The Methodologist's Dilemma: An Evidential Function for Mechanisms in Chemistry[1]

DRAFT

George Borg

Goodwin (2012) argues that mechanisms in organic chemistry support chemists' capacity to explain, predict and design organic reactions. He identifies a peculiarity in the way chemists use mechanisms, namely the fact that in general they do not pursue increasing detail and precision in the descriptions. In this article, I argue that this peculiarity has a significant function in dealing with a methodological impediment in organic chemistry research. Substrate scope studies provide a primary form of evidence that chemists use to demonstrate the reliability of a new synthetic method, namely a set of test cases for which the method is shown to work. Unfortunately, the set is necessarily limited, both in size and in the complexity of the test cases, leaving a gap in the information concerning the applicability of the method beyond the test cases. I argue that the peculiar form mechanistic descriptions take in this field aids in overcoming this information deficit. I thus identify an evidential function for mechanisms in organic chemistry, that of supporting the reliability of new chemical methods across a range of applications.

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[1] Word count: 7478.

1. Introduction. Practitioners of applied sciences are frequently faced with decisions requiring them to extrapolate methods, developed in one context, to unexplored contexts that differ significantly from the original. The problem is how to extrapolate a method with confidence, given that information about whether the method can be applied successfully in the new contexts is lacking. This problem is ubiquitous in synthetic organic chemistry, where one of the principal goals of the field is to develop a large repertoire of methods that are broadly applicable to the synthesis of novel compounds. A "method" in this field is a way of transforming one type of compound into another, in which the transformation centrally involves a chemical reaction. Chemists plan lengthy syntheses of complex molecules by drawing on this repertoire of methods. Decisions have to be made about synthetic steps on which the success of the synthesis depends, but whose experimental verification necessarily lies well in the future. A strategy is needed that allows the planner to judiciously compare cases on which the method has been tested to untested cases so that evidence can be marshaled to support the projected application of a method to a novel target.

A *substrate scope* study provides a primary form of evidence that chemists use to demonstrate the range of application of a new method. Usually, the goal is to show that the method is a reliable synthetic tool, that is, that one can use the method to effect a transformation in a broad range of synthetic contexts and that the method generally works well, i.e., affords synthetically useful yields. In this kind of study, the method is tested on a set of relatively simple compounds (a "substrate" being a test compound) and the results are presented in the original report disclosing the method. While the set is supposed to be representative of the method's range of application, it is usually small, and the disparity

between the simplicity of the test cases and the complexity of the synthetic targets to which the methods are to be applied can be great. Though chemists can increase the diversity and size of the study, in practice there are limits to how much increase is feasible, perhaps the most fundamental being that the range of possible applications includes not only naturally occurring substances, but also all those that can be designed by humans (e.g., drugs). Methods developers (called "methodologists" in chemistry) are therefore confronted with a pair of conflicting requirements: they need to make a case for the reliability of their methods, but they can only do so by appealing to a data set that is necessarily much narrower than the range of potential applications. The narrowness of the data set leaves a gap in the information concerning the applicability of the method beyond the test cases. I call these conflicting requirements "the methodologist's dilemma."[2]

On a standard empiricist view of theory testing, all the observable consequences of a theory are significant, whether they are observed in the past, present or future. In contrast, assessing the reliability of a method in organic chemistry is more like assessing the performance of a used car prior to purchase than it is like empiricist theory testing: what we are interested in is not so much whether it has performed well in observed cases, but whether it will perform well in future cases.[3] Past or present performance is significant, but only as an indicator of future performance. The analogy with a mechanical tool is not fortuitous, for the methodologist's dilemma arises from the nature of applied science, which is, to a large

[2] For a rare recognition and discussion in print, by chemists, of these conflicting requirements, see Collins and Glorius (2013) and (2015).

[3] The used car analogy is borrowed from Hausman (2007, 17-21).

extent, focused on creating the means for future manipulation, control and design of aspects of the world.

Since it is impossible to know everything about a method's future performance through direct testing, however, some other means of assessing its performance can be helpful. In this paper, I will argue that mechanisms describing organic reactions serve as such a means for synthetic methodologists. William Goodwin's ground-breaking 2012 chapter on "Mechanisms and Chemical Reaction" called attention to how researchers in synthetic organic chemistry use mechanisms. Goodwin uses the term "mechanism" to signify a characterization or description of the course of a chemical reaction and not, as in much of the philosophical literature on mechanisms in biology, a natural system or the concept of such a system.[4] According to Goodwin, mechanisms are important in this field because of how they contribute to understanding, where "understanding" is the capacity to explain, predict and design organic reactions (2012, 309-310). On his view, mechanisms allow chemists to explain the outcomes of chemical reactions, which in organic chemistry often involves providing an answer to a contrastive why-question. The ability to provide such explanations in turn allows them to plan syntheses, to predict the outcomes of untried reactions, to solve problems that arise in the course of syntheses, and to exploit unexpected results.

Goodwin identifies a peculiarity in the way chemists use mechanisms, namely the fact that in general they do not pursue increasingly detailed and precise descriptions of them.[5]

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[4] On the concept of a mechanism as a natural system, see for example Machamer, Darden and Craver (2000), Glennan (2002), Woodward (2002), and Bechtel and Abrahamsen (2005).

[5] Thus, even if Kaplan's (2011) assertion that "[a]s one incorporates more mechanistically relevant details into the model [of the mechanism] … one correspondingly improves the

He attributes this peculiarity to the role of mechanisms as tools of inquiry in synthetic work. The relative approximation, and abstraction from detail, allow mechanistic information about known reactions to be applied in novel contexts. Goodwin notes that this portability of the mechanisms allows chemists to use them to explain new reactions. He also notes that mechanisms enable chemists to apply the knowledge obtained in prior mechanistic investigations to the optimization of the new cases, for example by indicating which features of the new reaction, such as the substrate or solvent, should be modified in order to render it synthetically useful (326-327).

