

Snapshots

Peter Chen*

Abstract: Reactive intermediates – their generation, characterization, and manipulation – is the central theme running through the research program in the Chen group. The range of chemical systems studied spans organic, organometallic, and physical chemistry. The inherently multidisciplinary work leads to new insights in chemical reactivity, as well as applications in fields as diverse as drug discovery, homogeneous catalysis, and combustion chemistry.

Keywords: Physical organic chemistry · Reactive intermediates

Introduction

A stroboscopic photograph of a bullet passing through a sheet of plexiglas captures the instantaneous image of a transient event. While we could study the plexiglas and the bullet prior to the shot, or examine the shards left by the passage of the bullet, the snapshot of the instant of physical impact not only conveys detailed information on the event, but moreover imparts to the viewer an emotional impact that transforms a photographic image into art (Fig. 1).

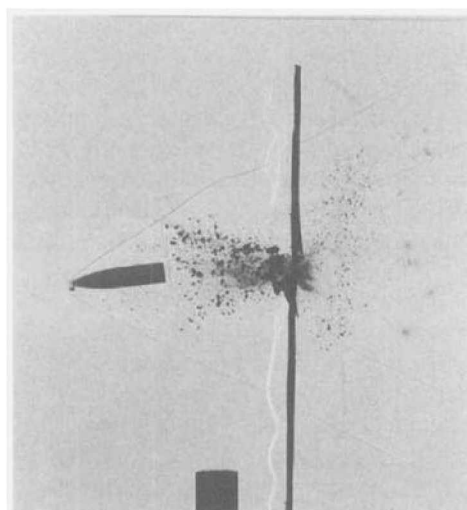


Fig. 1. 'Bullet Through Plexiglas', 1962, by Dr. Harold Edgerton

The chemical analogy to the snapshot is the unifying theme of investigation in the research group of Peter Chen. Chemical transformations – reactions – pass through one or more transient stages – reactive intermediates – on their way from reactants to products. Short-lived and highly reactive, these intermediates nevertheless determine the course of the reaction, meaning that a study of the properties and fate of reactive intermediates – the reaction mechanism – often brings not only a basic understanding of the underlying elementary steps of a complex reaction, but also the possibility to control or steer the reaction in a direction of our own choosing. Not surprisingly, the lifetime, lability, and low steady-state concentration of reactive intermediates

bring a host of technical problems to their study, which, in the Chen group, are addressed by continuing development of new, highly sensitive and selective experimental methods. *Investigation of reactive intermediates, their properties, and their reactions, is the central theme in the Chen group.* In this collection of snapshots, three active research areas will be introduced, through which the common thread, 'reactive intermediates', runs in a different way.

Electrospray Ionization Tandem Mass Spectrometry (ESI-MS/MS) of Metal-Organic Complexes and Homogeneous Catalysts

ESI brings high-molecular-weight metal-organic complexes into the gas-phase intact – in this sense, with all the ligands still attached. Using tandem mass spectrometry, the reactions of the complexes can be studied in detail and compared to the same reactions in solution. The key advantage is that the gas-phase chemistry can now be done with exactly the same catalyst as one finds in solution, with the benefit that the observation, manipulation, and characterization of the reactive intermediates is greatly facilitated by gas-phase methodology. Combining the new methodology with conventional synthesis, structure–activity studies, and kinetics, one creates a powerful new set of mechanistic tools for the study of catalysis. In the last five years, C-H activation [1], olefin metathesis [2][3], Ziegler-

