

# Catalysis of Organic Reactions by Inorganic Solids

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The methodology of organic synthesis has leaped forward during the last 15 years. Detailed study of these advances is out of place here. Suffice it to say that organic chemistry has received a powerful pull from the great strides of organometallic chemistry. I shall only mention Wilkinson's soluble hydrogenation catalysts,<sup>1</sup> Collman's reagent,<sup>2</sup> McMurry's carbonyl coupling reaction<sup>3</sup> as examples. It has also drawn upon use of heteroatoms below the first two periods: silicon with silyl enol ethers,<sup>4</sup> or organoselenium reagents.<sup>5</sup>

Organic synthesis of fine chemicals also stands much to gain from heterogeneous catalysis. This Account purports to give the underlying rationale, together with examples from this laboratory of important organic reactions markedly improved in this way.

## Heterogeneous Catalysis, a Major Resource for Chemical Industry

Examples of major industrial processes relying upon heterogeneous catalysis<sup>6</sup> include partial oxidations such as those of naphthalene or *o*-xylene into phthalic anhydride (supported V<sub>2</sub>O<sub>5</sub> catalysts), that of *p*-xylene into terephthalic acid, formation of acrylonitrile from propene, ammonia, and oxygen (mixed oxides such as tin-antimony or bismuth phosphomolybdate are catalysts).<sup>7,8</sup> Oxidations of ammonia into nitric acid (over 10% Rh-90% Pt catalysts) and of sulfur dioxide into sulfuric acid (catalyzed by V<sub>2</sub>O<sub>5</sub> promoted with K<sub>2</sub>SO<sub>4</sub>) are also assisted by heterogeneous catalysis.<sup>9</sup>

The food industry "hardens" fats by Raney nickel hydrogenation. The petrochemical industry steam-reforms hydrocarbons to produce hydrogen, or to provide hydrogen-carbon monoxide mixtures, using nickel-supported catalysis.<sup>10</sup> The Ziegler-Natta polymerization of alkenes and dienes is performed with titanium-triethylaluminum catalysis.<sup>11</sup> Ammonia synthesis is catalyzed by metallic iron stabilized by alumina and in the presence of potassium ions,<sup>12</sup> or by ruthenium metal supported on carbon and promoted by metallic alkali.<sup>13</sup>

The catalytic cracking of hydrocarbons, after being performed on natural and on modified clay minerals, has gained greatly in selectivity by the introduction of zeolite catalysts in 1964.<sup>14</sup> The synthesis of methanol (CO + 2H<sub>2</sub> = CH<sub>3</sub>OH) is done with copper-containing catalysts.<sup>15</sup> And the Mobil methanol-to-gasoline process relies on catalysis by HZSM-5 zeolites.<sup>14</sup> Quite a few other instances could be adduced. Clearly, the methodology of organic synthesis stands to gain by trying to emulate the reliance of the chemical industry upon heterogeneous catalysis.

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## Chemisorption Is Replete with Unanswered Questions

Interactions of molecules with surfaces of inorganic solids are basic to heterogeneous catalysis.<sup>16</sup> Yet the modest level of understanding that has been gained so far can (unfortunately) be summarized in just a few words: adsorption of atoms onto well-defined surfaces of metallic solids or of a few metallic oxides.<sup>17</sup> By contrast, *molecular* adsorption continues to be poorly understood. It obeys laws which cannot be extrapolated simply from the behavior of atoms.<sup>18</sup> Whether one is interested in chemisorption, in bond dissociation, or in the mechanisms for lateral diffusion and desorption, many a mystery lingers on.