Here, I propose to build on Goodwin's work by arguing that methodologists use mechanisms in organic chemistry as part of a strategy for providing evidence that a new method is reliable. A reliability claim in synthetic organic chemistry is a generalization about the method that involves both a prediction and a claim of invariance: that (i) in general, the reaction is likely to succeed under certain conditions, where "success" means that the product is effectively generated from the reactants; and (ii) the outcome is relatively insensitive to certain variations in the experimental and chemical details of the reaction. The invariance claim is especially important for dealing with the methodologist's dilemma, for it supports

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quality of the explanation" (347) is true, mechanistic investigations in chemistry do not seem to be guided primarily by the desideratum of incorporating ever more details into the characterizations of chemical reactions. See also Kaplan and Craver (2011, 613) for further elaboration of the view that the explanatory force of a mechanistic model is enhanced by increasing the model's level of relevant detail. It should be noted that, unlike Kaplan and Craver, my purpose in this paper is not to offer a theory of explanation, but to study the pragmatics of extrapolation in an applied science.

the broad applicability of the method. The mechanism allows empirical and theoretical evidence to be marshaled for a reliability claim in ways that complement the evidence provided by the substrate scope study. I identify two evidential strategies based on mechanisms that support these reliability claims, an empirical strategy and a theoretical one. Both support reliability claims by using mechanisms to bridge different reactions. In the empirical strategy, the bridging allows indirect empirical support to be marshalled, both for the prediction of a reaction, and the claim that the outcome is relatively insensitive to variations in the experimental and chemical details of the reaction. The theoretical strategy supports reliability claims by, on the one hand, identifying features of the reaction process that should be uniform across its instances and that determine its outcome, and on the other, identifying other features which can vary without significantly affecting the outcome. These two strategies allow chemists to supplement the information deficit created by the methodologist's dilemma by supporting generalization beyond the substrate scope study.

This article is intended to be a contribution to both the philosophy of chemistry and to general philosophical reflection on the nature of research in the applied sciences. It is organized as follows. In Section 2, I describe Goodwin's account of mechanisms in organic chemistry in more detail. In Section 3, I describe features of synthetic methodology reports that are important for understanding my arguments, using an example from catalysis research for illustration. In Section 4, I describe the two evidential strategies mentioned above. I also relate these strategies to Norton's (2003) "material theory of induction" on the one hand, and to the "common features accounts" of explanation identified by Batterman and Rice (2014) on the other. Section 5 compares the use of mechanisms to bridge reactions to Levy and

Bechtel's (2013) discussion of connectivity models in biology. I present concluding remarks in Section 6.

2. Goodwin on Mechanisms in Organic Chemistry. Goodwin (2012) identifies two senses of mechanism that arise frequently in organic chemistry. A mechanism in the "thick" sense is a complete characterization of the dynamic and continuous process of transforming a set of reactant molecules into a set of product molecules (310). Such a mechanism traces out the position of all the atoms of a set of molecules during the course of a reaction, and correlates these positions to the potential energy of the system (figure 1). On the other hand, a mechanism in the "thin" sense is a discrete characterization of a chemical transformation as a sequence of steps from reactants to products (310). Two features of thin mechanisms are especially noteworthy. First, usually only the important structures are shown, and these structures typically include stable intermediates as well as transition states. Second, each step is characterized in terms of a standard orientation and geometry of the reacting molecules, which allows plausible inferences to be made concerning the approximate trajectories and geometries of particular reactions. For example, the bimolecular nucleophilic substitution (S_N2) reaction is thought to proceed by way of a transition state with the incoming nucleophile and outgoing leaving group both partially bonded to the reactive carbon center. The nucleophile, reaction center and leaving group are arranged in a roughly trigonal bipyramidal geometry (figure 1).[6] Thin mechanisms are more abstract than thick ones

[6] A "nucleophile" is a molecule with a lone pair of electrons available for bonding. In the S_N2 reaction, one nucleophile, "Br^-" in the example of figure 1c, is displaced by another ("HO^-" in the figure) at the central carbon. The reaction is "bimolecular" because two reactant

because they leave out more details, and they are approximate because they describe other details inexactly. It should be noted that for both thin and thick cases, the "mechanism" is a description of a chemical transformation, and not the natural system itself that is undergoing the transformation.[7]

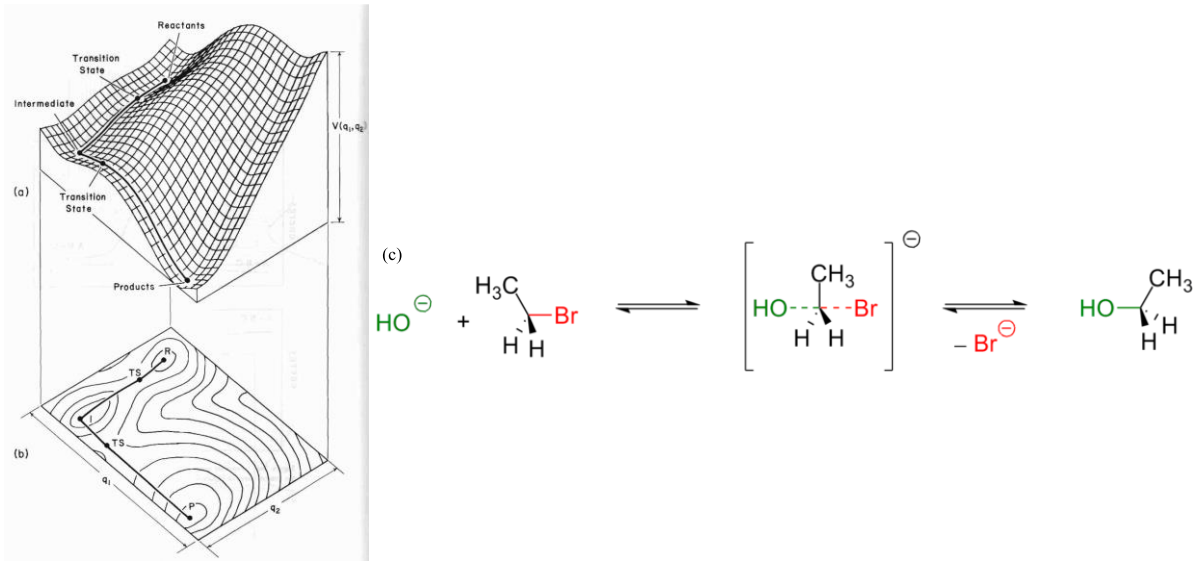

Figure 1. (a) and (b) represent a model thick reaction mechanism. (a) is a three-dimensional perspective and (b) is a contour map for a model chemical reaction. The solid line is the reaction path. From Steinfeld, Francisco, and Hase (1989, 222). (c) represents the thin mechanism for the nucleophilic substitution (S_N2) reaction between hydroxide and ethyl bromide. Note the trigonal bipyramidal geometry of the transition state (in brackets).