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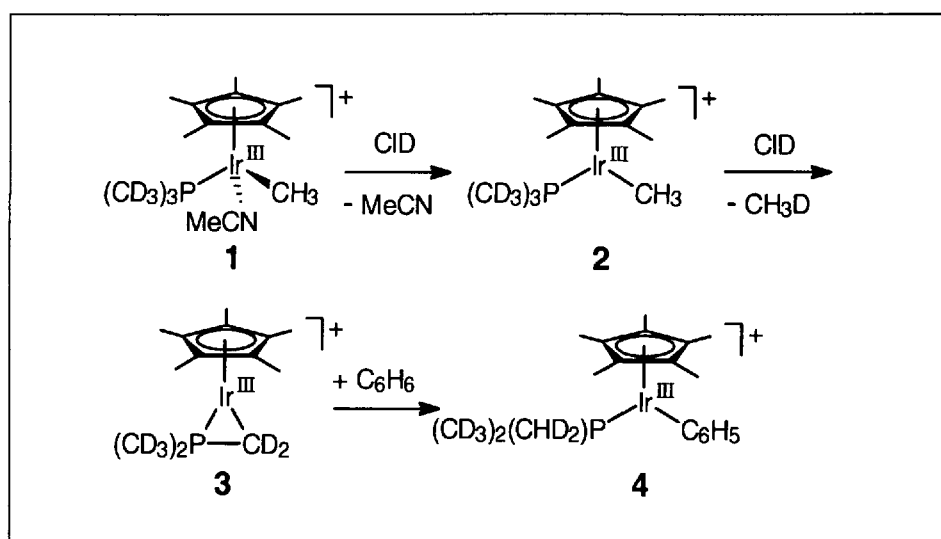
Natta polymerizations [4], and catalytic hydrogenation [5][6] have been studied. In each of the four areas, one salient result will be highlighted, with a subsequent view to the future.

For C-H activation [1], Bergman's Ir(III) complexes, at the time the most active C-H activation species reported, were chosen. The detailed question concerned the mechanism of the C-H activation reaction of benzene, *i.e.* whether the reaction $2 + \text{C}_6\text{H}_6 \rightarrow 4$ proceeded by a concerted (σ -bond metathesis) or stepwise by an associative mechanism. Surprisingly, the isotopic labeling results found a novel dissociative mechanism through a previously unseen intermediate, **3**, which was then subsequently found in solution (Scheme 1).

Moreover, even quantitative data on the ordinarily transient new intermediate **3**, or its close relative **6**, could be obtained by measuring the activation energy for its formation from **5** using the technique of collision-induced dissociation threshold determination, a technique by which quantitative ligand bond energies may be also determined [7] (Fig. 2).

The quantitative aspect of the C-H activation study is particularly important given the paucity of thermochemical data on even the most elementary organometallic complexes.

Olefin metathesis [2][3], catalyzed by organometallic complexes, is one of the few truly novel reactions discovered in the last decades (Scheme 2). It has achieved considerable academic as well as commercial importance, despite the poor state of mechanistic work on the reaction. Information obviously useful to



Scheme 1.

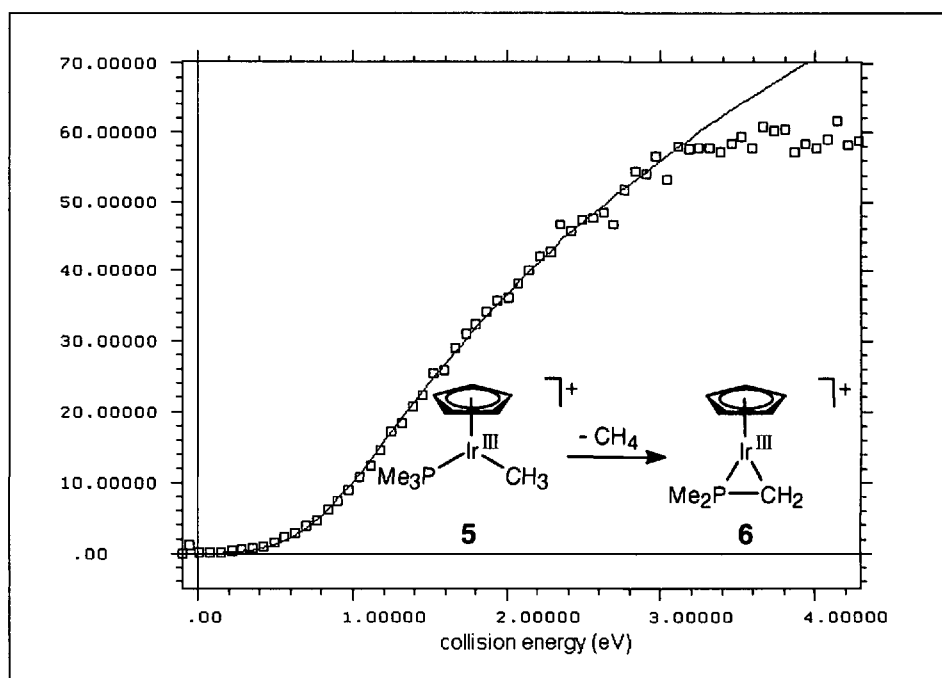
the application of metathesis catalysts in real settings, *e.g.* substrate selectivity, response to substitution on the catalyst, or even the number or steps in the reaction, had been largely inaccessible to experiment.

