

Perspectives and challenges of physical organic chemistry

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Biography: Detlef Schröder, born 1963 in Wilster, Germany, obtained his Ph. D. with Prof. Schwarz at the TU Berlin in 1992, and is currently working as research assistant in the laboratory of Prof. Schwarz. He is the recipient of the 1993 Schering Award. Christoph Heinemann, born 1968 in Kßln, Germany, obtained his Ph. D. with Prof. Schwarz in the field of gas-phase chemistry in 1995. In 1995 he received the “Young Scientist Award” of the Leopoldina and in 1996 the Schering Award. Currently he is working in the research management of Hoechst AG, Frankfurt. Wolfram Koch, born 1959 in Darmstadt (Hessen), obtained his doctorate in 1986 under the tutelage of Prof. Schwarz after studying chemistry in Darmstadt and Berlin. Since 1992 he works as Professor for Theoretical Organic Chemistry at TU Berlin. In between, he was an IBM post-doctoral fellow at the IBM Almaden Research Center in San Jose, CA and a research staff member at the Institute for Supercomputing and Applied Mathematics at the IBM Scientific Center in Heidelberg. He is the recipient of the 1987 Schering Award.

Helmut Schwarz, born in 1943, spent four years as a chemical technician before reading chemistry at the Technische Universität Berlin (TUB), where he obtained his Ph. D. under the supervision of F. Bohlmann in 1972 and his habilitation in 1974. Since 1978 he has been associated with the TUB as a Professor of Chemistry and has resisted all temptation to leave Berlin for good. He held visiting appointments in Cambridge, Lausanne, Jerusalem, Haifa, Auckland, and Canberra. Among his several awards are the Otto-Klung, Otto-Bayer, and Leibniz Prizes, and the Max-Planck Research Award, which he received jointly with C. Lifshitz. In 1992 the Hebrew University of Jerusalem conferred an honorary doctorate on him and he received in 1994 the J. J. Thomson Gold Medal. He is a fellow of the Leopoldina (Halle), the Academy of Sciences at Erfurt and at Berlin-Brandenburg, and an Overseas Fellow of Churchill College, Cambridge. His current interests, besides the topic of his review, focus on the generation and characterization of elusive molecules of interstellar and atmospheric importance.

Abstract: The seemingly narrow field of transition-metal ion mediated C-H bond activation of substituted alkanes in the gas phase serves as an example to illustrate some perspectives and challenges of physical organic chemistry.

INTRODUCTION

In the past, physical organic chemistry focussed on mechanistic questions, *e.g.*, why does a reaction yield the observed products, what are the elementary steps, or can general principles be deduced to predict new reactions? During the last three decades, however, the field has undergone a tremendous broadening, and today, physical organic chemistry encompasses various disciplines of chemistry, physics, and biology. This progress manifests itself in the increasing perfection of instrumental and theoretical methods, *e.g.*:

- Advanced spectrometric methods which permit one to probe ultrafast reactions (femtosecond chemistry) or to elucidate properties of transition structures.
- Significant improvements in the determination of reliable kinetic and thermodynamic data for numerous reactions.

- Sophisticated theoretical methods aimed at providing quantitatively accurate information on complete potential-energy hypersurfaces from first principles.
- Promising developments in reaction dynamics, cluster science, solvation modeling, *etc.*

However, significant progress is often limited to relatively small or highly symmetric molecules or molecular ensembles, and as far as empirical concepts are concerned, by definition these follow experimental findings. Thus, for an applied chemist the predictive capability of physical organic chemistry is rather limited (1). This holds true even more for reactions involving larger systems and occurring in complex environments. Thus, one of the upcoming challenges of physical organic chemistry is to provide a conceptual framework which will eventually permit even the description of bulk properties of matter. Nevertheless, this is not likely to happen in the near future, and model studies aimed at probing intrinsic features at a molecular level will have their place in the next decades. In this respect, gas-phase experiments are ideally suited in that the experiments can be conducted under well-defined conditions and the systems can be described by sophisticated theoretical methods.