## Layered vs. Porous Solids: the Fractal Dimension

Perhaps the greatest inducement to adsorb organic reactants onto the surface of an inorganic solid is the attendant reduction in the dimensionality of reaction space. This factor can best be understood in reference to the classical mathematical problem<sup>19</sup> of the drunkard: in three-dimensional space, even given infinite time, a person who has had too many Martinis has a 0.34 probability<sup>20</sup> of finding his or her bed. However, if help

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**Table I**  
The Fractional (or Fractal, See Text) Dimension  $D$  for  
Some Finely Divided Solids<sup>26</sup>

adsorbent	$D$
crushed glass	2.35
carbon black	2.25
charcoal	2.78
increasingly activated charcoals	3.03
	2.30
	1.94
silica gel	2.94

is given, by reducing the dimensionality of the problem, both in two-dimensional and in one-dimensional space the probability of the random walk ultimately being successful (homecoming) jumps to unity.<sup>20</sup>

To give another suggestive image for greatly accelerated encounters between reactive partners on a surface as compared to within a volume, if for the reaction  $A + B = AB$  to occur  $A$  has to wander around till it finds a  $B$ -occupied cell within a Euclidean lattice, it will take about 30 times less (a factor  $2402/80$ ) in two dimensions than in three dimensions, for an average distance of 10 cells: the number of neighbors, of order  $n$ , on Euclidean lattices of dimension  $d$ , is given by  $F(n,d) = (2n + 1)^d - (2n - 1)^d$ . In other words, as first pointed out by Adam and Delbrück,<sup>22</sup> the key reason for enzyme efficiency is that a diffusing particle finds a fixed target much more rapidly in a diffusion space of dimension  $d = 2$  than for  $d = 3$ . This obtains because most points of diffusion space are visited infinitely often for  $d = 1$ , essentially once for  $d = 2$ , and never for  $d = 3$ . Hence, diffusion restricted to  $d = 1,2$  dimensions should lead to increased rates for encounter of reactants and therefore it should cause shorter reaction times.<sup>23</sup> At the microscopic scale, in the range from a few angstroms to a few micrometers, many solids have *self-similar* surfaces, i.e., whatever the magnification of a microscope their texture would look the same. This feature, shared with many other properties of natural objects, has led IBM mathematician Benoît Mandelbrot to define the *fractal* dimension  $D$ .<sup>24</sup> This is the effective dimension, usually not an integer, of an irregular, rough curve or surface.<sup>25</sup> Thus, the fractal dimension  $D$  for the surfaces of porous solids, as determined from Langmuir-type monolayer adsorption isotherms, has values between 2 and 3 (Table I).<sup>26</sup>

Hence the conclusion that layered solids such as graphite or clays, with  $D \sim 2$  should be superior (from a reaction kinetics point of view) as diffusional supports to porous solids with  $D \sim 3$  such as charcoal or silica gel (Table I). Such a simple-minded inference is borne out by good experimental evidence: Taylor et al.<sup>27</sup> have shown that the oxythallation of acetophenone into the

methyl ester of phenylacetic acid occurs faster and with higher yields on lamellar than on porous, spongy surfaces.

However, I have greatly oversimplified the picture. A key aspect of heterogeneous catalysis is the presence of active sites in the solid for which there are no equivalents in the reference reaction run in the absence of a support; then a high  $D$  surface, as provided by a finely divided solid, is often optimal.<sup>28,29</sup>

Catalysis of organic reactions can usefully draw upon these principles. Well it might: contrary to the myth, organic reactions are not that easy! Often they require rather drastic conditions. To take just the example of facile, symmetry-allowed thermal processes, the Diels-Alder reaction dimerizing 1,3-cyclohexadiene demands heating at 200 °C for 20 h;<sup>30</sup> the Cope rearrangement occurs typically in the high temperature range of 150–200 °C<sup>31</sup> and likewise the Claisen rearrangement occurs in the high temperature range of 150–225 °C.<sup>32</sup>

The one class of undisputably easy organic reactions is the metabolic processes which, as a rule, are fast, quantitative, and stereospecific at 37 °C. Enzymes are responsible for such a high efficiency. They bring to their task this constraint of the substrate to a surface, an advantage first pointed out by Adam and Delbrück<sup>22</sup> as indicated above.

