How Hard Is Mechanism Elucidation in Catalysis? Combinatorial Analysis of C1 Chemistry

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Most chemical reactions occur over multiple steps whose identity is elucidated by experiment, yielding a reaction mechanism. Knowledge of cognitive science suggests that mechanism elucidation can be viewed as a knowledge-guided search within a combinatorial space. The MECHEM computer program searches this space comprehensively for the simplest plausible mechanisms. We use MECHEM to find mechanisms for Fischer−Tropsch chemistry and CO_2 re-forming of methane, both heterogeneous catalytic reactions of current importance. The results reveal hundreds of *equally simple* mechanisms consistent with evidence. Hence, mechanism elucidation in catalysis is a much harder problem than is ordinarily realized.

1. INTRODUCTION

In the 1880s, the physical chemist van't Hoff showed that many chemical reactions occur not as single elementary acts but as multiple steps.[1] His argument was based on conflicts between the chemical kinetic law of mass action, which he accepted, and the hypothesis of a single-step mechanism for certain reactions. Since then, a universal task for chemistry has been to elucidate the multistep character of reaction mechanisms, that is, to list the significant elementary steps that make up an overall reaction. Mechanism elucidation is a prototypical case of scientific model building, and thus the prevailing methodology in chemistry involves using current knowledge to propose one or several hypothetical mechanisms—preferably simple,[2] which then evolve on the basis of experimentation and other evidence gathering by the proposer or by others who build on these results. For example, computational quantum chemists follow up by studying in detail the energetics of a proposed mechanism.

Decades of progress in cognitive science and artificial intelligence[3] have shown that many tasks, including tasks of scientific model building,[4−6] can be well viewed as a search within a defined combinatorial space of solutions, where the search is guided by specific knowledge and heuristics which become critical when the space is very large. Chess play is a famous nonscience achievement of the method of heuristic search within a combinatorial space.[7]

The combinatorial space of reaction mechanisms has been established for some time. Its "parameters" include the facts that the large majority of elementary steps are uni- or bimolecular, both in the reactants and in the products. Thus, from a formal or combinatorial viewpoint, a good formulation of the space of mechanisms is that it consists of a set of steps, each having at most two reactants and two products,

such that there is a pathway from the known reaction starting materials to any observed reaction products or intermediates. This view of mechanism elucidation led to the design of the MECHEM program,[8] which comprehensively generates all the simplest (*fewest species or steps*) mechanisms that can explain how the observed products/intermediates are formed from the known starting materials. The program is not based on any catalogues of possible specific or schematic elementary steps or intermediates; rather, it generates steps and species from scratch using ad-hoc graph algorithms (e.g., see ref 9) that follow the basic principle that an elementary step involves few (e.g., at most three or four) changes to the connectivity of molecular graphs.

Since specific knowledge about a reaction is necessary to propose not just the simplest, but also plausible, mechanistic hypotheses, MECHEM lets the user select from a large menu of constraints to express this prior knowledge.[10] The typical interaction is to run the program, decide why the resulting mechanisms are implausible, express the reasons as constraints, and run the program again. When there are no further objections based on prior knowledge, the resulting mechanisms are the simplest from the space of mechanisms and are plausible. Typically, the user will also want to view the *next-simplest* mechanisms, i.e., *those mechanisms that have the same number of species but one or more extra steps, or that have one or more extra species*. These mechanisms are found by selecting an ad-hoc constraint that specifically rejects the mechanisms that were just found.

Our experience with MECHEM on a variety of reactions from both heterogeneous[11] and homogeneous[12,13] catalysis strongly suggests a key phenomenon: the number of *simpler* mechanisms that are consistent with the available evidence and other reliable prior knowledge is surprisingly large. Phrased differently, mechanism elucidation occurs within a combinatorial space that is dense with solutions that are not sufficiently ruled out by the available evidence. If true, this phenomenon, which can only be revealed by computational methods based on a comprehensive exploration of the space

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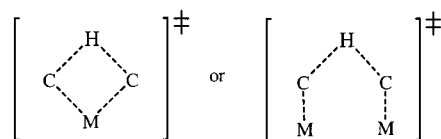‡ Lomonosov Academy of Fine Chemical Technology.

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Figure 1. Transition states for Thompson−Webb hydrogen transfer steps.