Here we would like to outline some of the challenges of physical organic chemistry by using an example which has been elaborated in our laboratories since 1987 in a series of mass-spectrometric and theoretical studies of the gas-phase chemistry of bare transition-metal ions with alkane derivatives (2).

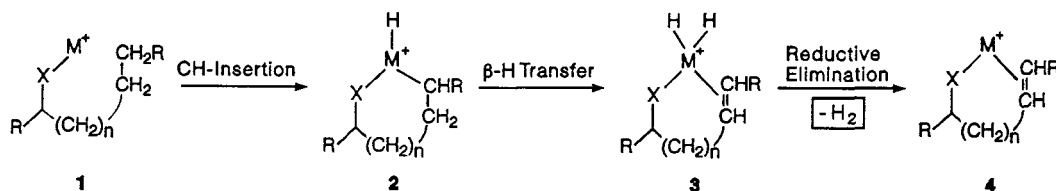
CHALLENGES

Let us begin with briefly mentioning some more general aspects which are also pertinent in the present context. Firstly, progress in physical organic chemistry will always be linked with the request for even more accurate thermodynamic and kinetic data for a broad variety of chemical reactions, thus providing the platform on which to build concepts for a predictive modeling of reactivity. Secondly, understanding the molecular origin of chemo-, regio-, and stereoselectivity is a prerequisite for the development of *de novo* chiral synthesis. Further, the design of tailor-made catalysts will depend on the progress made in quantitatively describing ligand and solvent effects in organometallic chemistry. Principal goals, among others, are:

- Selective C-H bond activation, in particular, concepts for the partial oxidation of hydrocarbons to valuable products, *e.g.*, oxidation of methane or benzene.
- Efficient photochemistry in order to ameliorate the use of sunlight as a cheap and ubiquitous energy source for chemical transformations.
- Design of chemical processes with explicit consideration of environmental aspects and, in particular, the limited access to natural resources ("sustainable development").

REMOTE FUNCTIONALIZATION OF ALKANES: THE STARTING POINT

Selective C-H bond activation of alkanes has been described as the chemists' Holy Grail (3), and one of the most attractive goals concerns the remote functionalization of alkanes (4). Here, a heteroatom in a functionalized hydrocarbon serves as an anchor for a reactive species, with the consequence that, due to conformational constraints, only a particular segment in the hydrocarbon backbone remote from the functional group X becomes accessible. This approach was realized in the gas phase by docking transition-metal cations M⁺ to certain groups X (*e.g.* CN, COOH, OH, *etc.*), followed by a metal-induced dehydrogenation of long alkyl chains (2), and it is the interplay of X and M which defines which part of the flexible alkyl chain is dehydrogenated.



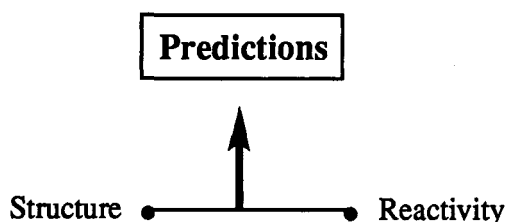
Scheme 1: Remote functionalization of alkane derivatives by bare transition-metal cations M⁺

Borrowing from textbook concepts of organometallic chemistry in the condensed phase, a first, phenomenological explanation of the experimental findings suggests a reaction mechanism (Scheme 1) which involves activation of a remote C-H bond (1→2), β -hydrogen transfer (2→3), and reductive elimination of H₂ (3→4). We will return to this rather simplistic, but intuitively pleasing picture further below.

GUIDELINE OF INTEREST: STRUCTURE/REACTIVITY STUDIES

Understanding the structure/reactivity relationship constitutes a necessary, though by no means sufficient, criterion to arrive at schemes with predictive capabilities (Scheme 2).

With respect to remote functionalization by bare metal ions, the observed reactivities need to be traced back to their chemical and physical origins, which may be translated into general concepts for structure/reactivity relationships. One way to accomplish this goal is to systematically study homologous rows, to vary the nature of X and M, respectively, and to examine substituent effects, in the hope that guidelines such as Hammett-like relationships will emerge.