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molecules are involved in the rate-determining transition state (middle structure in figure 1c). Finally, a "trigonal bipyramid" is a geometry wherein one atom is at the center and 5 other atoms are at the corners of a triangular bipyramid.

[7] Throughout this paper, I will use the term "mechanism" in the sense of a "description of a chemical transformation" unless otherwise noted.

According to Goodwin, the main function of mechanistic investigations in organic chemistry is to support the goal of total synthesis (2012, 322-323). A total synthesis in contemporary chemistry is the laboratory synthesis of a target compound from simple, commercially available starting materials. Mechanistic investigations support synthesis design, synthesis execution, and reaction development. For example, in synthesis design chemists evaluate proposed synthetic routes by using prior knowledge about the mechanism of the reactions and the structures of the intermediates. Such knowledge allows chemists to decide which routes should be attempted in the laboratory. Mechanistic information is also useful during the execution phase, for when a step fails, being able to explain the failure is a useful first step in addressing the problem. Furthermore, synthesis often leads to the discovery of novel, synthetically useful reactions, and a mechanism-based explanation of the novel reaction may permit one to predict how likely to succeed it will be in new cases.

Goodwin argues that the two types of mechanism serve different functions with respect to the goal of supporting synthesis. Thick mechanisms serve as a conceptual device for bringing thermodynamic and statistical models to bear in relating the principal experimental facts of organic chemistry—the rates and product distributions of chemical reactions—to relative energy differences represented on a potential energy surface (2012, 312).[8] The device provides a theoretical background structure that enables explanation. In organic chemistry, explanation often takes the form of an answer to a contrastive why-question, for example why one reaction pathway is more favorable than another, or why one

[8] The potential surface itself is derived from either molecular quantum mechanical calculations using the Born-Oppenheimer approximation or from classical molecular mechanics models.

product distribution is observed rather than another. Such questions can be answered by making assertions about the thick mechanism (Goodwin 2003).

Goodwin notes that in most cases, however, the two features of thin mechanism mentioned at the beginning of this section are sufficient for giving explanations or predictions of the sorts of features of reactions that organic chemists are interested in. First, the structural information they convey is important because it allows the chemist to explain or predict the relative energies of the intermediates in terms of the structures. The energy differences can then be used to infer observable features of chemical reactions, such as relative rates and product distributions.

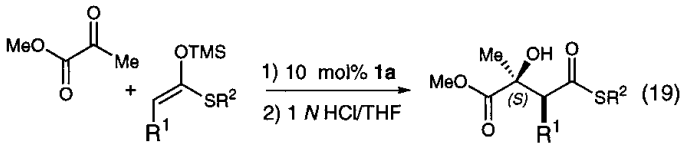
Second, the analysis of a reaction into steps allows complex structural changes to be decomposed into a sequence of standard small changes. Standardization allows prior mechanistic knowledge to be brought to bear in particular cases. This information in turn helps the chemist predict what structural features will make a difference to the observable features of the reaction.

Goodwin considers it "useful, and not too misleading, to regard the principal goal of organic chemistry to be the creation (and/or optimization) of total syntheses of novel compounds" (322). He therefore focuses on how mechanisms support explanation and prediction in total synthesis. The activity of total synthesis, however, presupposes that reliable methods be available for creation and optimization. In consequence, synthetic methodologists occupy an important position in the division of labor of modern organic chemistry. While explanation and prediction are, of course, important in methodology as well, methodologists have the specific task of providing widely applicable and synthetically

useful methods (Collins and Glorius 2013, 597). In the next two sections, I will describe how mechanisms support that task.

3. An Example of Research Results in Synthetic Methodology. The result of synthetic methodology research is, in large part, the knowledge of reaction conditions, reaction rates and product distributions that is acquired in learning how to synthesize a class of compounds in a novel way. Methodological reports in organic chemistry are centered around a general equation or "reaction scheme" relating a set of starting materials to the products of the reaction (figure 2). Usually, only the overall transformation is shown; mechanistic information is omitted. The table also provides information about the reaction conditions, completion times, product distribution and scope. In the equation, parts of the starting materials and products are represented as variables such as "R^1" and "R^2". The entries in the table show the results for instances of the reaction, where the values of the variables are specified. The experimental section of the report contains procedures for reproducing the experiments as well as the experimental data.

Table 9. Catalyzed Enantioselective Aldol Reactions between Methyl Pyruvate and Representative Enolsilanes (eq 19)[a]



entry	solvent	R^1	R^2	enolsilane geometry[b]	time/ T (°C)	*syn:anti*[c]	ee[c] %	yield %
1	CH_2Cl_2	Me	^{t}Bu	(*Z*)	8 h/-78	94:6	96	96
2	THF	Me	^{t}Bu	(*Z*)	1 d/-78	90:10	93	93
3	CH_2Cl_2	Me	^{t}Bu	(*E*)	1 d/-78	95:5	98	90[d]
4	**THF**	**Me**	**^{t}Bu**	**(*E*)**	2 d/-78	**97:3**	**99**	**88**[d]
5	CH_2Cl_2	Me	Et	(*Z*)	4 h/-78	90:10	95	95
6	THF	Me	Et	(*Z*)	1 h/-78	94:6	93	90
7	**CH_2Cl_2**	**Me**	**Et**	**(*E*)**	2 h/-78	**98:2**	**98**	**78(93)**[e]
8	**THF**	**Me**	**Et**	**(*E*)**	2 h/-78	**98:2**	**98**	**91**
9	CH_2Cl_2	^{i}Bu	^{t}Bu	(*Z*)	2 d/-78	93:7	97[f]	58
10	**CH_2Cl_2**	**^{i}Bu**	**Et**	**(*Z*)**	1 d/-78	**90:10**[f]	**93**[f]	**88**
11	CH_2Cl_2	^{i}Pr	^{t}Bu	(*Z*)	1 d/rt	66:34[f]	97	71[g,h]
12	**CH_2Cl_2**	**^{i}Pr**	**Et**	**(*Z*)**	12 h/-50	**90:10**	**99**	**80**[h]

Figure 2. A typical reaction scheme with an accompanying table of results. The chemical formula of catalyst **1a** is shown in figure 3 below. Source: Evans et al. (1999a, 691).