Table 1. Plausibility Constraints on Fischer−Tropsch Mechanisms

1. Every conjectured intermediate has at most one C atom
2. Every conjectured intermediate has at most two O atoms
3. Every conjectured intermediate has at least one M site
4. O atoms cannot be bonded to O atoms
5. All elements must be at full valence
6. Reject intermediate containing three adjacent atoms all bound by metal
7. Reject Eley−Rideal mechanisms
8. The site M must be present in all steps
9. Every step must change the bonding at a metal site
10. Reject hydrogen-transfer steps from one carbon atom bonded to the metal surface to another such carbon atom
11. No multiple occurrences of any reactant pair on the left-hand side of steps
12. CH_4 cannot appear on the left-hand side of a step
13. CH_3OH cannot appear on the left-hand side of a step

of mechanisms, has important implications for methodology in catalysis and potentially other branches of chemistry. There could be analogous implications for other areas of scientific model building.

2. METHODS

Here we explore this phenomenon in the context of Fischer−Tropsch (FT) chemistry, which was discovered in 1925 and has been studied for over 70 years but remains highly topical due to its value in producing fuel alternatives to oil (e.g., see ref 14). We follow our established method of formulating the relevant chemical constraints based on general chemical considerations and our specific reading of the literature. Thus, we define the reaction starting materials to be CO, H_2, a catalyst site denoted as M, and dual catalyst sites denoted by MM. The observed C_1 products are defined as CO_2, CH_3OH, CH_4, and H_2O. The constraints are listed in Table 1. Some constraints are not strictly justified, but they serve to reduce the problem combinatorics, without which the ensuing mechanisms would be even more numerous.

Constraint 10 merits discussion. Our experience with various hydrocarbon conversion reactions shows that the number of hypothetical mechanisms increases greatly if we allow hydrogen transfers from one carbon adsorbed on the metal surface to another adsorbed carbon, i.e., having the transition states shown in Figure 1. These hydrogen-transfer steps were first proposed by Thompson and Webb in 1976,[15] but they are poorly studied. Few researchers include them in mechanisms of hydrocarbon conversion over transition metals. Therefore, we excluded them from consideration without committing either way to their plausibility.
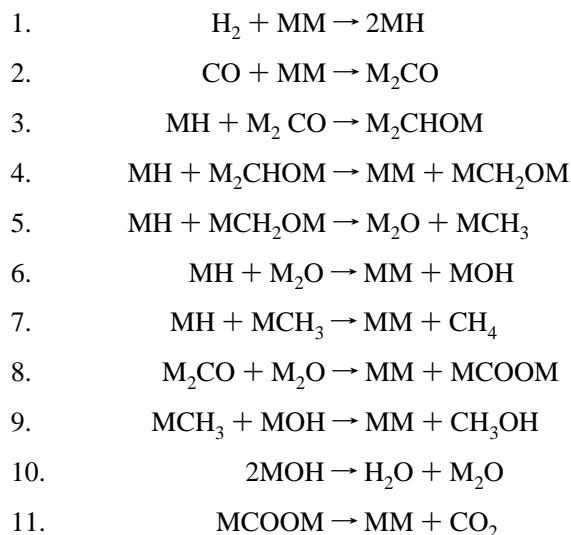
3. RESULTS AND INTERPRETATION

After about 2 h of computation, MECHEM found 848 simplest mechanisms each having 15 total species of which

Table 2. Conjectured Intermediates in 848 Fischer−Tropsch Mechanisms

freq	intermediate	freq	intermediate
848	M_2CO	409	$MC(O)OM$
848	MH	400	$MC(O)OH$
794	MOH	348	M_2CHOM
705	MCH_2OM	227	MCH_2OH
508	M_2O	108	M_2CHOH
483	MCHO	93	MOCHO
472	$MOCH_3$	81	M_2CH_2
433	MCH_3	17	M_3COH
		10	M_3CH

8 were conjectured intermediates (the species M did not appear in any of the mechanisms), and 11 elementary steps. These mechanisms are listed at http://www.cs.cmu.edu/sci-disc/mechem/fischer-tropsch. Histograms of the intermediates and steps that appear in them are shown in Tables 2 and 3.

MECHEM generated several mechanisms which might be considered more plausible than others because their individual steps contain precedents in the literature on FT synthesis, water-gas shift reaction, methanol synthesis, and CO and CO_2 methanation. One mechanism is the successive hydrogenation of adsorbed CO to form the CHO group on the surface, which then hydrogenates to form adsorbed formaldehyde capable of dissociating on the surface into methyl and oxygen. Methyl recombines with hydrogen or OH to form methane or methanol, respectively. H_2O is formed via OH disproportionation. CO_2 is the result of CO oxidation by oxygen on the surface. A specific mechanism output by MECHEM is