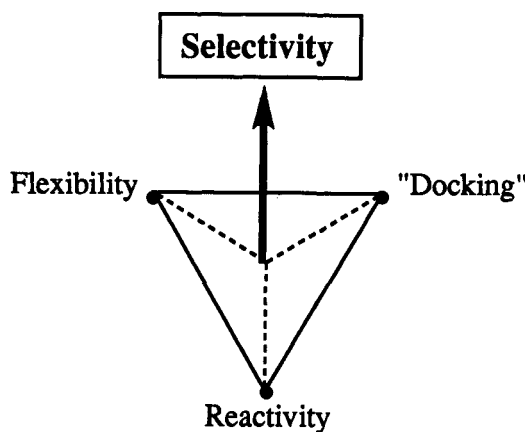


Scheme 2: Line of interest

Of particular importance are isotopic labeling experiments as these directly reveal which part(s) of a molecule is activated. In the context of remote functionalization, extensive studies of the chain-length dependence of C-H bond activation of alkane nitrile/M⁺ complexes (M = Fe, Co, Ni) demonstrate the power of this time-honored, empirical, yet extremely useful approach (5, 6). However, in the future such experiments (7) need to be complemented by theoretical studies, considering the complexity of the problems and the desired breadth of applications (8).

THE TRIANGLE OF CHEMO- AND REGIOSELECTIVITY

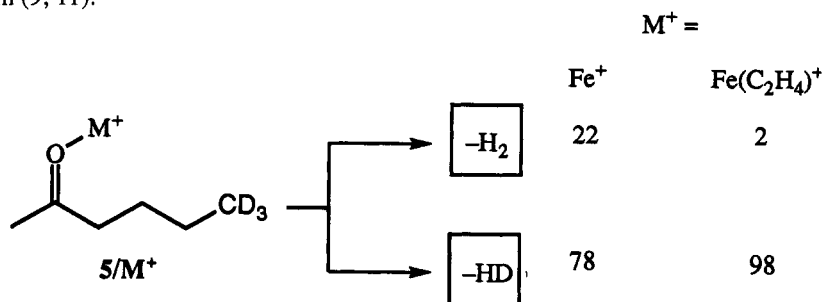
Selectivity in transition-metal mediated remote functionalization is determined by three factors (Scheme 3): Firstly, the reagent must be capable of activating the bond(s) of interest. This criterion excludes those parts of a substrate whose activation is prevented on thermochemical grounds. Next, complexation ("docking") of the reactant to a particular site of the substrate (*e.g.*, a functional group) provides a spatial region which is geometrically accessible to bring about a particular transformation. Docking of M⁺ together with the flexibility of the substrate determines to what extent chemically similar positions are available for bond activation, and hence controls the degree of chemo- and regioselectivity.



Scheme 3: Triangle of selectivity

As often noted, there exists a fundamental dilemma between reactivity and selectivity, because highly reactive species are usually not very selective and *vice versa*. This also applies, at least to some extent, for the gas-phase chemistry of metal ions. For example, a bare metal ion which is capable of initiating remote functionalization in the gas phase is in many cases too reactive to exhibit a high degree of regioselectivity. However, as in more traditional organometallic chemistry, the selectivity of a reagent can be tuned by ligand variation. Recently some gas-phase experiments were reported (9) in which the intrinsic reactivity of the reagent, the “docking” behavior, and also the flexibility of the substrate were modified by ligand effects. In general, however, enhancement in selectivity results in a decrease of reactivity (10).

The example shown in Scheme 4 may serve to illustrate this point: whereas dehydrogenation of 2-hexanone **5** by bare Fe^+ involves internal positions up to 22%, in the presence of an olefin ligand, *i.e.* $\text{Fe}(\text{C}_2\text{H}_4)^+$, this fraction drops to 2%, and dehydrogenation nearly exclusively (98%) involves the $\omega/(\omega-1)$ positions of the alkyl chain (9, 11).