In the article from which the table in figure 2 is taken, a mechanism is proposed for the reaction shown above the table (figure 3). This is common practice in methodology reports. The mechanism may be presented with more or less detail, as the contrast between the very general mechanism in figure 3b and the more detailed one of figure 3a illustrates. The evidence for the mechanism includes studies of solvent and substituent effects, X-ray crystallographic structures, and theoretical calculations. Each step in the mechanism is characterized by a term—complexation, addition, silyl transfer and decomplexation—that is a short-hand telling the chemist which functional groups, of the molecules drawn, are involved and how they are interacting. For example, the step labeled as "complexation" in the diagram means that methyl pyruvate (top right structure) bonds to the metal atom (copper) of catalyst **1**. This mechanism may be used to explain the results displayed in the

table, and to predict new instances of the reaction. Yet it is also true that none of the results displayed in the table would have to be discarded were the mechanism to be found inaccurate, for the tabulated results are ascertained by independent measurement techniques such as weighing and spectroscopy.

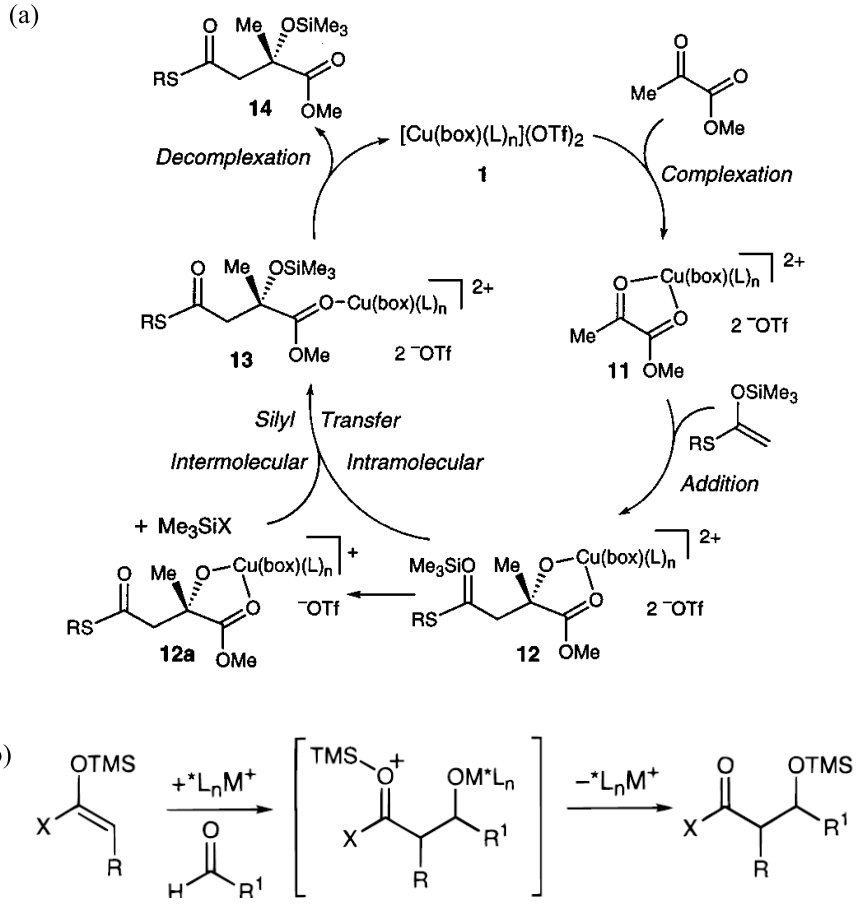


Figure 3. (a) The mechanism proposed for the reaction in figure 2. The catalyst **1a** of figure 2 is a variant of the copper species **1** shown here. Source: Evans et al. (1999a, 689). (b) A general mechanism for the type of aldol reaction depicted in (a). Source: Evans et al. (1999b, 669).

On the other hand, the aim of such research is not simply the entries in the table, which are of limited interest in themselves. The caption above the table in the figure says that

the cases are "representative," which means that we are to view them as evidence supporting the application of the reaction conditions to an indefinite number of cases with different values of R^1 and R^2. The number of such cases is indefinite because it is limited only by the number of energetically-stable structures, possessing the relevant features, that humans can design. It is worth noting that the structures are relatively simple, and that R^1 and R^2 only have five values (three for R^1 and two for R^2). Given that we are only provided with 12 simple test cases, and that there are an indefinite number of untested ones, on what grounds are we to trust that the range of application of the reaction extends beyond the observed cases? That answering this question is a live problem for chemists is illustrated by the complaint of Collins and Glorius (2015, 619) that

> [s]electing suitable protocols to transform a novel compound is not trivial, particularly when we consider new synthetic methods. We are often forced to make qualitative judgments based on the data available from a single substrate scope [study], and if we are lucky, from an occasional application. Although our ability to predict the outcome of a reaction precisely is typically very poor and reactions often fail, in the absence of an effective alternative, this is the dominant practice of synthetic chemists.

Of course, if we can explain the observed cases by means of a mechanism, then we can predict that unobserved cases will proceed by way of a similar mechanism and therefore afford a similar outcome. On what grounds can we infer that the operation of the mechanism will be invariant to differences between the cases? In the next section, I will argue that mechanisms such as the one shown in figure 3 are part of the evidential case chemists make for the reliability of new methods.

4. The Role of Mechanisms in the Evidential Reasoning of Organic Chemists. What evidence is there that a transformation is reliable? In the process of reaction optimization, various parameters of the reaction will be varied in order to determine the range of conditions that will afford the desired results. Examples of such parameters are the solvent, the temperature, the concentration of the reaction partners and the presence of additives. That a transformation is reliable is supported by the extent to which the results remain invariant as these parameters are varied. It is also supported by the precision with which the results can be characterized. For example, a reaction is more reliable if its yield, when it is repeated, fluctuates within a range of 1% rather than 10%. As noted in the introduction, substrate scope is one of the most important forms of evidence for reliability. The more the structures of the molecules undergoing the transformation can be varied without significantly affecting the outcome, the more confident we can be that the method will work in new cases. Though methodology reports tend to focus on positive results, reliability can also be characterized negatively, by studying the conditions under which the transformation fails. For example, it is useful to know which functional groups and structural motifs are unstable under the reaction conditions, or which ones inhibit the reaction (Collins and Glorius 2015, 620). Claims of reliability can be strengthened by addressing concerns that unnoticed variables may make a difference to the outcome of the reaction. Reactions that are considered difficult to reproduce may be so precisely because of failure to pin down subtle factors making a difference to the reaction outcome.