1. $$H_2 + MM \rightarrow 2MH$$
2. $$CO + MM \rightarrow M_2CO$$
3. $$MH + M_2CO \rightarrow M_2CHOM$$
4. $$MH + M_2CHOM \rightarrow MM + MCH_2OM$$
5. $$MH + MCH_2OM \rightarrow M_2O + MCH_3$$
6. $$MH + M_2O \rightarrow MM + MOH$$
7. $$MH + MCH_3 \rightarrow MM + CH_4$$
8. $$M_2CO + M_2O \rightarrow MM + MCOOM$$
9. $$MCH_3 + MOH \rightarrow MM + CH_3OH$$
10. $$2MOH \rightarrow H_2O + M_2O$$
11. $$MCOOM \rightarrow MM + CO_2$$

Some mechanisms differ only slightly from the above. For example, water may be formed by recombining H and OH, rather than by OH disproportionation. The type of adsorbate binding to the surface metal atoms may also differ (e.g., CHO may be either $M_2CH-O-M$ or $M-C(H)=O$. In the second mechanism below, the CHO group formed by CO hydrogenation on the surface binds to the surface via a single bond. Its hydrogenation yields adsorbed aldehyde reacting as in the first mechanism above. The CHO group can also be

Table 3. Conjectured Elementary Steps in 848 Fischer−Tropsch Mechanisms

no.	freq	elementary step
1	848	$H_2 + MM \rightarrow 2MH$
2	848	$CO + MM \rightarrow M_2CO$
3	483	$MH + M_2CO \rightarrow MM + MCHO$
4	472	$MH + MCH_2OM \rightarrow MM + MOCH_3$
5	463	$MH + MCHO \rightarrow MCH_2OM$
6	415	$MH + MOCH_3 \rightarrow CH4 + M_2O$
7	382	$MC(O)OM \rightarrow MM + CO_2$
8	373	$MC(O)OH \rightarrow CO_2 + MH$
9	348	$MH + M_2CO \rightarrow M_2CHOM$
10	319	$MH + MCH_3 \rightarrow MM + CH4$
11	291	$MOH + MCH_3 \rightarrow MM + CH_3OH$
12	267	$M_2CO + MOH \rightarrow MM + MC(O)OH$
13	242	$MH + M_2CHOM \rightarrow MM + MCH_2OM$
14	241	$MH + MOH \rightarrow MM + H_2O$
15	227	$MH + MCH_2OH \rightarrow MOH + MCH_3$
16	200	$M_2CO + MOH \rightarrow MH + MC(O)OM$
17	168	$2MOCH_3 \rightarrow CH_3OH + MCH_2OM$
18	158	$MH + M_2O \rightarrow MM + MOH$
19	152	$M_2CO + M_2O \rightarrow MM + MC(O)OM$
20	146	$MH + MC(O)OH \rightarrow H_2O + M_2CO$
21	129	$2MOH \rightarrow H_2O + M_2O$
22	113	$MOCH_3 + M_2O \rightarrow MCH_2OM + MOH$
23	112	$MCHO + MOCH_3 \rightarrow CH_3OH + M_2CO$
24	99	$MOCH_3 + MOH \rightarrow CH_3OH + M_2O$
25	93	$MOCHO \rightarrow CO_2 + MH$
26	87	$MCHO + MOH \rightarrow H_2O + M_2CO$
27	82	$MOCH_3 + MOH \rightarrow H_2O + MCH_2OM$
28	79	$MCHO + MOH \rightarrow MH + MC(O)OH$
29	76	$MH + M_2CHOM \rightarrow MM + M_2CHOH$
30	76	$MH + MCH_2OM \rightarrow MM + MCH_2OH$
31	76	$MCH_2OH + MCH_3 \rightarrow CH4 + MCH_2OM$
32	76	$2MCH_2OH \rightarrow CH_3OH + MCH_2OM$
33	70	$MCHO + M_2O \rightarrow M_2CO + MOH$
34	68	$MH + MCH_2OM \rightarrow M_2O + MCH_3$
35	62	$MH + M_2CH_2 \rightarrow MM + MCH_3$
36	61	$MCH_2OM + MOH \rightarrow H_2O + M_2CHOM$
37	57	$MH + MOCH_3 \rightarrow MOH + MCH_3$
38	57	$MCHO + M_2O \rightarrow MH + MC(O)OM$
39	56	$MCH_2OM + MOCH_3 \rightarrow CH_3OH + M_2CHOM$
40	54	$MCHO + MOH \rightarrow MH + MOCHO$
41	48	$MCH_2OH + MOH \rightarrow H_2O + MCH_2OM$
42	48	$MCHO + MCH_2OM \rightarrow M_2CO + MCH_2OH$
43	47	$MH + M_2CHOH \rightarrow MM + MCH_2OH$
44	46	$MCH_2OM + M_2O \rightarrow M_2CHOM + MOH$
45	46	$MH + MC(O)OM \rightarrow M_2CO + MOH$
46	39	$MCHO + M_2O \rightarrow MM + MOCHO$
47	38	$M_2CHOH + MCH_3 \rightarrow CH4 + M_2CHOM$
48	33	$MH + M_2CHOH \rightarrow MOH + M_2CH_2$
49	28	$M_2CHOH + MCH_2OH \rightarrow CH_3OH + M_2CHOM$
50	28	$2M_2CHOH \rightarrow M_2CHOM + MCH_2OH$
51	28	$2MCH_2OM \rightarrow M_2CHOM + MCH_2OH$
52	25	$MH + M_2CHOM \rightarrow M_2O + M_2CH_2$
53	24	$M_2CHOH + MOH \rightarrow H_2O + M_2CHOM$
54	22	$MCH_2OH + MOH \rightarrow H_2O + M_2CHOH$
55	20	$MH + MCHO \rightarrow M_2CHOH$
56	18	$MOCH_3 + MC(O)OM \rightarrow MCH_2OM + MC(O)OH$
57	18	$MOCH_3 + MC(O)OH \rightarrow CH_3OH + MC(O)OM$
58	18	$MH + MC(O)OM \rightarrow MM + MC(O)OH$
59	17	$MH + M_2CO \rightarrow M_3COH$
60	14	$MH + MOCHO \rightarrow MCHO + MOH$
61	13	$MH + MCH_2OM \rightarrow MOH + M_2CH_2$
62	12	$MH + M_3COH \rightarrow MM + M_2CHOM$
63	12	$MCHO + MC(O)OM \rightarrow M_2CO + MC(O)OH$
64	10	$M_2CHOH + M_2CH_2 \rightarrow M_2CHOM + MCH_3$
65	10	$MH + M_3CH \rightarrow MM + M_2CH_2$
66	9	$M_2CH_2 + MOH \rightarrow M_2O + MCH_3$
67	7	$M_2O + MCH_3 \rightarrow M_2CH_2 + MOH$
68	6	$MCH_2OM + MC(O)OM \rightarrow M_2CHOM + MC(O)OH$
69	5	$MH + M_2CHOM \rightarrow MOH + M_3CH$
70	5	$MH + M_3COH \rightarrow MOH + M_3CH$
71	4	$MOH + M_2CH_2 \rightarrow H_2O + M_3CH$
72	4	$M_2CHOH + MOH \rightarrow H_2O + M_3COH$

