

Toward Predicting Full Catalytic Cycle Using Automatic Reaction Path Search Method: A Case Study on $\text{HCo}(\text{CO})_3$ -Catalyzed Hydroformylation

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 Supporting Information

ABSTRACT: Toward systematic prediction of reaction pathways in complex chemical reaction systems by quantum chemical calculations, a new automatic reaction path search approach has been proposed on the basis of the artificial force induced reaction (AFIR) method [*J. Chem. Theory Comput.* **2011**, *7*, 2335–2345.]. We demonstrate in this Letter that this approach enabled semiautomatic determination of the full catalytic cycle of the $\text{HCo}(\text{CO})_3$ -catalyzed hydroformylation. The search was fully systematic; no initial guess was required concerning the entire reaction mechanism as well as each transition-state structure. This approach opens the door to nonempirical prediction of complex reaction mechanisms involving multiple steps in multiple pathways, such as full cycles of catalytic reactions.

Since the first success in obtaining all transition state (TS) and intermediate geometries in the full catalytic cycle of the organometallic catalysis,^{1,2} mechanisms of a variety of catalytic cycles have been elucidated by theoretical calculations.^{3–12} In general, two or more mechanisms may be suggested, and the true mechanism of the reaction is identified by comparing corresponding theoretical activation energies. Theoretically unveiled TS structures have provided very useful information, such as frontier orbitals driving the reaction, steric repulsions hindering the reaction, hydrogen-bonding interactions accelerating or decelerating the reaction, and so forth, which are all useful for deep understanding of the reaction as well as for designing novel catalysts. Such mechanistic insights have also been very valuable in explaining or estimating regioselectivity and enantioselectivity.

Various tools for exploring potential energy surfaces (PESs) have been available.^{13–16} Most of these theoretical methods require some estimate of a reaction pathway (such as collective reaction variable) or product or TS structures to initiate the structure optimization. Such estimates are usually obtained based on experimental or theoretical data, for instance, those of known similar reactions or even chemical intuitions. In using such tools, exhaustive trial-and-error and guess-and-check processes are required for finding all (hopefully) important reaction pathways. It should be noted that in such an approach, some pathways totally unknown/unexpected or far from estimates may possibly be missed. It is also hard to judge whether anything is missed or not. Thus, fully systematic search is highly desired especially for complex chemical reactions that may involve multiple reactants in multiple pathways and multiple steps in each pathway. Applications of some fully automated methods have been limited to unimolecular reactions in small systems.^{17–21}

Very recently, we proposed a method which permits automatic exploration of ($\text{A} + \text{B} \rightarrow \text{X}$ type) associative reaction pathways.^{22–24} The initial idea was pretty simple; just press reactants to each other by artificial force.²² Hence, the method is called artificial force induced reaction (AFIR) method.²³ Starting from this idea, we discovered a function called AFIR function, and all reactive sites among multiple reactants can be identified as local minima on an AFIR function.²⁴ The most important chemical interaction driving majority of chemical reactions is the (frontier) orbital interaction as had been demonstrated in early theoretical studies.^{25,26} The artificial force turns sites where the attractive orbital interaction become maximal into local minima on the AFIR function. Once a reactive site is located, an additional force causes geometrical changes that are similar to those in a reaction pathway and provides *approximate* TS and *approximate* product structures. These *approximate* structures are then immediately reoptimized easily to converge to the *true* TS and product structures, which of course will be used to construct potential energy profiles. The discovery of the AFIR function reduced the problem of “finding all associative reaction channels” to a much simpler one of “locating all local minima on the AFIR function”. In other words, minimization of the AFIR function starting from all possible mutual orientations and approach directions finds all associative pathways. Details of the AFIR method are described in a previous paper.²⁴

In this Letter, we report that semiautomatic determination of a full catalytic cycle of a homogeneous catalysis without using any initial guess was achieved for the first time by AFIR. This has