I submit that another part of the evidence for reliability comes from the ability to explain the transformation by providing a mechanism for it. The mechanism shows that the

transformation is consistent with chemical theory. By doing so, the mechanism enables the empirical strategy for supporting reliability that I mentioned in the introduction. This strategy provides indirect evidence in a manner that resembles what Hempel (1966) calls "theoretical support" or support "from above." Theoretical support is support for a hypothesis, which for Hempel is a statement under test (1966, 19). This support comes from "more inclusive hypotheses or theories that imply the given one and have independent evidential support" (1966, 38). In the case at hand, the more inclusive hypothesis could be a standardized step or a general mechanism, which could be used to marshal indirect evidence that a special case of the step or mechanism occurs or could occur in an actual or proposed transformation. For example, in the mechanism shown in figure 3, the complexation step involves the formation of bonds between two of the oxygen atoms of methyl pyruvate with the copper atom of **1**. This is a special case of a standardized step in which Lewis bases (electron-pair donors) form bonds with Lewis acids (electron-pair acceptors). The research leading to the publication of the report in which the mechanism of figure 3a appears was in fact motivated largely by the prior knowledge that such steps occur (Evans et al. 1999b, 669-670).

To see how indirect evidence is marshaled, consider the table in figure 2 again. The equation above the table is what I will call a "reaction schema." It does not represent any particular reaction, but rather represents parts of the molecules involved as variables (R^1 and R^2). The table entries represent observed reactions, having specific values of the variables, that instantiate the reaction schema. The reaction schema and its instances are proposed to occur by way of the sequence of steps described in the corresponding "mechanism schema" of figure 3a. I use the term "mechanism schema" in a sense strictly analogous to that of "reaction schema," as a mechanism in which parts of the molecules are represented as

variables.[9] Labeling this schema as M_1, the reaction schema as R_1 (not to be confused with the variable R^1), and the instances as $r_1^{(1)}$, $r_1^{(2)}$, … , $r_1^{(n)}$, we can say that R_1 and hence $r_1^{(1)}$, $r_1^{(2)}$, … , $r_1^{(n)}$ can be derived from M_1. I use "derive" here to mean that the product can be shown to be produced from the starting materials by way of the sequence of steps described in the mechanism, as for example the mechanism in figure 3a shows how product **14** is produced from methyl pyruvate and **1**. The reaction instances can be derived from M_1 by way of mechanism instances $m_1^{(1)}$, $m_1^{(2)}$, … , $m_1^{(n)}$ that instantiate the mechanism schema for particular values of the variables.

A mechanism schema may itself be an instance of a more general mechanism schema, "GM." GM may be more general in the sense of having more variables, or in leaving out more details (both features are exhibited in figure 3b). GM may have known instances M_2, M_3, … , M_m in addition to M_1. To each M_i corresponds a reaction schema R_i and reaction instances $r_i^{(1)}$, … , $r_i^{(k)}$. The relations between GM, the mechanism schemata, the reaction schemata and the reaction instances may be represented as shown in figure 4:

[9] The term is also used by Machamer, Darden and Craver (2000), in their discussion of mechanisms in biology, to signify "a truncated abstract description of a mechanism that can be filled with descriptions of known component parts and activities" (15). Though my use of the term is similar to theirs, my argument does not depend on their analysis of mechanisms in biology.

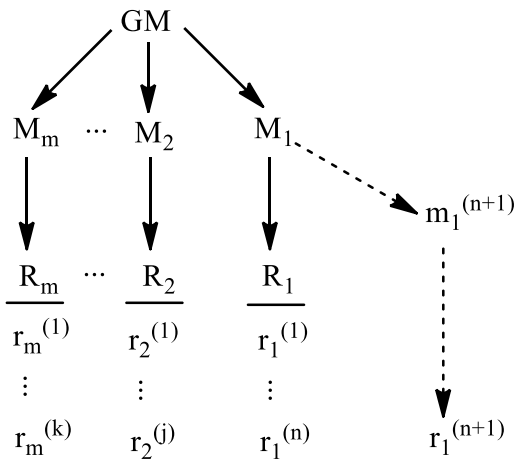


Figure 4. The relations between the general mechanism schema (GM), the mechanism schemata (M_i), the reaction schemata (R_i) and the reaction instances (r_i).

Let us further suppose that we are considering applying the method corresponding to reaction schema R_1 to a new case corresponding to instance $r_1^{(n+1)}$. What is our evidence for thinking the reaction will work in the new context? Part of the evidence will come from the observations $r_1^{(1)}, \ldots, r_1^{(n)}$ of R_1, that is, by performing a substrate scope study. If we know the mechanism schema M_1, however, we can derive $r_1^{(n+1)}$ from M_1, symbolized in figure 4 by the dashed arrows. If M_1 itself can be related to a more general mechanism schema, GM, the inductive base for the prediction can be broadened by relating $r_1^{(n+1)}$ to the observed instances of the general pattern of reactivity represented by $R_1, \ldots, R_m$ and $M_1, \ldots, M_m$. Without the bridging provided by GM, $r_1^{(n+1)}$ could be related to reaction schemata $R_2, \ldots, R_m$ only in virtue of its similarity, e.g., the similarity of the overall transformation and of the structures involved. Without the mechanistic bridging, it is unclear on what grounds similarity could support the extrapolation to $r_1^{(n+1)}$; the bridging, on the other hand, provides a principled reason why similarity should matter.

This strategy is particularly useful when the new context of application of $r_1^{(n+1)}$ is significantly different from the observed instances of R_1. For example, the original test cases (like those shown in figure 2) are often too simple to be very telling in a more complex system. Such a circumstance is quite common in total synthesis, where reactions are often applied to systems that are both significantly different from and much more complex than the original test cases. In such circumstances, additional empirical support for a proposed application of a method can be marshaled by relating the application to other reactions that share mechanistic features with the proposed reaction.[10]

The strategy does not require a complete mechanism. A single standardized step may suffice. A virtue of a standardized step is that it contains general features that are shared across the reaction schemata in which it occurs. For example, the "complexation" step shown in figure 3a was shown by the researchers to be a general feature of reactions involving bidentate ligands and a certain class of copper catalyst, allowing many different reaction types to be catalyzed in the same way (Evans and Johnson, 2000). The same step also occurs when other metals are substituted for copper (Evans, Masse and Wu, 2002). For these researchers, the generality of the complexation step was not just a conclusion of the research, but allowed them to successfully predict new reactions involving this step by appealing to accumulated evidence for complexation in known reactions (Evans et al. 1999b).