oxidized by surface oxygen to form adsorbed CO_2 and water (steps 8 and 9).

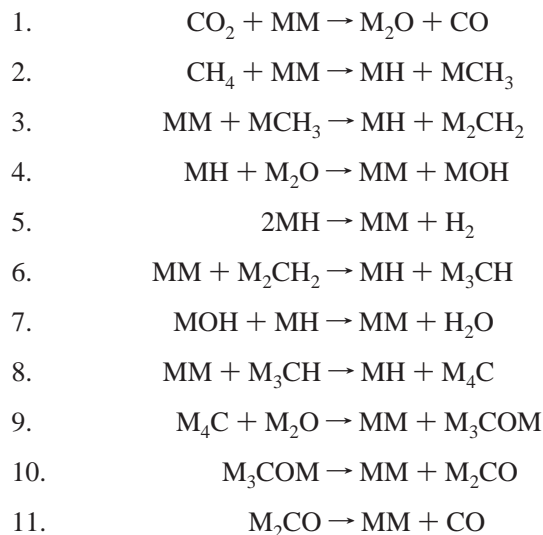| 1.	$H_2 + MM \rightarrow 2MH$
2.	$CO + MM \rightarrow M_2CO$
3.	$MH + M_2CO \rightarrow MM + MCHO$
4.	$MH + MCHO \rightarrow MCH_2OM$
5.	$MH + MCH_2 OM \rightarrow M_2O + MCH_3$
6.	$MH + M_2O \rightarrow MM + MOH$
7.	$MH + MCH_3 \rightarrow MM + CH_4$
8.	$MCHO + M_2 O \rightarrow MH + MCOOM$
9.	$MH + MOH \rightarrow MM + H_2O$
10.	$MCH_3 + MOH \rightarrow MM + CH_3OH$
11.	$MCOOM \rightarrow MM + CO_2$

Our larger point is that the phenomenon of the abundance of seemingly plausible mechanisms recurs in FT chemistry: the number of *equally simple* mechanisms is exceedingly large, without even trying to generate the next-simplest mechanisms, i.e., that have an extra step or an extra intermediate. It may be that intimate details of FT chemistry may enable ruling out several of the steps or intermediate shown, but we do not believe that current knowledge of FT chemistry permits reducing the number of mechanisms to a handful.