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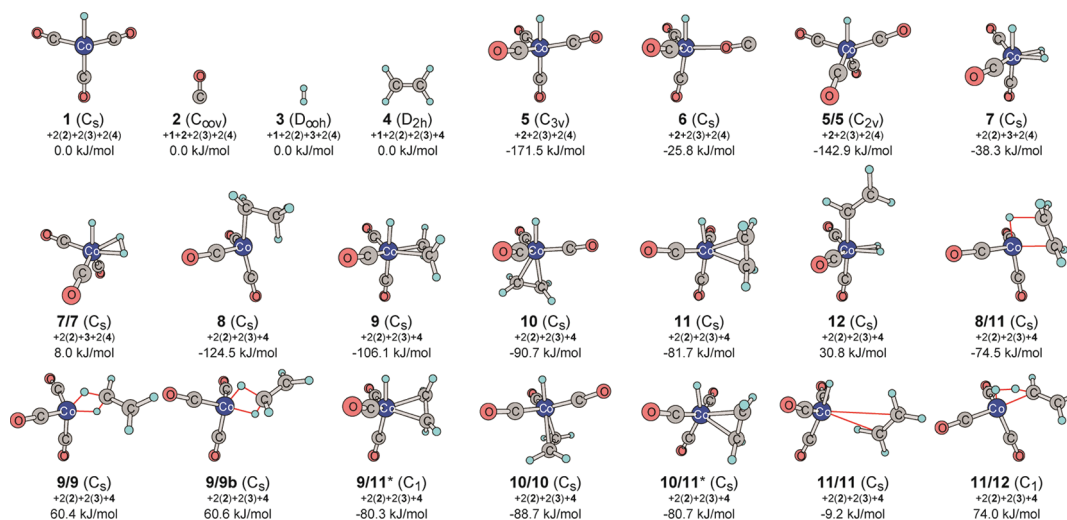


Figure 1. All critical points for the first step of the HCo(CO)_3 -catalyzed reaction with each of CO , H_2 , and C_2H_4 , obtained by the AFIR search at the B3LYP/6-31G level. Energies (in kJ/mol) are relative to the total energy of the catalyst and two sets of the reactants ($1 + 2(2) + 2(3) + 2(4)$). TS structures connecting intermediates n and m are labeled as n/m . TS structures connecting an intermediate n with a dissociation channel (DC) are labeled as n/DC , and corresponding fragments are indicated in the square brackets. The bonds being formed or broken at each TS are shown by thin red lines. TSs with * marks in their labels were obtained by applying the d-GRRM method between a pair of (connected) intermediates found in the AFIR search. See also Supporting Information.

been accomplished in two stages. First, as has been done in previous applications,²⁴ minimization of the AFIR function is made starting from many random relative orientations and approach directions between a reactant molecule and the catalyst to find all associative pathways. A majority of AFIR minimization paths reached coordination complexes where the reactant molecule coordinated on the metal center in the catalyst. Some pathways for direct reactions between the reactant and one of the ligands, without involving the metal center, were also found. Second, the coordinated reactant molecule is reacted with one of ligands by minimization of the AFIR function between the reactant and the ligand. This second stage is applied to all possible reactant–ligand pairs in all coordination complexes obtained in the first stage. As shown below, many intermediate species have been obtained by these calculations. Among all intermediates that have been found in the search, the most populated ones are estimated on the basis of the activation energy to form them and their thermodynamic stability. At each step of catalytic cycle, this two-stage AFIR procedure was applied to the most populated intermediate and was repeated with next most populated intermediate until a reaction pathway was found.