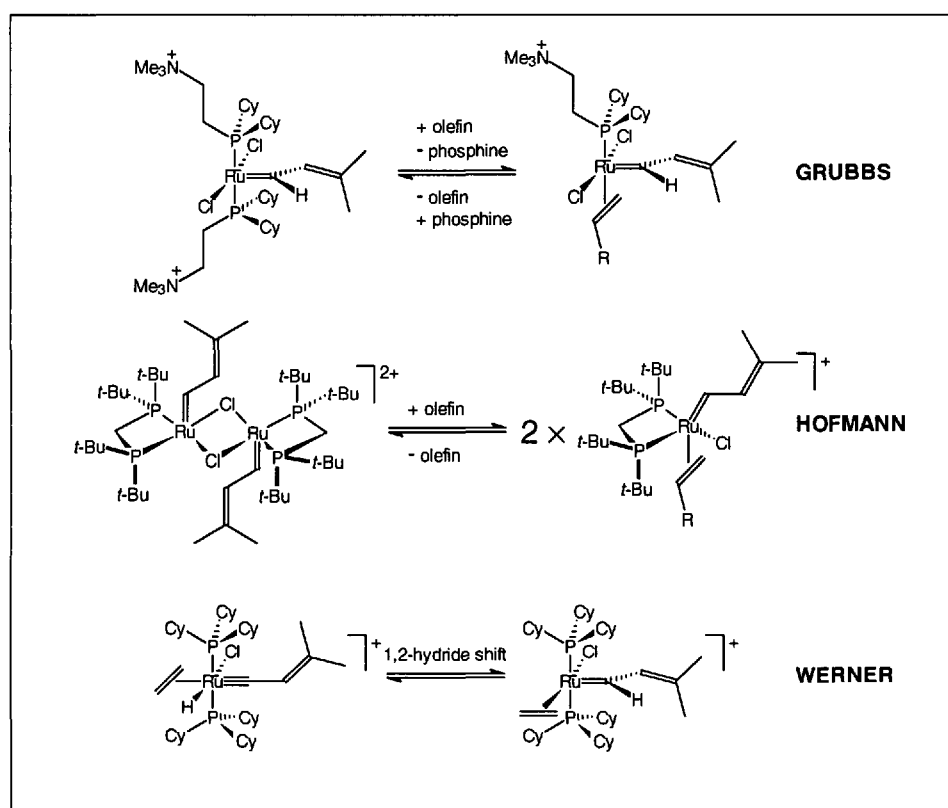
Using electrospray ionization tandem mass spectrometry to isolate the reactive species and study the metathesis reaction, the separate influences of the initial ligand and exchange reaction and the metathesis itself could be quantitatively assessed. Moreover, classical physical organic techniques such as linear free energy relationships and kinetic isotope effects shed light on a potential surface whose complexity lies just at the edge of possibility of computation by quantum chemical methods. Among the key findings are:

- 1) For ruthenium carbenes, the metallacyclobutane structure is a transition state;
- 2) Electron withdrawal by substituents accelerates the metathesis reaction;
- 3) The solution-phase reactivity ordering of different ruthenium-based metathesis catalysts is largely determined by the preequilibrium that generates active species rather than the specific metathesis rate of the particular active species.

Ziegler-Natta polymerization of olefins is the basis for over half of the 160 Mio tons of polymers produced yearly. The identity of the reactive species is generally inferred from indirect studies; some *in situ* NMR studies have begun to bring new insights. For this important class of

Fig. 2. Collision-induced dissociation (CID) threshold curve for the reaction, $5 \rightarrow 6 + \text{methane}$, showing the dependence of the dissociation cross-section (σ , 10^{-16} cm^2) against collision energy (eV, center-of-mass frame), and the fit to Armentrout's threshold function. The fit covered data between 0 and 3 eV, and yielded the following parameters: $E_0 = 0.58(2) \text{ eV}$, $\sigma = 52.8(3)$, and $n = 1.42(4)$, meaning an activation energy of 13.4 kcal/mol.