[10] Though space does not permit me to discuss it here, a good example of this reasoning at work is Layton, Morales and Shair's (2002) solution to a macrocyclization selectivity problem in the total synthesis of longithorone A. A helpful analysis of their solution is provided by Nicolaou and Snyder (2003, 469-473).

It should be noted that the evidential situation is more complex than is suggested by figure 4. The reaction instances provide evidence for the accuracy of the mechanism schemata merely by the ability of the latter to entail the instances. It is often the case, however, that more direct evidence is obtained for the mechanisms. Evidence that a proposed mechanism accurately characterizes how a reaction proceeds can be obtained by a variety of means, including the analysis of thermodynamic and kinetic data, studies of substituent effects, isotopic labeling, characterization of the reaction intermediates, studies of catalyst and solvent effects, and the study of the stereochemical course of the reaction.[11]

The bridging of different reaction schemata afforded by the general mechanism expands the inductive base for a method and in so doing supports the claim that a given method is likely to succeed under certain conditions. Furthermore, since the reactions so bridged differ both with regard to the structure of the reactants and to experimental conditions, the bridging supports the claim that the outcome of the process described by the mechanism is relatively insensitive to certain variations in the experimental and chemical details of the reaction. In short, the bridging supports the claim that the method is reliable.

So far I have only discussed the empirical strategy mentioned in the introduction, which works by increasing the empirical support for reliability. Reliability can also be supported by theoretical considerations. Theory, in the form of a mechanism-based explanation, can help identify properties of the reaction process that should be uniform across its instances and that determine its outcome. By explaining how the combination of a certain array of structural features with certain reaction conditions triggers a process that leads to a certain kind of outcome, we can identify the determining properties of the process. New

[11] See Carey and Sundberg (2000, ch. 4) for an overview of these techniques.

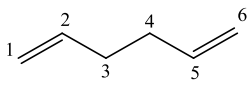
cases of the same combination will most likely be uniform in those properties. Theory can also help identify properties that do not significantly affect the outcome, such as functional groups that are inert to the reaction conditions. By the identification of properties that are relevant and irrelevant to the outcome, we can infer that the new cases will afford a similar outcome to the ones that have been tested. The more the relevant properties are able to determine a unique outcome, the more support there is for the claim that the process is reliable.

For example, consider the claim made by Nicolaou and Sorensen (1996, 214) that "[t]he anionic oxy-Cope rearrangement is among the most reliable processes for the synthesis of functionalized cyclodecanoid frameworks." The use of the term "cyclodecanoid framework," which signifies a generic ten-membered ring system capable of bearing any number of different functional groups, signals that the authors are making a claim about the range of application of a reaction. The anionic oxy-Cope rearrangement is a member of a family of rearrangements that includes the original Cope rearrangement and the related oxy-Cope rearrangement (figure 5).

Nicolaou and Sorensen's claim about the reliability of the anionic oxy-Cope rearrangement is supported by an argument based largely on mechanistic considerations, which I will now summarize. The Cope rearrangement itself is the thermally-induced rearrangement of the bonds of a 1,5-diene, as shown in figure 5a.[12] This rearrangement

[12] A 1,5-diene has a substructure bearing two carbon-carbon double bonds, in which the terminal carbon of one double bond is separated by three carbon atoms from the internal carbon of the other double bond, as illustrated here by 1,5-hexadiene:

produces an impressive structural transformation and moreover proceeds through a highly ordered six-membered transition state, structure II in figure 5a, that determines the stereochemical consequences of the reaction, that is, the relative disposition of the atoms in space. In figure 5, for example, the *cis/trans* geometry of the double bonds(s) formed in the reaction is determined by this transition state. The utility of this reaction is sometimes diminished, however, by an unfavorable equilibrium between the starting material and the product. In contrast, when a hydroxyl (OH) group is attached to the carbon skeleton, as in figure 5b, the reaction is more synthetically useful because the rearrangement is now driven thermodynamically by the further rearrangement of the immediate product, e.g., V, to an unsaturated ketone (e.g., VI). A significant rate enhancement may be achieved by conducting the oxy-Cope rearrangement in the presence of base. In this case, the reaction proceeds through a negatively charged (anionic) alkoxide species (VIII in figure 5c). Theoretical calculations suggest that the presence of the alkoxide might accelerate the process by weakening one of the carbon-carbon bonds involved in the rearrangement. The rate enhancement thus achieved allows the rearrangement to be induced at lower temperatures. The possibility of performing the reaction at lower temperatures is significant, for it suggests that more functional groups and structural motifs will survive the reaction conditions.