COMPUTATION

In this study, we considered HCo(CO)_3 (**1**) as a catalyst and CO (**2**), H_2 (**3**), and C_2H_4 (**4**) as a set of reactants. The catalysis involving this catalyst and these reactants is known as hydroformylation,^{27,28} and the mechanism of the full catalytic cycle has been proposed by Heck and Breslow²⁹ and confirmed by theoretical calculations.^{5,30–33} The primal focus in this study is whether the AFIR semiautomatic search can find the Heck–Breslow hydroformylation mechanism to be the most favorable pathway for the reaction. The only parameter γ_{MAX} needed to be given in AFIR calculations was set to 100 kJ/mol. γ_{MAX} is called maximum model collision energy parameter, and an AFIR search finds TSs with barriers below about γ_{MAX} .²⁴ A search with the larger γ_{MAX} will find more pathways but will consume more

computer time. Although it should be set to a sufficiently large value, 100 kJ/mol was enough in the present case. The AFIR search was performed with a relatively cheap B3LYP/6-31G method to save the computation time. The AFIR method is implemented in a local development version of the GRRM11 program,³⁴ where energy, gradient, and Hessian were computed by the Gaussian 09 program.³⁵ All structures shown below are fully optimized local minima or first-order saddles (without the artificial force).

FIRST STEP OF THE CATALYTIC CYCLE

At first, each of the reactants **2–4** was reacted with the active catalyst, HCo(CO)_3 , **1**. Figure 1 lists all intermediates (**5–12**) and related TSs obtained in the search. As noted above, an efficient optimization from the AFIR minimum and from the highest energy point along each AFIR minimization path converged respectively to the *true* minimum structure and TS structure. In a few cases, however, TS optimization starting from the highest point using the TS optimizer in the GRRM11 program did not converge. However, even when this happens, one already has a pair of a reactant and a product for the reaction along the AFIR minimization path, and the TS connecting them can be readily obtained by one of double-ended methods^{13–16} without using any guess. In this study, such TSs were obtained by the double-ended GRRM (d-GRRM) method in the GRRM11 program³⁶ and are marked by * in their structure labels.

SECOND STEP

Among **5–12**, **5** and **8** are expected to have large population because of their thermodynamic stability as well as (no or very low) barriers for their formation. Since **5**, an HCo(CO)_4 species, is expected to be more populated than **8**, a $\text{Co(CO)}_3(\text{CH}_2\text{CH}_3)$ species, as the second step of the catalytic cycle, each of **2–4** was reacted with the intermediate **5**. However, these AFIR calculations with $\gamma_{\text{MAX}} = 100$ kJ/mol gave no reaction pathways. The intermediate **5** is thus considered to be a dead end intermediate