### Selection of Reactions Ripe for Improvement

Tradition crowns those organic reactions deemed important: the name reactions. Among these, carbon-carbon bond forming and ring forming transformations stand at the leading edge for organic synthesis. However, even venerable reactions such as Robinson annulation<sup>33</sup> can be surprisingly inefficient. Often fraught with multiple secondary products, such textbook classics will go on display only at rather high temperatures (80–120 °C) and/or at high pressures (>20 atm), with mediocre isolated yields (<50%), and with poor selectivities (chemi-, regio-, stereo-, enantio-).

The need for overhaul is obvious. And *all* these parameters call for improvement. Catalysis of organic reactions has been defined operationally by the lowering of the reaction temperature, or temperature range.<sup>34</sup> This is too restrictive.

### The Friedel-Crafts Reaction

The carbocationic graft of an alkyl group onto an aromatic ring requires an acidic medium. Organic chemists are unfamiliar with solid acids: they prefer homogeneous over heterogeneous reaction conditions: and, as another probable factor, pH is defined for aqueous solutions. Yet Olah in his monograph<sup>35</sup> had the foresight to predict that inorganic solids would be

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put to advantage as catalysts for the Friedel-Crafts reaction.

It is not widely known, or sufficiently appreciated, that natural montmorillonite clays have surface acidities, as measured by the Hammett  $H_0$  acidity function ranging from 1.5 to -3. Yet more interesting: simple washing with mineral acid—exchanging the interlayer  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{NH}_4^+$ , etc. cations with protons—brings their surface acidity to  $H_0$  values between -5.6 and -8.<sup>36</sup> By this token, these clays show (surface) acidities in-between the acidities of nitric and concentrated sulfuric acid!

The conjunction of a layered structure, making for increased diffusional encounters of reactants, and of such high acidities appeared to us as extremely promising. Indeed quite a few carbocationic processes occur readily on montmorillonite clays.<sup>37</sup> We elected adamantane as a probe, to ascertain if we could induce Friedel-Crafts type substitutions, using an acidic clay catalyst, *directly on the hydrocarbon* RH, thus bypassing the usual requirement of halide RX or acid halide RCOX as starting material.<sup>35</sup>

The catalyst was prepared by depositing ferric chloride, or by exchanging the interstitial cations with  $\text{Fe}^{3+}$  ions, on the commercial K10 acidic clay. This is a modified bentonite, used industrially as a catalyst (hydrocarbon cracking) and it is thus a well-defined, invariant, and quite reliable material. We figured that the Lewis acidic ferric ions might boost the Brønsted activity of coordinated hydroxyl groups. In order to activate yet further our  $\text{Fe(III)}$ -doped catalyst (and so that it would remain highly acidic), we used strongly dehydrating conditions: azeotropic distillation using a reverse Dean-Stark trap.

Chlorination of adamantane by carbon tetrachloride is rather easy in the presence of a Lewis acid such as aluminum chloride.<sup>38</sup> We found likewise that we could obtain good yields of the 1-adamantyl chloride or of the 1,3-adamantyl dichloride with the K10 or the  $\text{Fe(III)}$ -K10 catalyst, respectively, in refluxing carbon tetrachloride.<sup>39</sup> This suggested the presence of the 1-adamantyl tertiary cation under our reaction conditions. Indeed, determination by deuterium NMR of the protium/deuterium distribution in the recovered deuterium-enriched starting material<sup>40</sup> showed hydride abstraction, prior to formation of the chloro-substituted products.<sup>41</sup>

This success led us to attempt arylation of adamantane in the presence of K10- $\text{Fe(III)}$ , by changing from carbon tetrachloride to an aromatic solvent. Indeed, with benzene as solvent, we obtained good yields of 1-phenyl- and of 1,3-diphenyladamantane.<sup>39</sup> Normal Friedel-Crafts processes favor toluene over benzene, the

**Table II**  
Distribution of Products in Nitration of Phenol

	method		
	classical procedure <sup>42</sup>	Kagan et al. <sup>47,a</sup>	"clayfen"
ortho, %	36	55	40.5
para, %	25	26	50
overall yield, %	61	81	90.5
starting material, %	7	8	0
ortho/para	1.44	2.1	0.81

<sup>a</sup> Using lanthanum nitrate as catalyst.