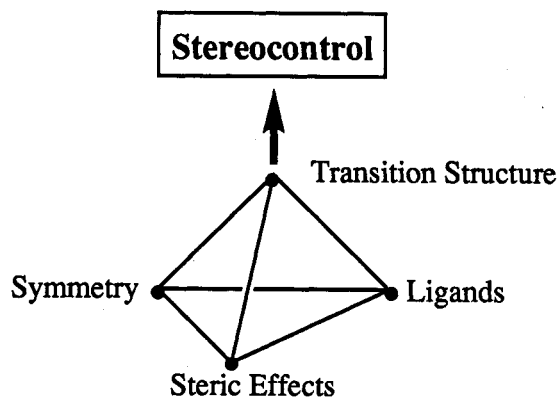


Scheme 4: Ligand effects on the regioselectivity in the remote dehydrogenation of [6,6,6- D_3]-2-hexanone

THE TETRAHEDRON OF STEREOCONTROL

The role of chirality in biology, medicine, chemistry, and nearly all aspects of life is unquestioned. Hence understanding the underlying principles of stereocontrol in chemical reactions is of supreme importance. However, in spite of the large number of methods existing in enantioselective synthesis, the understanding of the origin of enantioselectivity at a molecular level is still in its infancy. This holds true in particular for the mechanisms of those reactions in which organometallic reagents are employed. Ironically, it is precisely this area which on the one hand is rather promising for the future of organic synthesis, *e.g.*, the concept of chiral amplification (12), and which at the same time is rather poorly understood.

What are the reasons for this apparent complexity and how can physical organic chemistry help to bring about insight into the origin of stereocontrol?

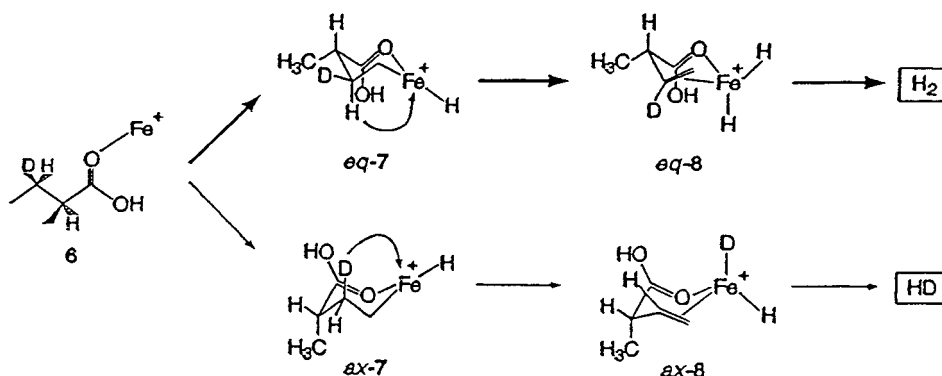


Scheme 5: Tetrahedron of stereocontrol

In general, stereocontrol in chemical reactions is the result of a subtle interplay of several factors (Scheme 5). One of them is steric hindrance in reactants, transition structures, and products. Further, symmetry plays a role and it goes without saying that symmetry consideration can be used advantageously in the design of chiral catalysts and the choice of (prochiral) precursors.

Of crucial importance in metal-mediated reactions are ligands and/or functional groups in the reactants which demand a fine tuning of reaction conditions and often render the outcome of a reaction non-predictable when a certain group is changed, *e.g.*, free versus protected hydroxyl groups. Further, solvation and aggregation of the reactants, let alone temperature, have a major influence on stereocontrol.

In practice, it is the complicated interplay of these effects which determines the result of a stereoselective synthesis, *i.e.*, the enantiomeric excess and the chemical yield. The elucidation of the origin of stereocontrol is a considerable challenge for physical organic chemistry. In fact, even under the relatively “clean” conditions prevailing in gas phase ion/molecule reactions no decisive example of chiral induction in bond formation has yet been accomplished; however, there exist a series of examples for diastereoselective bond cleavages (13). In the context of remote functionalization, we refer to the Fe⁺-mediated dehydrogenation of methyl-substituted fatty acids (14), *e.g.*, **6**. (Scheme 6). Here, the methyl group, which does not take part in the reaction itself, steers the reaction such that those intermediates are favored in which the methyl group is located in equatorial positions, *i.e.*, the intermediates **7** and **8**.