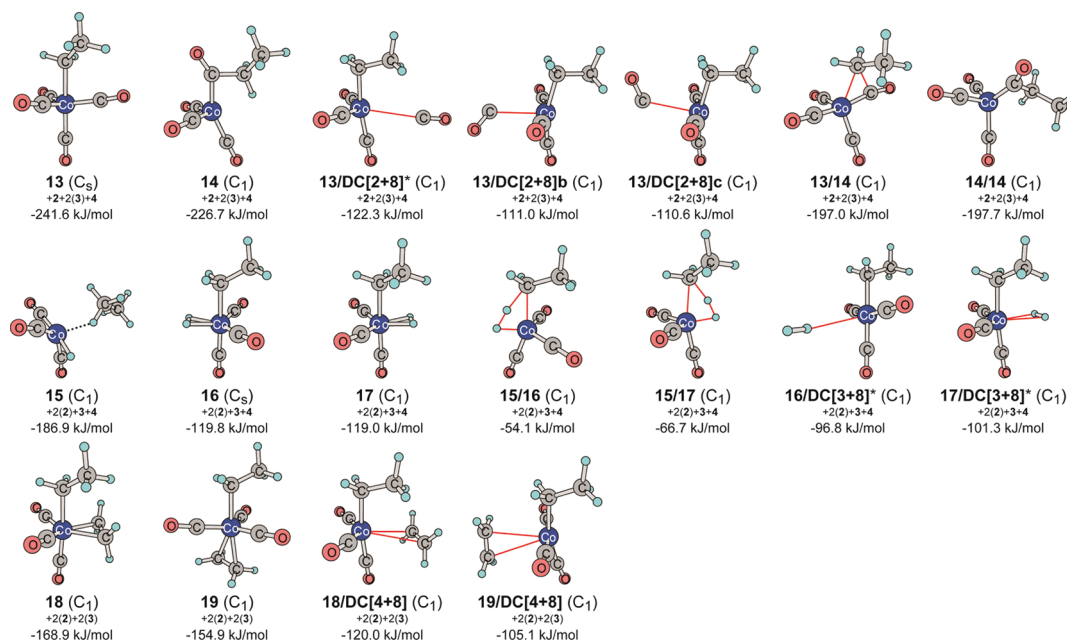


Figure 2. All critical points for the second step of the $\text{HCo}(\text{CO})_3$ -catalyzed reaction among CO , H_2 , and C_2H_4 , obtained by the AFIR search at the B3LYP/6-31G level (also see the captions of Figure 1 for further description). See also Supporting Information.

or a resting stage of the catalyst and was dropped from further consideration. Now **8** was chosen as the intermediate for the second step and reacted with each of **2–4**. This calculation gave new intermediates **13–19** and related TSs listed in Figure 2. By this search, the most populated intermediates after the second step are **13** and **14**, which will be used as the reactive intermediate for step 3. No further reaction of other intermediates **6**, **7**, and **9–12** was considered.

THIRD STEP

In Figure 2, **13**, a $\text{Co}(\text{CO})_4(\text{CH}_2\text{CH}_3)$ species, and **14**, a $\text{Co}(\text{CO})_3(\text{C}(\text{O})\text{CH}_2\text{CH}_3)$ species, are in equilibrium, and **13** is more populated. Hence, **13** was reacted next with each of **2–4** but gave no pathway with $\gamma_{\text{MAX}} = 100$ kJ/mol. Then **14** was reacted with **2–4** to obtain intermediates **20–29** and related TSs in Figure 3. Among them, **20** and **27** should have large population because of low barriers to form them and their high thermodynamic stabilities. However, the AFIR search applied to neither **20** nor **27** gave any new pathway. Since generation of **26** has a pretty high barrier of 90.6 kJ/mol and **27** is likely to go back to **4** + **14**, production of **21** is next most probable; **21** is a weak complex of the regenerated original catalyst **1**, $\text{HCo}(\text{CO})_3$, and the overall product of the reaction, acetaldehyde, $\text{CH}_3\text{C}(\text{O})\text{CH}_3$, **30**. The formal dissociation of **30** from **21** gives back the catalyst **1** and completes a full catalytic cycle. The reaction: $2 + 3 + 4 \rightarrow 30$ at the present theoretical level is exothermic by 213.1 kJ/mol.

FULL CATALYTIC CYCLE

Figure 4 summarizes the most preferable path and some competing pathways obtained in the present search and confirmed at the M06³⁷/6-311++G** level (including repotimization) with the zero-point energy and free-energy corrections in an experimental condition (403.15 K, 200 atm). Results at the M06 level are qualitatively similar to those in Figures 1–3 at the B3LYP

level. As seen in Figure 4, the major product of this reaction is acetaldehyde, which is the experimental product of the $\text{HCo}(\text{CO})_3$ -catalyzed hydroformylation. The catalytic cycle for this path is illustrated in Scheme 1, which agrees with the Heck–Breslow mechanism. The profile suggests that **26**, a $\text{Co}(\text{CO})_3(\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{CH}_2\text{CH}_3)$ species, may also be generated as a minor product. This is also consistent to an experiment in which **26** is a suggested intermediate and diethyl ketone is a major product in the absence of hydrogen.³⁸

CONCLUSIONS AND PERSPECTIVES

In this AFIR search, gradient and Hessian at the B3LYP/6-31G level were computed 55 449 and 2266 times, respectively. Although elapsed computation time strongly depends on the hardware, it took 138.2 h (5.8 days) on two CPUs (Intel Xeon, X5670, 2.93 GHz, hexacore) that have 12 cores in total. In this study, intermediates that are further reacted with reactants **2–4** were selected manually after each step on the basis of the activation energy to form them and their thermodynamic stability. Hence, the present approach is semiautomatic and still has some arbitrariness or “intervention by hand” in this part. Although it has not been implemented in the present case study, it would not be too difficult to make the selection mentioned above automatically. We emphasize that no initial guess concerning the reaction mechanism was required in the present search.