**Table III**  
Role of the Montmorillonite Clay Support

	method		
	$\text{Fe(NO}_3)_3$ unsupported in THF	$\text{Fe(NO}_3)_3$ unsupported in PhMe	"clayfen"
ortho, %	35	23	40.5
para, %	33	28	50
overall yield, %	68	51	90.5
starting material, %	<10	15	0
ortho/para	1.1	0.82	0.81

**Table IV**  
Nitration of Various Phenols Using "Clayfen"

phenol	nitration		
	ortho, %	para, %	conditions
-	39	41	ether, 20 h
4- $\text{CH}_3$	58	-	ether, 20 h
3- $\text{CH}_3$	20	34	ether, 20 h
4-Cl	88	-	ether, 20 h
4-F	69	-	toluene, 5 h
$\beta$ -naphthol	63	-	THF, 2 h
4- $t\text{-C}_4\text{H}_9$	92	-	toluene, 1.5 h
3-OH	58	-	ether, 2 h
4-CHO	93	-	toluene, 72 h
estrone	55	-	toluene, 24 h

selectivity varies between a factor of 1.6 and 16.<sup>35</sup> Under our conditions, with an equimolar benzene-toluene solvent mixture, the three monosubstituted (phenyl, *m*-, and *p*-tolyl) and the six disubstituted products formed in *purely statistical* distribution.<sup>39</sup> This surprising finding could have been the index to a radical rather than a cationic pathway. But we failed to find any 2-aryl-substituted product, as would form profusely in a free-radical reaction. Clearly an interesting mechanism is at play, due to the surface reaction. Presumably, an adamantyl cation appears in a "hot" enough state for it to attack indiscriminately *any* aromatic neighboring molecule at *any* position except at the sterically excluded *ortho* position of toluene.

### Nitration of Phenols

Nitration of phenols is performed classically with mixtures of nitric and sulfuric acids.<sup>42</sup> The overall yield is only a modest 61% in the nitration of phenol. And the normal *ortho*- and *para*-substituted derivatives are accompanied by the meta isomer, and also by products of polynitration.

We opted for a clay-supported metallic nitrate in order to improve significantly this reaction. Why a

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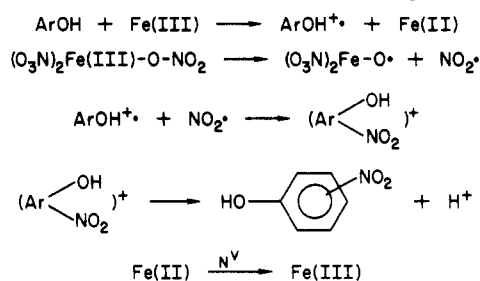
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clay? Because phenols generate radicals and radical cations upon contact with clays, the oxidant being a transition metal such as iron normally present in natural clays in low amounts.<sup>41</sup> Moreover, an attractive alternative to both the nitrosonium (NO<sup>+</sup>) and the nitronium (NO<sub>2</sub><sup>+</sup>) ion pathways for electrophilic aromatic nitration is the radical cation route championed by Perrin.<sup>44</sup> A further argument for use of a clay is the high surface acidity of montmorillonites, already mentioned. Hence, we activated ferric nitrate by dehydration and deposited the highly reactive species thus generated on the quite acidic K10 catalyst (H<sub>0</sub> ~ -8).

This clay-supported ferric nitrate ("clayfen" for short<sup>46</sup>) proved its worth for phenol nitration (Table II). Clearly the inorganic layered solid is important (Table III). In this manner, we could nitrate a variety of phenols with exclusive ortho, para mononitration (Table IV).