Scheme 2. Preequilibria in several ruthenium-based metathesis catalysts. Comparison of the gas-phase and solution-phase reactivity of the carbene complexes reveals the important role that the preequilibria play.

reactions, direct isolation and reaction of the presumed alkyl zirconocenium active species from solution has been achieved [4]. Moreover, the first stages of the polymerization can be directly observed by reaction of the isolated active species with α -olefins in a high-pressure ion guide (Fig. 3).

For catalytic hydrogenation, we have investigated the mechanism [6] by which H_2 is cleaved by Noyori's ruthenium catalyst: *trans*- $RuCl_2[(S)$ -BINAP][*(S,S)*-DPEN] and excess base (presumably forming the dihydride). Surprisingly, we find that the extraordinary activity of the

catalyst, *i.e.* substrate-to-catalyst ratios between 100 000 and 1000 000 can be attributed to the presence of a Lewis acid cocatalyst. In the usual case, the Lewis acid cocatalyst is an alkali metal cation, typically K^+ , which comes into the system incidentally as the counterion for the needed base.

Its activity-enhancement derives presumably from a precise fit in an accidental, pre-organized cation binding pocket formed by one phenyl group on the BINAP, a second phenyl group on the DPEN, and the amide nitrogen formed when the DPEN is deprotonated (Fig. 4).

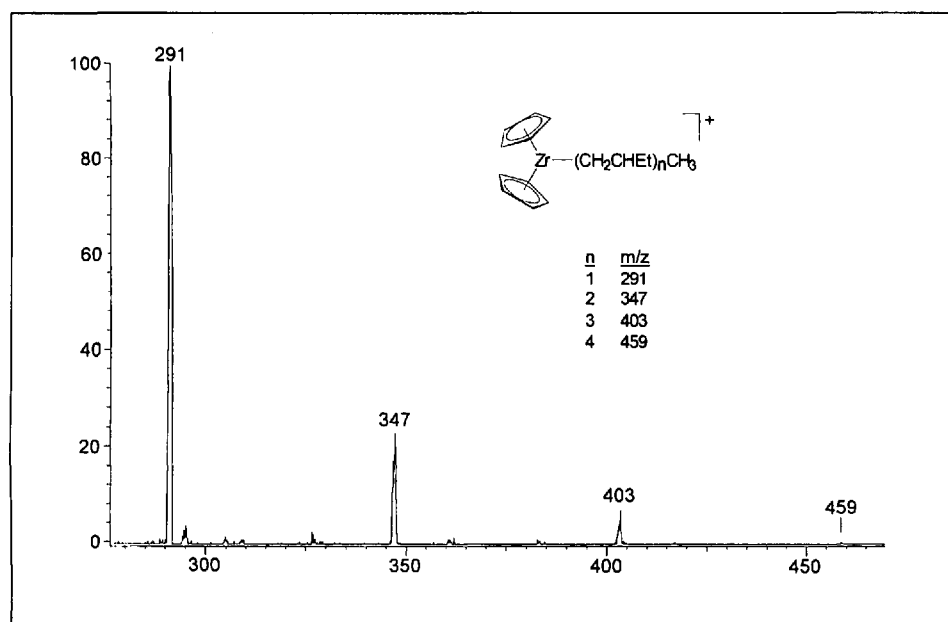


Fig. 3. Daughter-ion mass spectrum taken by electrospray of $[Cp_2ZrCH_3]^+ B(C_6F_5)_4^-$ in dilute CH_2Cl_2/CH_3CN solution, thermalization and reaction in octopole 1 with 1-butene, mass-selection of $m/z = 291$ in quadrupole 1, further reaction with more 1-butene in octopole 2 under near-zero energy, multiple-collision conditions, and finally mass analysis in quadrupole 2. Addition of up to four units of 1-butene is evident in the gas-phase reaction, clearly showing that the Ziegler-Natta polymerization reaction proceeds in the mass spectrometer with completely unsolvated complexes.