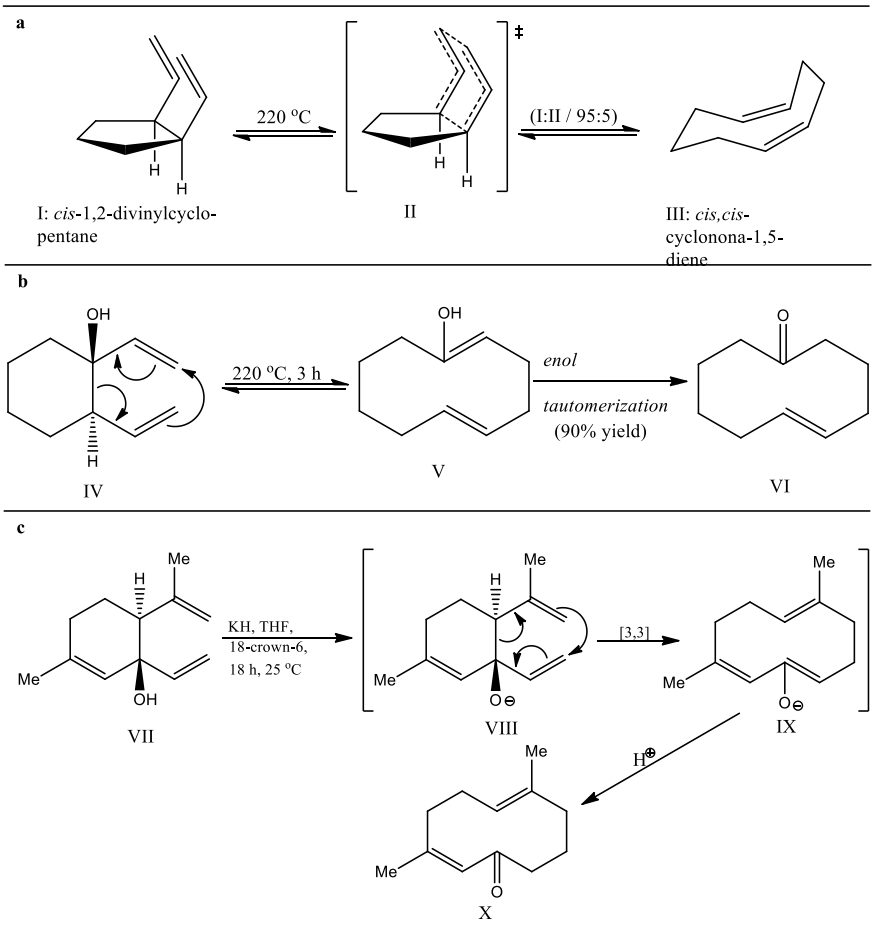


Figure 5. Representative Cope (a), oxy-Cope (b), and anionic oxy-Cope (c) rearrangements. A bold line represents a bond pointing out of the plane of the page, whereas a hashed line represents a bond pointing below the plane of the page. Adapted from the original in Nicolaou and Sorensen (1996, 213).

For Nicolaou and Sorensen, then, the reliability of the anionic oxy-Cope rearrangement is a consequence of its irreversibility, its predictable stereochemical consequences, and its accelerated rate relative to the oxy-Cope and Cope. The irreversibility entails that the equilibrium ratio of product to starting material will be great. This satisfies the first part of the reliability claim, as presented in the introduction: the transformation is likely

to succeed under certain conditions. The second part of the reliability claim, that the outcome is relatively insensitive to certain variations in the experimental and chemical details of the reaction, is supported by the following characteristics of the reaction. First, the emphasis on the order of the transition state, as opposed to the specific characteristics of the system in which it occurs, suggests that the stereochemical outcome will be relatively insensitive to compositional and structural variations among 1,5-dienes. Second, the low temperatures at which the rearrangement occurs strongly indicates that the experimental conditions will be tolerant of a wide variety of organic functional groups and structural motifs. For these reasons, conclude Nicolaou and Sorensen, the rearrangement could be successfully employed in W. C. Still's (1979) periplanone B synthesis.

If they had simply pointed to actual instances of this reaction to support its reliability, we would be entitled to ask how many instances are needed to accept it. Having identified the properties of the reaction process that determine its outcome, on the other hand, we can confidently infer that new instances will afford a similar outcome to the old because of the uniformity of those properties across instances, and the insensitivity of the outcome to other properties.

The theoretical strategy for dealing with the methodologist's dilemma is related to a problem in the philosophical literature on induction, the problem of enumerative induction. As Norton (2003) puts it, the problem is how to account for the fact that inferences such as the one from

1. "Some samples of the element bismuth melt at 271 ºC" to
2. "All samples of the element bismuth melt at 271 ºC"

are secure whereas inferences such as the one from

3. "Some samples of wax melt at 91 ºC" to
4. "All samples of wax melt at 91 ºC"

are fragile (649). There is no formal explanation of the difference, for both arguments have the same logical form and both are deductively invalid. Norton argues that the bismuth induction is secure (which means the conclusion is "most likely true" (651)) because of a fact about chemical elements, that "their samples are generally uniform in their physical properties" (651), of which melting point is one. Building on Norton's argument, Bogen (2011) claims that "epistemically prudent" commitments to the truth, the approximate truth, or the high probability of the truth of inductive generalizations of regularity phenomena, such as the melting point of bismuth, require commitment to hidden causal factors.

The methodologist's dilemma requires chemists to extrapolate from a limited data set. The use of mechanisms to support such extrapolations involves the recognition of a fact about the instances of a reaction, that their mechanisms have certain features in common. Furthermore, it seems plausible that mechanisms refer to causal factors, as I will discuss in the next section. In this regard, the use of mechanisms in organic chemistry is consonant with Norton's and Bogen's claims. Superficially at least, arguments for the reliability of a synthetic method do not have quite the same structure as the bismuth example, however.[13] Arguments like the bismuth example proceed from the observation that some individuals of a given type have a common property to the conclusion that all individuals of that type have

[13] I say "superficially" because inductions like the bismuth example require criteria distinguishing facts that are relevant from facts that are irrelevant to the matter of the induction.

that property. The inference is supported by a fact about the elements, which could involve a causal mechanism. In contrast, abstraction from differences between individuals (reactions) plays a more prominent role in arguments for the reliability of a synthetic method based on the theoretical strategy. These arguments assume that the details that distinguish the mechanism in one instance from the mechanism in other instances are irrelevant to the outcome of the reaction. For example, the S_N2 reaction illustrated in figure 1 always proceeds with inversion of the chirality or "handedness" of the substrates, regardless of differences among nucleophiles, the substitution pattern of the central carbon atom, or the precise bond angles and lengths of the transition state, and so it can be relied on to do so in new applications.

As a first approximation, mechanism-based arguments for the reliability of synthetic methods have the following basic structure:

5. A class of untested cases (e.g., 1,5-dienes beyond those involved in substrate scope studies) has in common with the tested cases certain features that determine the outcome of the reaction.
6. The details that distinguish the tested cases from the untested cases are unlikely to affect the outcome of the reaction.
7. Therefore, the reaction can be relied on to have a similar outcome in the untested cases as in the tested ones.