It should be noted that in estrone nitration—a process of importance to the pharmaceutical industry, as the gateway to various estrogenic drugs—the yield of 55% (Table IV) not only improved significantly<sup>48</sup> upon the best isolated yields achieved just a few months earlier (39%),<sup>49</sup> it also decreased the cost per gram of product by a factor of six!<sup>50</sup>

A plausible mechanism is the following:



Observations consistent with the proposed mechanism include inhibition of the reaction by radical cation scavengers such as tertiary amines, nitration of phenol by ammonium nitrate in the presence of ferric chloride (but not of ferrous chloride) in a slow reaction, and significantly increased product yields when ferric chloride is added to a stoichiometric amount of ferric nitrate.<sup>46</sup>

### The Diels–Alder Reaction

Another indication for the intermediacy of radical cations came from an altogether different quarter. Spurred by the excitement generated by reports of catalysis of unactivated Diels–Alder reactions by triarylammonium radical cations, enabling them to be run at room temperature in high yield,<sup>51</sup> we tried coupling the two reactions in one pot, the phenol nitration and the Diels–Alder.

This went like a charm: when 1,3-cyclohexadiene was codissolved with "clayfen" and with 4-*tert*-butylphenol, 92% conversion into the cycloadduct was achieved; and the phenol, normally nitrated quantitatively in a few minutes under these conditions, was left unscathed as long as trace amounts of the unsaturated hydrocarbon lingered in the reaction mixture.<sup>52</sup>

In the second part of our Diels–Alder triptych we dealt with aqueous Diels–Alder reactions. These had been pioneered by the group of Professor Ronald Breslow at Columbia.<sup>53</sup> Due to the tight congregation of diene and dienophile in water—a manifestation of hydrophobic forces or, in different but equivalent terms, of the strong internal pressure—this astute ploy gave rise to spectacular stereoselectivities, such as an endo preference of 21.4 for the cycloaddition of cyclopentadiene and methylvinylketone.<sup>53</sup>

Our rationale was the presence of internal pools of water in clays. Thus, we might get away with using an *organic* solvent, in the presence of a clay catalyst. Such a system might show yields and stereoselectivities comparable to those resulting from the use of aqueous solutions, while maintaining the advantage of an easier-to-evaporate organic solvent for workup (the legendary cake, to be both owned and eaten). This idea worked too: when 15 mM of cyclopentadiene were commixed with 15 mM of methylvinylketone in 50 ml of methylene chloride in the presence of 2.5 g of K10–Fe(III) catalyst already referred to, at -24 °C in a few hours we obtained a quantitative (96%) yield of the cycloadduct, with an endo preference of 21.<sup>54</sup>

The third part of our Diels–Alder triptych addressed the vexing question of the troublesome cycloadditions with furans as dienes. A "brute force" solution had been evolved by Professor Dauben at Berkeley: 15 kbars of pressure would give ca. 50% of the cycloadducts.<sup>55</sup> By that time, we had faith in our clay catalysts, polyvalent because of the Lewis and Brønsted acidic and basic catalytic sites, and because of the internal water. And we argued to ourselves that such furan Diels–Alders ought to be receptive to catalysis by Lewis acids, as embodied in a system such as the K10–Fe(III) catalyst. The only problem was to avoid the cycloreversion being likewise catalyzed: work-up would have to be done quickly (which of course is easier when a mere filtration removes the catalyst). Such a procedure gave improved yields, under mild conditions (-43 °C, atmospheric pressure), by comparison with the high-pressure results.<sup>56</sup>

Indeed, a variety of reactions can be catalyzed by an acidic clay such as the K10 montmorillonite. For instance, we have devised a convenient protective tetrahydropyranylation of alcohols and phenols (ROH → ROTHF) using the K10 solid acid catalyst.<sup>57</sup>

### Design of a Solid Basic Catalyst

In parallel with the improvement of acid-catalyzed reactions, we worked also at renovating some important base-catalyzed reactions. Many organic reactions are

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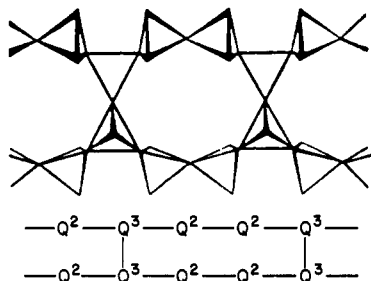
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initiated by base pulling off a proton. The carbanion thus generated then proceeds to attack an electron-acceptor center.