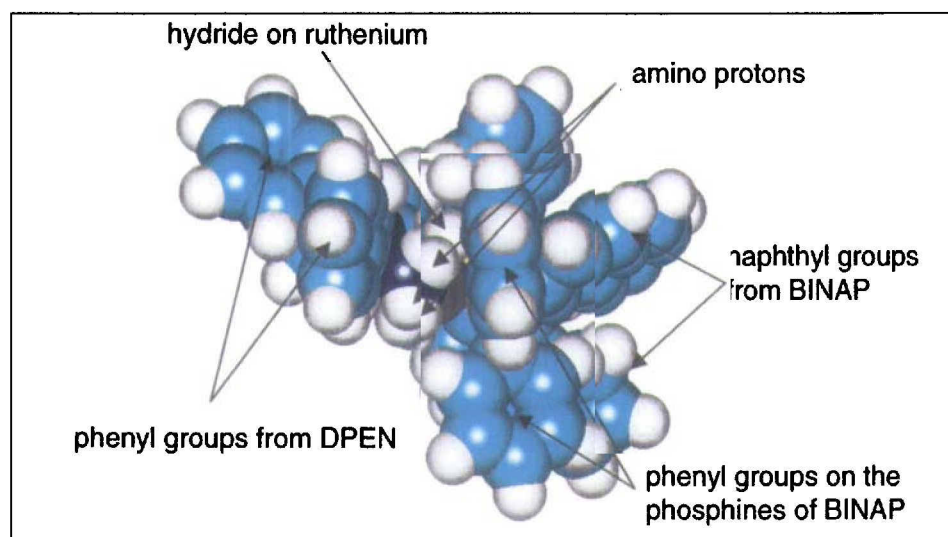


Fig. 4. Structure of *trans*-RuH₂[(*S*)-BINAP][(*S,S*)-DPEN], computed by molecular mechanics using the MMX forcefield, viewed along the N-Ru bond, showing the two phenyl groups, one from BINAP and one from DPEN) oriented face-to-face with a separation of 5.6 Å. The N-H bond is too short to place the proton between the centers of the rings, but the longer K-N bond in *i*-PrOK coordinated to deprotonated DPEN would be ideal.

a 'quencher' can yield the kinetic parameters that characterize the catalyst performance (Fig. 5). These kinetic parameters, in turn, can be used to compute the polymer molecular weight and molecular weight distribution that the catalyst would produce – without ever actually producing the polymer itself. The assay works, moreover, with only a few milligrams of catalyst and requires about one hour for the reaction, and a few minutes for the analysis. A key technical feature of both the mechanistic and applied organometallic chemistry projects is the ability to directly observe the active species in homogeneous catalysis, even if

that species is only present in minute concentrations as one component in a mixture. In the best cases, a complete mechanistic and kinetic characterization of a catalyst can be performed without prior isolation of the pure complex. This methodology formed the basis for the founding of Thales Technologies AG, a spin-off company of the ETH Zürich [10]. The key technology that distinguishes Thales from other companies seeking to develop and optimize catalysts is the ability to directly observe and manipulate the reactive intermediates – catalyst-bound substrates in this instance – rather than simply the products of a catalyzed reaction.