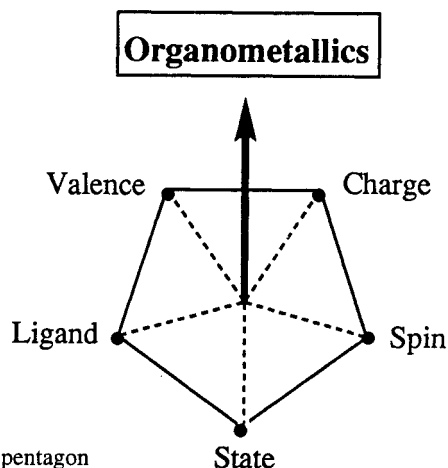


Scheme 6: Diastereoselective dehydrogenation of 2*S*,3*R*-[3-D₁]-2-methylbutanoic acid/Fe⁺

More recently, examples for transition-metal mediated diastereoselective C-C bond activations were also reported (15), and it remains to be seen whether these experiments will permit enantioselective bond activation and if general concepts can be uncovered.

THE PENTAGON OF ORGANOMETALLIC CHEMISTRY

While medium-sized organic systems may be tractable computationally at an adequate theoretical level within the next decade, major parts of organometallic chemistry will continue to remain a serious challenge, and the pentagon (Scheme 7) was deliberately chosen to visualize the problems to be tackled.



Scheme 7: The organometallics pentagon

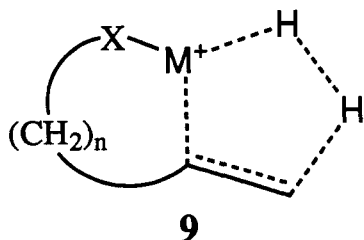
The reactivity of a transition-metal compound toward a given substrate is determined by several factors: the net charge, the formal oxidation state (“valence”), the ligand environment, the number of unpaired elec-

trons (“spin”), and the geometric and electronic structure; in addition, relativistic effects have to be considered for heavier elements. A major difficulty in the proper description of transition metal compounds is the vast number of quasi-degenerate electronic states; in fact, the state splitting may be so small that the definition of an “electronic ground state” becomes even questionable. Moreover, these factors may change during a transformation and thereby tremendously influence the energetic and entropic requirements of the transition structures associated with reactions of transition-metal compounds.

In the condensed phase the situation may be even more complicated, due to the flexible ligand environment, facile ligand-exchange processes, and solvent effects.

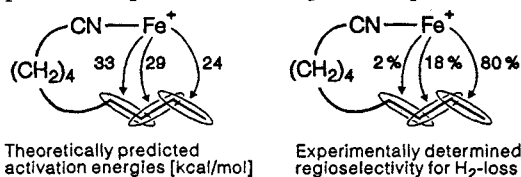
Let us illustrate this complexity by briefly mentioning two examples: (i) spin conservation is a time-honored criterion for reactivity, and its validity was also demonstrated for reactions of bare transition metals (16). However, more recently two-state reactivity turned out to be of vital importance in organometallic reactions in that spin multiplicity can change along the reaction coordinate (17). Thus, a quantitative account of spin-orbit coupling in organometallic chemistry is one of the great challenges for spectroscopists and theoreticians. (ii) In analogy to the condensed phase, dihydrido species, *e.g.* **3** or **8**, were postulated as intermediates in the gas-phase dehydrogenation of alkanes by transition-metal ions (2, 5, 6, 9).

However, recent computational studies (18) revealed that, at least for cationic species involving late 3*d*-elements, such metal dihydrides do not represent minima. Instead, dehydrogenation occurs directly from the insertion intermediates (*e.g.*, **2** or **7**), to form the corresponding products presumably via multi-centered transition structures such as **9** (Scheme 8).



Scheme 8: Multicentered TS

Despite this obvious complexity, there is now good reason to argue that by a careful choice of the computational methods a semi-quantitative prediction of the preferred positions of dehydrogenation is feasible.