The blueprint for a new catalyst called here for combining the reduction of dimensionality stemming from reaction on a smooth surface—or fiber, even better?—and the presence of catalytic Brønsted basic sites. Silicates and aluminosilicates appeared to us as worthy candidates because they would associate good basicity and poor nucleophilicity, with negative charges dispersed over entire sheets of oxygen atoms. This would minimize competition for the electrophilic center between the generated carbanion and its progenitor.

Xonotlite thus came to our attention. This is a fibrous calcium silicate  $\text{Ca}_6\text{Si}_6\text{O}_{17}(\text{OH})_2$ . Akin to a railroad track, it has two parallel chains of silicate units (the rails) cross-linked at every fourth silicon (the ties) as follows:



The parallel chains are interleaved with sheets of  $\text{Ca}^{2+}$  ions. This structure is well-established, both from X-ray and from high-resolution silicon-29 NMR.<sup>58,59</sup> Another big advantage is that this is a pure mineral, hence no lack of reproducibility in its properties needs be feared. And the linear topology appealed to us because of the inherent reduction in dimensionality for reaction space.

Furthermore, this mineral, which serves in construction as an asbestos replacement, is accordingly abundant and inexpensive. Recently, it has been conditioned by controlled crystal growth into spherical granules, peaking at 75–100  $\mu\text{m}$  in size, associating the needlelike crystals in the manner of a sea urchin or of a chestnut. Its BET specific surface, while not commensurate with the huge specific surfaces of montmorillonite clays (500  $\text{m}^2\cdot\text{g}^{-1}$ ), is respectable: 60  $\text{m}^2\cdot\text{g}^{-1}$ .

The technical booklet for this material (sold as Promaxon) gives a “pH value” of 10. Whatever the exact significance of this information, xonotlite is strongly basic.

We could boost its basicity yet further under strong dehydrating conditions. This leads presumably to coordinate unsaturation of the calcium ions on the outside of the crystalline needles, which enabled us to hook onto them alkoxide groups, the *tert*-butoxide group from  $t\text{-BuO}^-\text{K}^+$  in particular. The resulting solid is a superb basic catalyst: some examples follow.

### Olefin Synthesis: Knoevenagel and Gattermann Condensations

The closely related aldol and Knoevenagel condensations share initial attack, after ionization of the parent carbon acids, of a carbanion donor upon a carbonyl

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**Table V**  
Comparison of Isolated Yields (%) in Knoevenagel Condensations (Benzaldehydes + Ethyl Cyanoacetate) with Different Heterogeneous Catalysts<sup>63–65</sup>

<i>p</i> -R group	xonotlite- <i>tert</i> -butoxide, <sup>a</sup> 100 mg/10 mM	$\text{AlPO}_4\text{-Al}_2\text{O}_3$ , 1.5–3 g/10 mM	$\text{Al}_2\text{O}_3$ , 3 g/10 mM
$\text{CH}_3$	80	60	62
$\text{OCH}_3$	86	—	52
$\text{N}(\text{CH}_3)_2$	78	7	—
Cl	82	85	47
$\text{NO}_2$	83	94	85

<sup>a</sup> 15 g/12 g, 1 h reaction time.