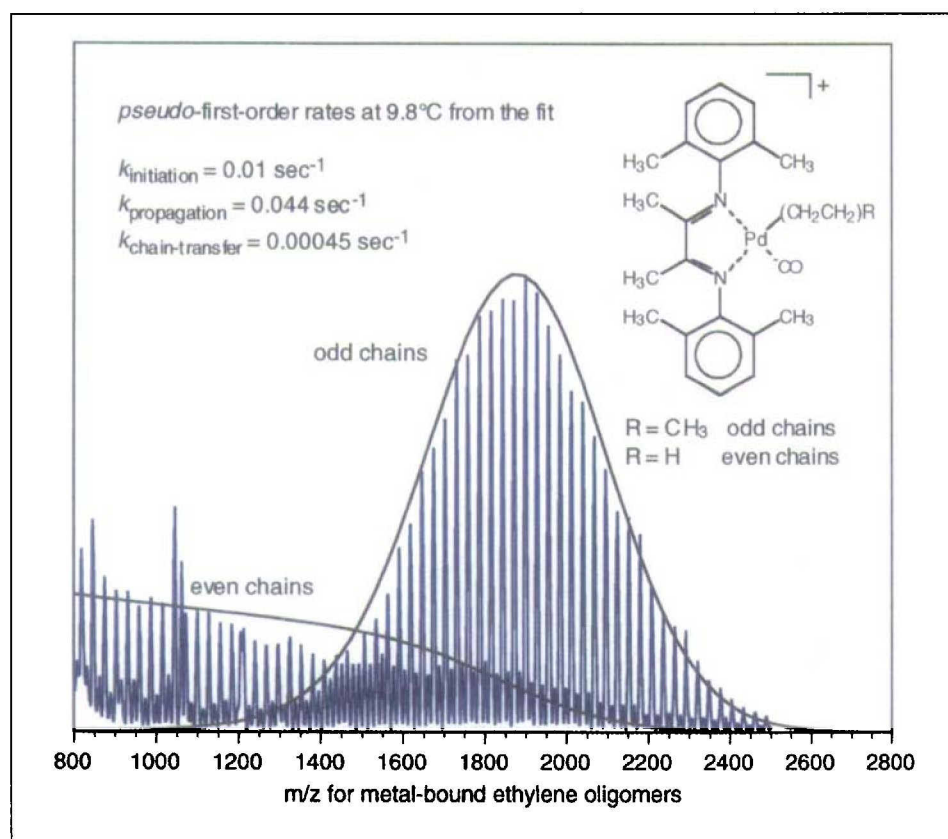


Fig. 5. Fit of the oligomer distributions and the derived kinetic parameters for the interrupted polymerization of ethylene by a Pd(II) catalyst. The propagation rate is determined uniquely by the maximum of the 'odd' distribution; the initiation rate comes from the width of the 'odd' distribution; the ratio of the 'odd' to 'even' distribution gives the rate for chain transfer.

Laser Spectroscopy and Photodissociation Dynamics of Gas-phase Radicals

Spectroscopic, thermochemical, and especially kinetic data for hydrocarbon radicals are experimentally difficult to obtain. We exploit a high-intensity supersonic jet radical source, and nano- and picosecond laser sources to address all three of these important areas. High temperature data for these radicals is needed for reliable numerical modeling of combustion or hydrocarbon cracking, but is ordinarily not available. These data are extracted from the experiments in this series.

Laser spectroscopic studies using a variety of techniques are done. With resonant multiphoton ionization (MPI), the excitation spectrum of a radical may be obtained in which the carrier of the spectrum is labeled by mass [11]. The extensive vibrationally and (partially) rotationally-resolved spectra of allyl and its isotopomers represent some of the most complete electronic spectroscopy for any polyatomic radical.

Similarly, high-resolution photoelectrons spectra of radicals are obtained using the **Z**ero **K**inetic **E**nergy **E**lectron/**P**ulsed **F**ield **I**onization technique (ZEKE/PFI), from which precise thermochemical and structural information may be extracted [12] (Fig. 6).

In a further development, radicals cleanly generated from custom precursors are used to probe the dissociation dynamics. Photochemical deposition of a defined amount of energy in the radical allows the measurement of microcanoni-