The argument depends on a combined appeal to common features and invariance to differences among cases. As stated in the introduction, it is not my purpose in this paper to offer a theory of explanation in chemistry, but to study how mechanism-based explanations help chemists deal with the methodologist's dilemma. Nevertheless, this combined appeal

raises the philosophically interesting question of how mechanism-based explanations in chemistry are related to certain explanatory models discussed in the the broader philosophical literature on explanation. In my view, mechanism-based explanations in organic chemistry bear an interesting resemblance to what Batterman and Rice (2014) have identified as "common features accounts" of explanatory models. Acccording to Batterman and Rice, these accounts hold that "a model is explanatory because it has certain relevant features in common with the model's target system(s)" (2014, 351). The theoretical strategy I have described above relies on the uniformity of properties across instances, and so appears to depend on common features highlighted by mechanism-based explanations, such as a common transition state structure. The strategy also requires invariance among instances of a reaction, which requires identifying the details that distinguish the systems but that are irrelevant. In the example of the anionic oxy-Cope rearrangement, these details were identified by substrate scope studies and also by mechanistic considerations such as the reaction rate. Since the reaction proceeds at a fast rate and therefore can be performed at low temperature, differences in functional groups and structural motifs are, to some extent, irrelevant to the outcome. The use of mechanism-based explanations in the theoretical strategy may thus be an instance of what Strevens' (2009) describes as the distinguishing of those causal factors that are difference-makers from those that are not, or perhaps of distinguishing what Woodward (2003) calls "contributing causes" from those factors that do not contribute to the outcome of the reaction. The question as to which account of explanation, among the many in the literature, is most appropriate for mechanism-based explanations in chemistry is well worth further study.

5. On Mechanisms-Based Unification in Chemistry and Biology. Much of the philosophical literature on mechanisms in science has focused on questions such as the conceptual analysis of mechanisms, or how mechanistic explanations unify the scientific understanding of the world.[14] The question I have been concerned with in this paper is how mechanisms support claims for the reliability of novel methods. Nevertheless, given the important role of bridging in my account, some comments are in order concerning how my account relates to the covering-law account of explanation, from which the philosophical discourse on explanatory unification derives (Kitcher 1981).

I have argued that mechanisms help chemists deal with the methodologist's dilemma by bridging different reactions or, what is much the same in this context, by unifying them. My reference to Hempel in Section 4, and my talk there of "deriving" reaction instances or schemata from mechanism instances or schemata, may make it look as if I am appealing to a covering-law model of explanation and prediction, according to which all the different instances of a reaction would be subsumed under a general law. To the contrary, I think the situation in organic chemistry may be similar to that of areas in biology where connectivity models are used, as described by Levy and Bechtel (2013). These authors focus on how biologists use such models to explain the regulation of gene expression. According to Levy and Bechtel, biologists use graph-theoretic models to represent the organization of the mechanisms of regulation at a high level of abstraction, that is, to abstract from many of the

[14] On the conceptual analysis of mechanisms, see for example Machamer, Darden and Craver (2000), Glennan (2002), Woodward (2002), Bechtel and Abrahamsen (2005). On the question of how mechanistic explanations unify scientific understanding, see for example Glennan (2002) and Craver (2007).

specific properties of the parts and operations occurring in regulatory mechanisms.[15] What is left after the process of abstraction is a model that represents the basic organizational features of the mechanism. The regulation of gene expression is explained as an effect of these features. Because the models are abstract, they tend to be general and so have been used to explain why the same behavior occurs in all the mechanisms that have that basic organization (258). Though Levy and Bechtel concede that these mechanistic explanation are lawlike, they deny that the models explain in virtue of deriving particular cases from laws. Rather, they maintain that these general models explain in virtue of pointing to a common causal structure underlying the different mechanisms that have this basic organization (259).

The comparison with Levy and Bechtel's analysis of connectivity models in biology raises the question of whether mechanisms in chemistry bridge different reactions in virtue of pointing to a common causal structure. Mechanisms such as the one shown in figure 3a seem to point to elements of causal structures. The processes signified by the terms in the diagram—complexation, addition, silyl transfer, decomplexation—may plausibly be interpreted as bonding activities. According to Machamer, Darden, and Craver (2000, 6, 14), interpreting them thus would qualify these processes as causes. On the other hand, chemists often appeal to structural features, such as the one depicted by the transition state structure shown in figures 5a and 1c, to explain observable features of reactions. In the example of the anionic oxy-Cope rearrangement discussed in the previous section, Nicolaou and Sorensen seem to attribute the stereochemical outcome to the degree of order of the transition state, not the bonding processes causing that order. But as noted in Section 2, structural analyses in

[15] Levy and Bechtel use "mechanism" to signify a natural system that is organized so as to cause some effect or behavior.

chemistry are usually related to relative energy differences between alternative structures, and hence differences in bonding, though the relation may not always be made explicit.

Prima facie, then, a good case can be made for a positive answer to the question posed at the beginning of the last paragraph. If that is indeed the correct answer, then the bridging that supports the reliability of novel methods should not be viewed as the subsumption of particular cases under a law, but rather as bridging by pointing to a common (causal) structure.

6. Conclusion. A widely-shared presupposition of philosophical reflection on mechanisms in biology has been that the fundamental aim of discovering mechanisms in nature, and describing them, is explanation. Wimsatt (1972, 67) observes, for example, that "at least in biology, most scientists see their work as explaining types of phenomena by discovering mechanisms." Machamer, Darden and Craver begin their seminal (2000) paper by remarking that "[i]n many fields of science what is taken to be a satisfactory explanation requires providing a description of a mechanism" (1). In the applied sciences, however, an aim that is at least as important as explanation is to obtain knowledge of reliable methods for the manipulation, control and design of aspects of the world. This aim presents a special challenge for marshalling evidence, which I have called the methodologist's dilemma. Contrary to a commonplace view of scientific testing, it is not sufficient, to meet this challenge, to deduce observable consequences and check for agreement with observation. In this paper I have argued that mechanisms in organic chemistry support this aim by fulfilling a distinct evidential function, that of supplementing the information gap created by the methodologist's dilemma. Applied fields like organic chemistry thus offer an opportunity to think about mechanisms in a different way—not just as enabling explanation, but as

alternative means for assessing the reliability of methods when direct empirical information is wanting.[16]

[16] An example outside of organic chemistry of the use of mechanisms to support applications is target-based drug discovery, which focuses on using drugs to intervene on the mode of action of a target enzyme (Sams-Dodd 2013). Another example is David Lewis' (2006, 2009) proposal to use the disease process of schizophrenia as the basis for drug and treatment design. His idea is to look for molecular changes, conserved across individuals, in critical cellular pathways that mediate clinical features of the disease. I thank Jim Bogen for this example.

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