**Table VI**  
Reaction Times for 50% Conversion in the Knoevenagel Condensation of 2-Furaldehyde with Ethyl Cyanoacetate Catalyzed by Xonotlite

solvent	$t_{1/2}$ , h	solvent	$t_{1/2}$ , h
ethyl acetate	>>48	toluene	6.1
nitromethane	>>48	dimethylformamide	1.2
diethyl ether	>>48	dimethyl sulfoxide	1
chloroform	56	pyridine	0.8
acetone	38	cyclohexane	3
acetonitrile	24	pentane	1
carbon tetrachloride	22	ethane	2
methylene chloride	16	methanol	1.2
tetrahydrofuran	8.8	water	0.1–0.2

acceptor. This condensation step is followed by re-protonation. And, in the Knoevenagel condensation, water elimination finally takes place, leading to an olefin:  $\text{R}^1\text{R}^2\text{C}=\text{O} + \text{H}_2\text{CR}^3\text{R}^4 \rightarrow \text{R}^1\text{R}^2\text{C}=\text{CR}^3\text{R}^4 + \text{H}_2\text{O}$ . Indeed, one of the first conversions of the carbonyl group into an olefin, dozens of years before the Wittig<sup>60</sup> or the McMurry<sup>3</sup> routes, was devised by Knoevenagel.<sup>61</sup> This venerable reaction, now nearly a century-old, assumes continued importance.

It is catalyzed by weak bases under homogeneous conditions.<sup>62</sup> When we applied our basic solid catalyst xonotlite-*tert*-butoxide, the results were gratifying; yields of 80% and above are often obtained.<sup>63</sup>

Comparison with recent reports of catalysis of the Knoevenagel condensation by alumina-based catalysts<sup>64–65</sup> shows that we reach comparable and entirely satisfactory yields with *truly catalytic* amounts of our new catalyst (Table V):

The solvent effects on the percentage of conversion to the olefinic products (Table VI) were remarkable. The two features of interest, both empirical and mechanistic, in these effects, are the vastly increased rates in hydrocarbon solvents and in water solution. These findings are apparently paradoxical: that low dielectric and high dielectric media *alike* are conducive to faster reaction was a surprise. That the Knoevenagel condensation, a net dehydration, is speeded up in water offered another big surprise.

These results nevertheless admit of plausible and simple explanations, if the rate-determining step (at least for the reactions submitted to systematic study

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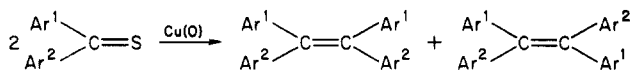
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of the influence of the solvent) is ionization of the carbon acids into the corresponding carbanions, at the interface between the solution and the catalyst. The latter, in this series of results, is undoped xonotlite. In the low dielectric hydrocarbon solvents, carbanion formation is favored by an electrostatic enthalpic effect: the resulting negative charge of the ion, immersed in a medium of low dielectric constant, exerts a large electrostatic field whose effect is to orient surface dipoles on the catalyst (such as  $\text{H}_2\text{O}^\delta$ ,  $\text{Ca}^{2+}$ ) so as to create *image charges* within the highly polar, high dielectric solid, with the opposite sign. The resulting attractive, stabilizing Coulombic interaction favors appearance of carbanions. Protic solvents (methanol, ethanol) greatly accelerate the reaction. The reactivity increase in water solution is spectacular. The simplest interpretation is that these solvents, able to coordinate onto the calcium ions of xonotlite, will thus bring the organic acids in close proximity to the surface of the basic catalyst, favoring their ionization into carbanion donors.

Solvent effects also enabled us to devise a vastly improved procedure for turning activated thiobenzophenones into tetraarylethylenes.<sup>66</sup> Gattermann had developed such an olefin synthesis using copper(0). Unfortunately, it requires elevated temperatures (180–200 °C).<sup>67</sup> We saw in this reaction a potential rival to McMurry's procedure,<sup>3</sup> with the advantage of using the much cheaper copper metal instead of titanium:



Formation of thioketyls, which would then couple, prior to extrusion of sulfur to copper sulfide, appears as plausible. Thus our rationale was to increase solvent polarity, since ion pairs presumably occur. In our hands, dimethyl sulfoxide gave the best results.