Although the present reaction involves only a single metallic atom, the above procedure may be applicable to reactions catalyzed by the metallic cluster or surface. Application of the AFIR method to such reactions is one of the future subjects. Another subject is to apply the AFIR method to reactions with very bulky catalysts as well as enzymatic reactions in proteins in combination with the QM/MM hybrid method.^{39,40} Spin flipping may take place in some organometallic reactions involving a high-spin metallic element, such as Fe.^{41,42} Minima on the seam of crossing (MSX) structures are often considered as critical points

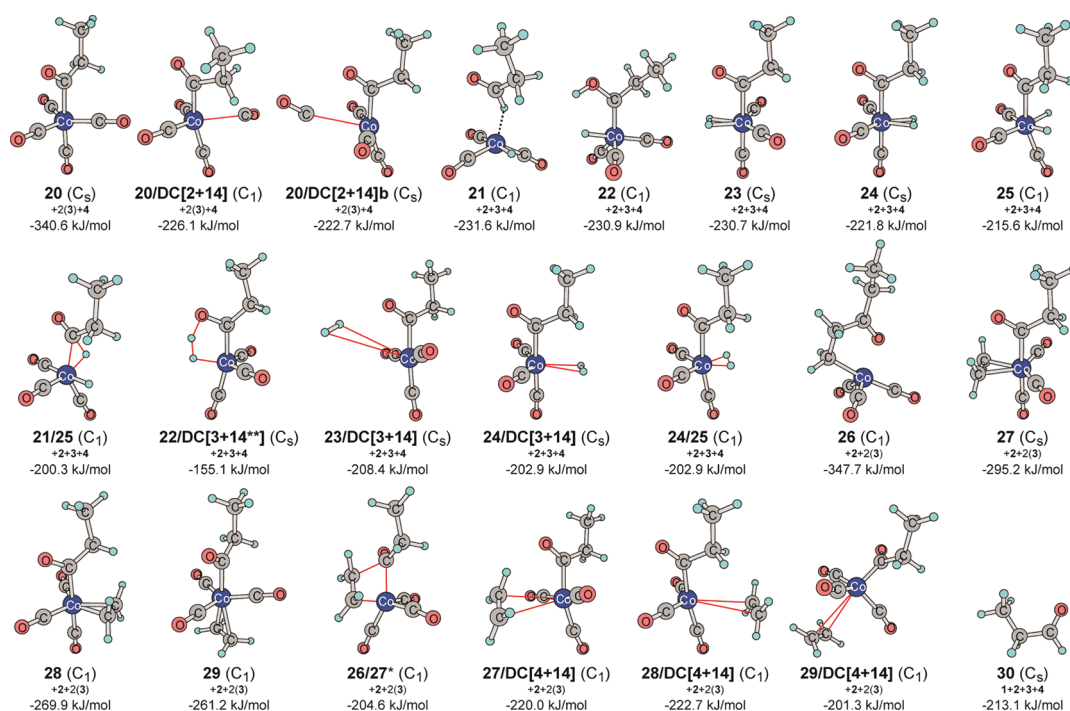


Figure 3. All critical points for the third step of the HCo(CO)_3 -catalyzed reaction among CO, H_2 , and C_2H_4 , obtained by the AFIR search at the B3LYP/6-31G level (also see the captions of Figure 1 for further description). In the label of 22/DC, 14** is an isomer of 14. See also Supporting Information.