It may be objected that FT is too complex and that simpler reactions will not exhibit this phenomenon or that stipulating an overall reaction stoichiometry will prevent it. Our experience with such cases suggests otherwise. As a second experiment, we formulated the CO_2 re-forming of methane with the same constraints 1−11 from Table 1, but added an overall stoichiometry, following ref 16, of $CH_4 + 2CO_2 \rightarrow 3CO + H_2 + H_2O$. Thus, any plausible mechanism must account for this stoichiometry by exhibiting stoichiometric numbers for individual steps that sum to the overall reaction.

This time we obtained many mechanisms that contain seemingly implausible steps and intermediates, so we rejected them on a partly subjective (but explicit) basis. We decided to guide the program toward the themes that are current in the literature, which of course risks missing potentially plausible mechanisms.

Currently, there is no commonly accepted mechanism for carbon dioxide re-forming. However, on most transition metals the following steps are believed to occur:[16−18] (1) dissociation of methane to form surface hydrogen and CH_x species (including surface carbon); (2) dissociation of CO_2 to form surface CO and oxygen; (3) oxidation of surface carbon to form CO; and (4) hydrogen recombination. Also, it is known that water-gas shift is an inevitable side reaction in methane reforming. Other commonly considered steps are the reactions of CH_x species with oxygen leading to the formation of CO and H_2 (e.g., CH_2 (ads) + O(ads) 6 CO-(ads) + H_2 or CH(ads) + O(ads) 6 CO(ads) + H(ads)), formation of OH by the reaction CO_2 (ads) + H(ads) 6 CO + OH, recombination of hydroxyl and hydrogen, and disproportionation of OH groups on the surface.

Thus, we declared the following intermediate and final products: MOH, MH, M_3 COM, M_4C, M_2O, M_2CO, H_2O, H_2, CO, M_3CH, MCH_3, and M_2CH_2. We also rejected several implausible steps (e.g., $M_2CH_2 + MOH \rightarrow M_3CH + H_2O$) and defined precursor relations among some species (e.g., MCH_3 is a necessary precursor of M_2CH_2). Of course, by using these constraints, we decreased the number of mechanisms that can be generated. The program found eight mechanisms similar to this one:
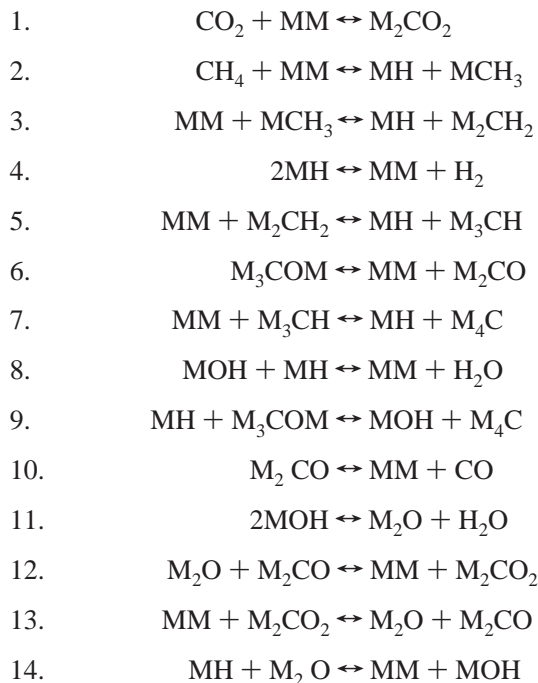
1.	$CO_2 + MM \rightarrow M_2O + CO$
2.	$CH_4 + MM \rightarrow MH + MCH_3$
3.	$MM + MCH_3 \rightarrow MH + M_2CH_2$
4.	$MH + M_2O \rightarrow MM + MOH$
5.	$2MH \rightarrow MM + H_2$
6.	$MM + M_2CH_2 \rightarrow MH + M_3CH$
7.	$MOH + MH \rightarrow MM + H_2O$
8.	$MM + M_3CH \rightarrow MH + M_4C$
9.	$M_4C + M_2O \rightarrow MM + M_3COM$
10.	$M_3COM \rightarrow MM + M_2CO$
11.	$M_2CO \rightarrow MM + CO$

Some minor variations were associated with the multiplicity of pathways to H_2O: $2MOH \rightarrow M_2O + H_2O$ vs $MOH + MH \rightarrow MM + H_2O$ and involvement of M_3CH in the reaction with adsorbed oxygen. In all of these eight mechanisms, the first step was $CO_2 + MM \rightarrow M_2O + CO$ with the release of CO into the gas phase. The program also generated 70 more complex mechanisms with one additional conjectured species and 11 or 12 steps. Those contained, for example, stepwise CO formation from CO_2

$$CO_2 + MM \rightarrow M_2CO_2$$
$$M_2CO_2 \rightarrow M_2O + CO$$
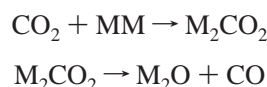
and mechanisms with other conjectured species (MCOOH and $HO-CM_2-OM$).