Indeed reaction of the easily obtainable thiobenzophenones<sup>68</sup> with copper powder in  $\text{Me}_2\text{SO}$  leads to formation of the duplication olefin *at room temperature* within 30 h, provided that one of the aromatic rings at least bears an electron-withdrawing substituent, such as 3- $\text{NO}_2$  or 4-F, -Cl, - $\text{NO}_2$ , - $\text{CF}_3$ .<sup>66</sup>

### The Michael Reaction

Michael additions unite a carbanionic donor and an  $\alpha,\beta$ -unsaturated ketone acceptor. Their importance stems also from their being component parts of Robinson annulations.<sup>33,69</sup> Side reactions to be avoided are aldol additions ( $\alpha^1$  rather than  $\alpha^3$  synthon) and coupling of the carbanion with its activated methylene precursor. We latched upon the Michael reaction, because of its importance. Here again we resorted to inorganic solids to prop up and renovate an organic reaction.

Rational design of a catalyst has to answer the need here for a Brønsted base, improved by neighboring storage areas in which to dump the abstracted protons; we thought of inorganic supports of the metallic oxide

type, with their numerous oxygens, for this ancillary role; the primary basic function could be fulfilled, we figured, by doping with strongly basic anionic centers.

Two solutions were evolved: (A) use alumina<sup>70</sup> (a solid acid which contains intrinsic basic sites too, already used in aldol reactions<sup>71</sup>) and boost the basicity by adsorption of fluoride ions from KF; (B) use our new catalyst, xonotlite-*tert*-butoxide (see above).

An example of the former A is the 100% isolated yield achieved in the reaction of 5,5-dimethyl-1,3-cyclohexanedione (dimedone) with methylvinylketone.<sup>72</sup> The latter solution B was also found to be highly functional, giving 60–80% isolated yields, in THF at room temperature, with 1–3 day reaction times, with acrolein or methylvinylketone as Michael acceptors, and with acetylacetone, ethylacetoacetate, or diethylmalonate as the Michael donors.<sup>72</sup> Based upon the quantity of catalyst used, a minimum of 150 catalytic cycles are effected with this new method.

### Outlook

There are limitations at present to heterogeneous catalysis of organic reactions. Organic theory has gained a limited understanding only of the mechanisms for catalysis. Take the example of triarylammonium radical cation catalysis of the Diels-Alder reaction between unactivated dienes. It has been ascribed by Bauld<sup>73</sup> to a converted ( $4_\pi + 2_\pi$ ) reaction. Schuster<sup>74</sup> has mustered good arguments in favor of a radical chain mechanism. And Gassman has shown convincingly protic acid catalysis in the case of 2,4-dimethylpenta-2,4-diene.<sup>75</sup> Organic practice also lags behind at times: even though this is a relatively rare occurrence, sometimes the inorganic solid will gobble up the organic products and never disgorge them again!

Fortunately, the assets and the promises far outweigh the liabilities. Inexpensive and efficient catalysts for making fine chemicals only require simple modifications of existing inorganic solid materials available in boxcar quantities. Solid acids and bases are among these. They make for advantageous use as catalysts. And these are operator applicable to a wide variety of organic reactions catalyzed by Lewis or by Brønsted acids or bases.

Exciting future prospects include the use of films, that of coated glass or metal walls as supports for the catalyst, in addition to the "silts" or "muds" (divided particles suspended in solution) used predominantly at present. Another development, around the corner so to say, is the devising of "pendulum" reactions oscillating between dual anchored catalysts and allowing pairs of mutually exclusive transformations to be run smoothly in one and the same pot: protonation/deprotonation, oxidation/reduction, condensation/fragmentation, addition/elimination, etc. A few extremely promising examples already exist.<sup>76</sup>

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Catalysis of organic reactions by inorganic solids is a form of biomimetic chemistry, where this expression is taken in a very broad sense: it makes use of the reduction of dimensionality inherent in the functioning of enzymes; often it is an aqueous chemistry; water sees increasing use as a solvent for organic reactions, and this is an important ingredient in some of the processes featured in this account; it is a compartmentalized chemistry, as in the operation of most if not all bio-

systems. One may venture to predict fast growth for this important new chapter of organic chemistry.

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