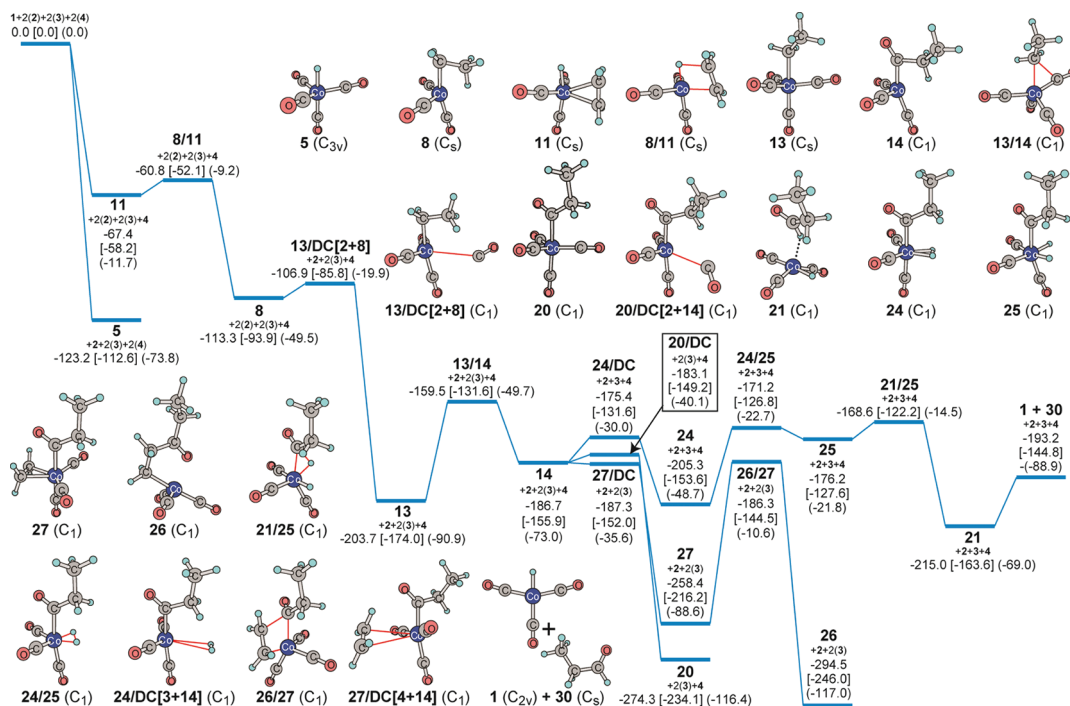
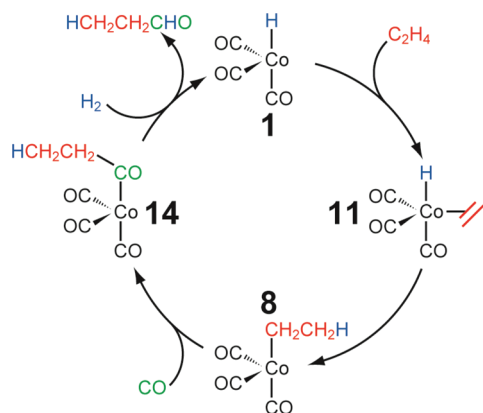


Figure 4. An energy profile of the most preferable and some competing pathways for the HCo(CO)_3 -catalyzed reaction obtained in the present AFIR search reproduced at the M06/6-311++G** level (also see the captions of Figure 1 for further description). Energies in square brackets and parentheses include the (harmonic) zero-point energy and free-energy corrections with an experimental condition (403.15 K, 200 atm), respectively. See also Supporting Information.

for spin flipping reactions. Hence, the method we developed recently to automatically find MSX structures on the basis of AFIR⁴³ may also be employed in future studies.

A remarkable merit of automated systematic reaction path search is that not only the lowest path but also many low-lying pathways can be discovered, as seen in the present results. If a

Scheme 1



desired path is not the lowest one, synthetic chemists, once all low-lying paths are known, may be able to turn the desired path to the lowest one by redesigning the process, for instance by modifying substituents and/or ligands. Moreover, such a search may find a totally unexpected pathway as either the lowest or low-lying ones, which may lead to a discovery of a novel reaction. In short, automatic reaction path search can provide useful information to realize desired or novel bond rearrangements. Thus, in the future, the present approach is expected to become a very powerful tool in efficient design of novel reactions as well as in reliable analysis of catalytic cycles.

■ ASSOCIATED CONTENT

Supporting Information. Cartesian coordinates of all structures shown in Figures 1–4. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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