Computer-generated mechanisms often differ from those reported in the literature, which tend to contain steps whose role is to account for phenomena that are outside the current scope of MECHEM, e.g., kinetics, or the quantitative distribution of products in isotopic labeling experiments. Also, published mechanisms often contain reversible and irreversible steps to account for observed or hypothesized trends in reaction kinetics. Here we have not dealt with kinetic aspects, so all our conjectured steps have an unspecified direction.

Nevertheless, the steps proposed in the literature were conjectured by the program, except for steps that violate our chosen constraints, which were formulated subjectively on the basis of general principles. (Specific knowledge of various aspects of this reaction might refine these constraints.) For example, the mechanism reported by Efstathiou et al.[18] was within the list of conjectured steps:

1.	$CO_2 + MM \leftrightarrow M_2CO_2$
2.	$CH_4 + MM \leftrightarrow MH + MCH_3$
3.	$MM + MCH_3 \leftrightarrow MH + M_2CH_2$
4.	$2MH \leftrightarrow MM + H_2$
5.	$MM + M_2CH_2 \leftrightarrow MH + M_3CH$
6.	$M_3COM \leftrightarrow MM + M_2CO$
7.	$MM + M_3CH \leftrightarrow MH + M_4C$
8.	$MOH + MH \leftrightarrow MM + H_2O$
9.	$MH + M_3COM \leftrightarrow MOH + M_4C$
10.	$M_2 CO \leftrightarrow MM + CO$
11.	$2MOH \leftrightarrow M_2O + H_2O$
12.	$M_2O + M_2CO \leftrightarrow MM + M_2CO_2$
13.	$MM + M_2CO_2 \leftrightarrow M_2O + M_2CO$
14.	$MH + M_2 O \leftrightarrow MM + MOH$

In this second of our experiments, we formulated the constraints in order to closely approach the published mechanistic ideas. Nevertheless, the program still turns up many mechanistic variants even within the narrowly formulated task. Thus, the phenomenon of the plethora of simpler plausible mechanisms repeats itself.

4. DISCUSSION

Although many mechanisms have been proposed for FT since this reaction was discovered, a direct comparison of the MECHEM-generated mechanisms of FT synthesis to those reported in the literature is difficult for various reasons:

(1) We generated only the simpler mechanisms to illustrate the idea that there are more mechanisms than usually expected. Therefore, some of the mechanisms proposed in the literature would appear in the next-simplest MECHEM-generated mechanisms, which are not discussed here.

(2) We used constraints that eliminated some of the species proposed in the literature. Some of these constraints are relevant to the type of binding to metal atoms on the surface. In the literature mechanisms, coordination to the surface is not explicitly treated, whereas MECHEM does treat binding to metals explicitly, although specific binding to the metal is just a model of adsorption. In the published mechanisms, binding to the surface is sometimes not considered at all, which makes comparisons difficult.

(3) Many of the published mechanisms include termolecular reactions, as well as steps that do not seem elementary from the standpoint of the complexity in bond scission and formation that take place in a single step. Such compound, nonelementary steps are not generated in MECHEM.

(4) We restricted the formulation to C_1 products (methane, methanol, carbon dioxide, and H_2O) because the comprehensive generation of all mechanisms of hydrocarbon and oxygenate formation was not the goal of this paper.

Generally, the mechanisms of FT synthesis can be divided into two groups: (a) carbide (or dissociative) mechanisms, implying the formation of carbon on the catalyst surface,

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and (b) others in which carbon is not formed. Although carbide mechanisms are somewhat more straightforward in terms of chemistry, they usually have more steps and species. Therefore, they were not generated by MECHEM since we stopped the program after it generated the simplest mechanisms. However, the steps listed in the table include some aspects of carbide mechanisms since some of the steps produce CH(ads), which is an immediate successor of carbide.

The mechanisms of FT synthesis, methanation, and methanol synthesis have been reviewed in several papers; these agree that there may be multiple pathways to the key products,[14,19−23] depending on the conditions and catalyst. Rofer-DePoorter[20] provided a comprehensive review of the FT mechanisms that were reported by 1981 and the mechanisms of related reactions (water-gas shift reaction, CO disproportionation, methanation, etc.). Krylov and Matyshak[23] provided a comprehensive review of intermediates observed by different methods.[24]

Some of the proposed elementary steps are missing in MECHEM's mechanisms due to various reasons. Thus, carbide and $M_2=C(OH)_2$ are absent because they do not appear in the simplest mechanisms. Multiple variants of physisorption states of molecules and charged species are currently outside the scope of MECHEM. So intermediates such as MH_2 were not considered by MECHEM. The constraints on species that we formulated lead to rejecting intermediates that form higher hydrocarbons and oxygenates, which are common in FT synthesis.