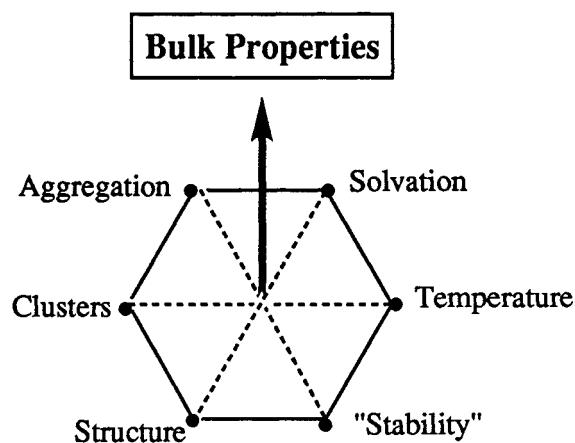
Scheme 9: Theoretically predicted activation barriers (relative to relaxed nonanonitrile/ Fe^+) and experimental results for the preferred sites in the Fe^+ -mediated dehydrogenation of nonanonitrile.

Similar to a recent combined force-field/*ab initio* approach (19), the transition structures associated with dehydrogenation of nonanonitrile/ Fe^+ were computed and qualitative predictions for the regioselectivity were made. After these computations appropriately labeled nitriles were synthesized and their reactions with Fe^+ were probed by mass spectrometry (20).

The agreement between the predictions and the experimental findings is remarkably promising (Scheme 9): Dehydrogenation occurs preferentially from the terminus of the chain (80%), for which the energy demand associated with the rate-determining, multicentered transition structure is lowest as compared to those involving the inner positions of the alkyl chain in nonanonitrile/ Fe^+ .

THE HEXAGON OF BULK PROPERTIES

As already mentioned, a central task of physical organic chemistry is to aid in the interpretation of molecular phenomena for the benefit of applied chemistry.



Scheme 10: The bulk properties hexagon.

In this respect reliable predictions of bulk quantities deserve major attention. However, while the previously discussed aspects dealing with isolated molecules or small aggregates may be handled within the next decade(s), the transposition of molecular properties to macroscopic behavior will remain an ongoing challenge for the most part of the next century.

Bulk properties are dependent on several effects which are coupled to a high degree. Moreover, many of the precise definitions existing on atomic scales become vague (if not useless) when macroscopic properties are concerned, and the term "stability" in Scheme 10 speaks for itself. This ambiguity becomes even more obvious when we turn to "criteria" like hardness/softness or nucleophilicity/basicity, not to mention molecular definitions for sensual properties such as color or odor.

With respect to metal-ion mediated remote functionalization in the gas phase, the central issue would be to use the information from gas-phase experiments for a transposition of this reaction into a "real" chemical process in the condensed phase. Obviously, for the time being this task cannot be tackled by physical organic chemistry alone, and rather extensive collaboration with other areas of chemistry, biology, and physics will be required.

On a more general note, the concepts of physical organic chemistry provide at best only one of several approaches which contribute to the understanding of matter, ranging from the study of atomic and molecular properties to the features of supramolecular chemistry, describing properties of nanomaterials and aiming at an understanding of condensed matter.

CONCLUSIONS

Major progress in science mostly occurs in interdisciplinary fields and this trend will become even more pronounced in the future; this does not only parallel the historical development of science, it is also enforced by economic and social boundaries for scientific research.

In view of the increasing complexity of the scientific problems which have to be faced in the future, *e.g.*, the design of enzyme-like catalysts or the prediction of the metabolism of a particular drug, the ongoing importance of intuitive concepts which can provide general concepts for the prediction of chemical reactivity can hardly be overemphasized. However, there exist serious limits as far as a *de novo* description of (complicated) reactions is concerned. Notwithstanding these more general remarks, there remain several achievable tasks to deal with in the near future. First of all, the evaluation of accurate thermodynamic and kinetic data must continue, because it simply forms the basis of (physical organic) chemistry and provides benchmarks for the advance of experiment and theory. Second, physical organic chemistry should continue to develop molecular monitors which are applicable in a broad variety of cases in different environments, as for example the concept of "radical clocks" (21) or the recently reported thianthrene-5-oxide (SSO) probe for the detection of active species in oxygen-atom transfer processes (22), to mention a few.

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