The overall reaction profile of the PCM calculations is presented

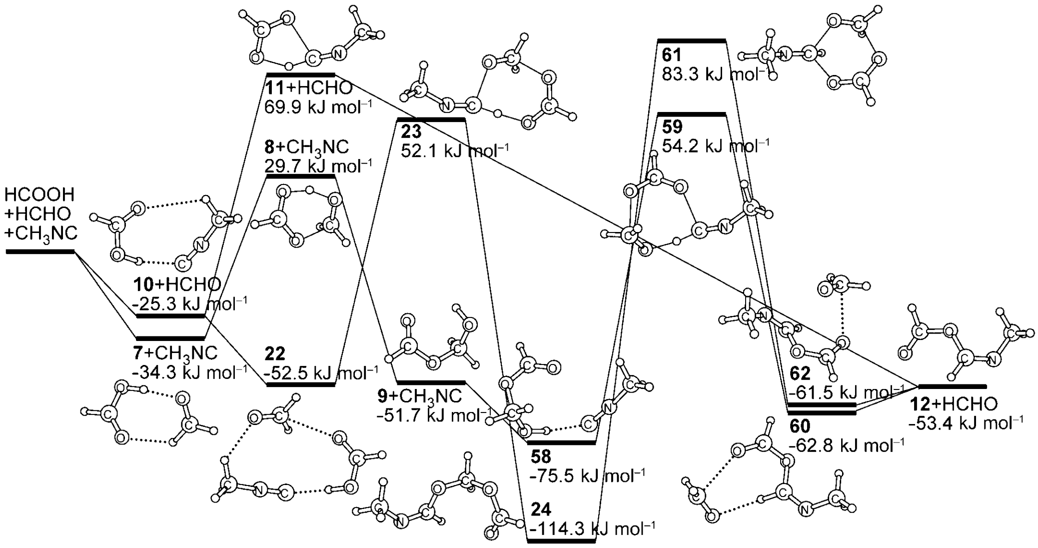
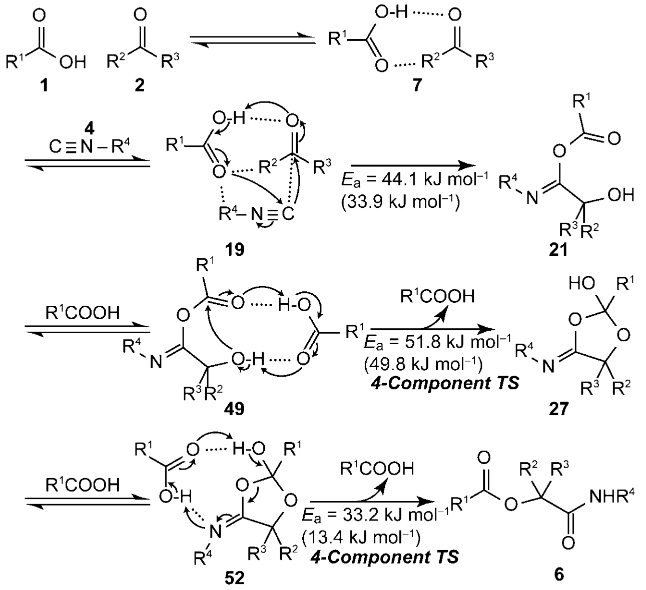


Figure 5. Potential profiles leading to a byproduct **12** at the M06/6-31+G** level. Energies (including ZPE corrections) are relative to the separated three reactant molecules.



Scheme 2. Detailed mechanism of the Passerini reaction proposed in this study. E_a for the present set of reactants in gas-phase at the M06/6-31+G** level and in dichloromethane solvent (shown in parentheses) at the PCM-M06/6-31+G** level are shown. An extra carboxylic acid molecule participates in the reaction as the fourth component.

in the Supporting Information. Since the effect of solvent is not dramatic, we believe that this mechanism can be applied to real reactions, at least in apolar solvents, which are preferred in conventional Passerini reactions.[2i] The first step of the Passerini reaction is generation of an H-bonded cluster (**7** in Figure 3). Reaction between isocyanide and the H-bond cluster produces an intermediate (**21** in Figure 3) with small E_a. Although, in this step, an extra HCOOH molecule may coordinate to TS **20** as well as **19** to lower the barrier slightly (see Figure 3), an illustration without the extra HCOOH is shown for clarity, as the coordination is not critically important. On the other hand, intermediate **21** itself cannot be transformed into **6** because all three bond rearrangement steps have very high barriers. An extra carboxylic acid is necessary as the fourth component. The initial barrier of 160.1 kJ mol^{-1} (TS **43**) is lowered by 108.3 kJ mol^{-1} by the participation of HCOOH in four-component TS **50**. The second and third rearrangement steps are replaced by a single step via further four-component TS **53**, which also change the barrier heights dramatically, from 147.4 and 124.2 kJ mol^{-1}, respectively, to only 33.2 kJ mol^{-1}. Thus, the Passerini reaction, formally a three-component reaction, is actually a four-component reaction via four-component TSs in the final bond rearrangement steps. This mechanism does not change if $\Delta G^{\neq,0}$ (at 0 °C) values or potential-energies obtained with the B3LYP functional or G3 scheme are considered, as shown in the Supporting Information.

In conclusion, we have demonstrated for the Passerini reaction as an illustrative example that the present AFIR method has the ability to predict possible associative channels among given components systematically without any arbitrariness. Thus, we believe that the AFIR method will provide a new paradigm for finding TSs for MCRs. Although our original motivation for development of the AFIR was to systematically explore detailed mechanisms of MCRs, in principle it can be applied to any type of reaction. The broader applicability should be examined in the future, including complex organometallic catalysts, as well as reactions in the presence of other promoters.

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