Conversely, some plausible species generated by MECHEM are missing from the published mechanisms. For example, the simple plausible intermediate $M_2=C(H)OM$ is usually not proposed. Intermediates such as $MOCH_3$ and $MOCH=O$ appear more often in MECHEM than in the literature mechanisms, where their role is considered to be small. Sometimes intermediates are rather exotic: $MOCH=O$ has been proposed by Deluzarche et al.[24] in a somewhat strange mechanism with a symmetry-forbidden step of CO insertion into the O−H bond to form this intermediate. Also, the species is formed in the following reaction cited by Rofer-DePoorter: $MOH + MCO \rightarrow MOCH=O$. Both of these steps are not in the MECHEM-generated mechanisms because our formulated constraints prohibit them. Instead, MECHEM generated two steps of $MOCH=O$ formation (steps 40 and 46). $MOCH_3$ is often considered to be an intermediate in heterogeneously catalyzed methane oxidation, but rarely in FT reactions. Adsorbed CO_2, which is modeled in MECHEM as $MC(O)OM$, is also rarely considered because most researchers include CO_2 desorption in the steps where CO_2 is formed, e.g., $O(ads) + CO(ads) \rightarrow CO_2$ instead of $O(ads) + CO(ads) \rightarrow CO_2 (ads) \rightarrow CO_2$.

Overall, almost all of the C_1 intermediates proposed in the literature appear in the simplest mechanisms proposed by MECHEM if they are not explicitly rejected by the constraints. The following steps appear both in MECHEM and in the literature: 1−5, 7, 8, 10, 11, 14, 16, 19, 21, 22, 30, 35, 43, 55, 58, 59, 62, and 65. We have not found the others among the published mechanisms.

5. CONCLUSION

Some chemists are aware of the potential for many plausible mechanisms, even an infinite number if the number of species and steps is allowed to increase without limit. For example, Hoffmann, et al.[2] approvingly quote Smalley—one of the discoverers of fullerenes—who stated that "Of course, there must be hundreds of mechanisms whereby a fullerene like C_{60} can form." In Fischer−Tropsch chemistry, two papers[20,25] systematically consider the formation of hydrocarbons and oxygenates of up to C15 and list hundreds of possible steps which imply a large number of mechanisms. However, to our knowledge, this is the first demonstration with hard data (a list of specific mechanisms) that the number of *simplest* mechanisms consistent with the evidence can be very large even for small-molecule chemistries such as C_1. We suggest the following implications of this phenomenon:

(1) Mechanism elucidation in catalysis is a much harder problem than is ordinarily realized.

(2) Proposing mechanisms without consideration of the potential for numerous alternatives is demonstrably risky.

(3) Possibly the right view of catalytic reactions is that many significant mechanisms are operating simultaneously, not just one or two. There is no shortage of pathways from which Nature can choose.

(4) As argued by Chamberlin over 100 years ago,[11,26] a deliberate consideration of multiple hypotheses from the outset of an investigation is advisable, and now even practical.

(5) Practical theoretical and experimental methods for discriminating among masses of alternative mechanisms should be a high priority. We have developed automated methods for testing large numbers of mechanisms against data on isotopic labeling[27] and activation energies,[28] but more are needed.

REFERENCES AND NOTES

(1) van't Hoff, J. *Etudes de dynamique chimique* (Studies of Chemical Dynamics); F. Muller and Co.: Amsterdam, 1884.
(2) Hoffmann, R.; Minkin, V. I.; Carpenter, B. K. Ockham's Razor and Chemistry. *HYLE* **1997**, *3*, 3−28.
(3) Newell, A.; Simon, H. A. Computer science as empirical inquiry: Symbols and search. *Commun. ACM* **1976**, *19*, 111.
(4) Simon, H. Scientific discovery and the psychology of problem solving. In *Mind and Cosmos*; Colodny, R., Ed.; University of Pittsburgh Press: Pittsburgh, PA, 1966; pp 22−40.
(5) Langley, P.; Simon, H.; Bradshaw, G.; Zytkow, J. *Scientific Discovery: Computational Explorations of the Creative Processes*; MIT Press: Cambridge, MA, 1987.
(6) Lindsay, R.; Buchanan, B.; Feigenbaum, E.; Lederberg, J. *Applications of Artificial Intelligence for Organic Chemistry: The Dendral Project*; McGraw-Hill: New York, 1980.
(7) Will a computer checkmate a chess champion at last? *Science* **1996**, *271* (5249), 599.
(8) Zeigarnik, A. V.; Valdes-Perez, R. E.; White, B. S. Proposed methodological improvement in the elucidation of chemical reaction mechanisms based on chemist-computer interaction. *J. Chem. Educ.* **2000**, *77* (2), 214.
(9) Valdes-Perez, R. E. Algorithm to infer the structures of molecular formulas within a reaction pathway. *J. Comput. Chem.* **1994**, *15* (11), 1266.
(10) Valdes-Perez, R. E. Principles of human computer collaboration for knowledge discovery in science. *Artif. Intell.* **1999**, *107* (2), 335.
(11) Zeigarnik, A. V.; Valdes-Perez, R. E.; Temkin, O. N. Metal-catalyzed ethylene hydrogenation: The method of interactive search for multiple working hypotheses. *Langmuir* **1998**, *14*, 4510.
(12) Zeigarnik, A. V.; Valdes-Perez, R. E.; Temkin, O. N.; Bruk, L. G.; Shalgunov, S. I. Computer-aided mechanism elucidation of acetylene

hydrocarboxylation to acrylic acid based on a novel union of empirical and formal methods. *Organometallics* **1997**, *16*, 3114.

(13) Bruk, L. G.; Gorodskii, S. N.; Zeigarnik, A. V.; Valdes-Perez, R. E.; Temkin, O. N. Oxidative carbonylation of phenylacetylene catalyzed by Pd(II) and Cu(I): Experimental tests of forty-one computer-generated mechanistic hypotheses. *J. Mol. Catal. A: Chem.* **1998**, *130* (1−2), 29.

(14) Dry, M. E. Practical and theoretical aspects of the catalytic Fischer-Tropsch process. *Appl. Catal. A* **1996**, *138*, 319.

(15) Thompson, S.; Webb, G. Catalytic hydrogenation of olefins on metals: A new interpretation. *J. Chem. Soc., Chem. Commun.* **1976**, 526.

(16) Bradford, M.; Vannice, M. CO_2 reforming of CH_4. *Catal. Rev.*−Sci. Eng. **1999**, *41* (1), 1.

(17) Wang, S.; Lu, G.; Miller, G. Carbon dioxide reforming of methane to produce synthesis gas over metal-supported catalysts: State of the art. *Energy Fuels* **1996**, *10*, 896.

(18) Efstathiou, A.; Kladi, A.; Tsipouriari, V.; Verykios, X. Reforming of methane with carbon dioxide to synthesis gas over supported rhodium catalysts: II. A steady-state tracing analysis: mechanistic aspects of the carbon and oxygen reaction pathways to form CO. *J. Catal.* **1996**, *158*, 64.

(19) Wojciechowski, B. The kinetics of the Fischer-Tropsch synthesis. *Catal. Rev.*−Sci. Eng. **1988**, *30*, 629.

(20) Rofer-DePoorter, C. A comprehensive mechanism for the Fischer-Tropsch synthesis. *Chem. Rev.* **1981**, *81* (5), 447.

(21) Muetterties, E.; Stein, J. Mechanistic features of catalytic carbon monoxide hydrogenation reactions. *Chem. Rev.* **1979**, *79*, 479.

(22) Deluzarche, A.; Hindermann, J.; Kieffer, R.; Cressely, J.; Kiennemann, A. Mechanism of Fischer-Tropsch Reactions in heterogeneous catalysis. *Bull. Soc. Chim. Fr.* **1982**, *17*, 171.

(23) Krylov, O.; Matyshak, V. *Intermediates in Heterogeneous Catalysis*; Nauka: Moscow, 1996 (in Russian).

(24) Deluzarche, A.; Hindermann, J.; Kieffer, R.; Muth, A.; Papadopoulos, M.; Tanielian, C. Fischer−Tropsch (carbon monoxide, hydrogen) synthesis. II. Mechanism of reaction and application of gas-phase chromatography to the heterogeneous catalyzed reaction. *Tetrahedron Lett.* **1977**, 797.

(25) Lox, E.; Froment, G. Kinetics of the Fischer−Tropsch reaction on a precipitated promoted iron catalyst: 2. Kinetic modeling. *Ind. Eng. Chem. Res.* **1993**, *32*, 71.

(26) Chamberlin, T. The method of multiple working hypotheses. *Science* **1965**, *148*, 754, (reprinted from vol. 15, p 92, 1890).

(27) Zeigarnik, A. V.; Valdes-Perez, R. E. Systematic prediction of the products and intermediates of isotopic labeling in reaction pathway studies. *J. Comput. Chem.* **1998**, *19* (7), 741.

(28) Valdes-Perez, R. E.; Fishtik, I.; Zeigarnik, A. V. Catalyst screening via combinatorial pathway generation and energetics: Coking in CO_2 reforming of methane on transition metals. Submitted for publication.

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