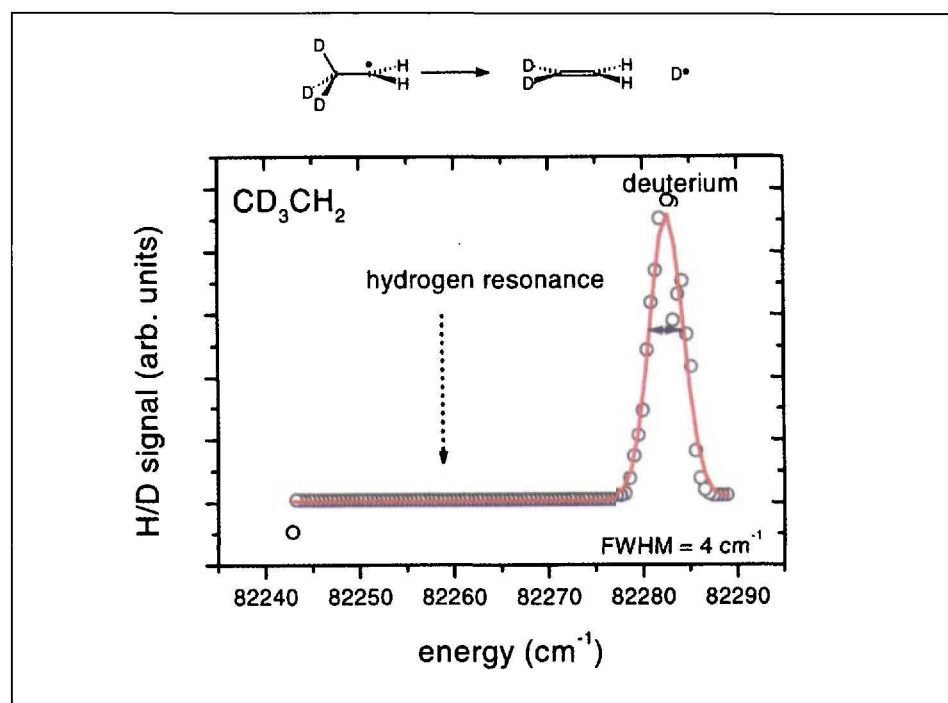
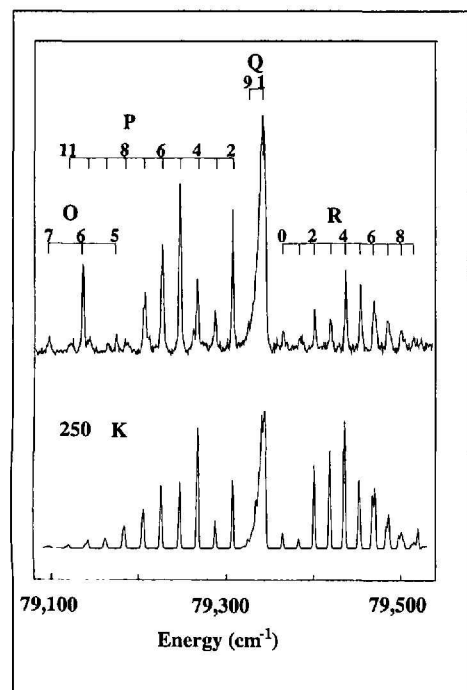


Fig. 7. Mass-detected 1+1' MPI spectrum of hydrogen and deuterium atoms produced by the dissociation of site-specifically labeled ethyl radical. The absence of isotopic scrambling and the Doppler width of the deuterium spectrum contain dynamic information on the dissociation process.

cal rates as well as the energy partitioning between different products.

The studies [13] on allyl (C_3H_5), propargyl (C_3H_3), and ethyl (C_2H_5) (Fig. 7) cover some of the most important radical species in high energy processes, and have the advantage that the full range of frequency- and time-resolved techniques (from the visible to the vacuum-UV, and from the picosecond to the microsecond range) are available in a single laboratory. In the end, although radicals show the typical high lability and low lifetime typical for reactive intermediates, the specialized physical techniques begin to bring the level of information on the radicals up to the norm for ordinary stable molecules.

Fig. 6. Rotationally-resolved ZEKE-PFI photoelectron spectrum of methyl radical, CH_3 , with approximately 2 cm^{-1} resolution. Tunable laser light around 126 nm (79365 cm^{-1}) was generated by resonant difference-frequency mixing in krypton. The band has the form of a simple parallel transition with O, P, Q, and R branches from the overlap of K sub-bands. The simulation assumes $T_{\text{rot}} = 250\text{ K}$, and constant rotational line strength factors. The frequency markings are in cm^{-1} . An ionization potential of $79349 \pm 3\text{ cm}^{-1}$ ($9.8381 \pm 0.0004\text{ eV}$) can be extracted from the spectrum.

Rational Manipulation of Biradical Reactivity for Drug Design

Biradical reactivity matters not only for discussions of qualitative bonding theory, but also in the mode of action of a family of highly potent cytotoxins that show potential as antitumor agents [14]. Rational tuning of that reactivity impacts both fields. Some years ago, we proposed and experimentally verified a qualitative bonding model which predicted that 1,4-arene biradicals related to *p*-benzynes should show unusually slow hydrogen abstraction kinetics [15], which directly pertained to the step by which the natural products produced DNA cleavage.

The next logical step was to use the model to engineer a biradical precursor which would produce a biradical whose reactivity could be enhanced or quenched by external factors, so that a future DNA-cleavage agent could be externally switched. The new structures, azaenediynes, which cyclize to derivatives of the 2,5-didehydropyridine biradical (the orbitals of which are shown in Fig. 8), did display H^+ -dependent behavior, but unfortunately, the compounds were too sensitive to side reactions to be used under anything close to physiological conditions. The development of more robust azaenediynes is currently underway.

Fully integrated with the experimental program is a computational program

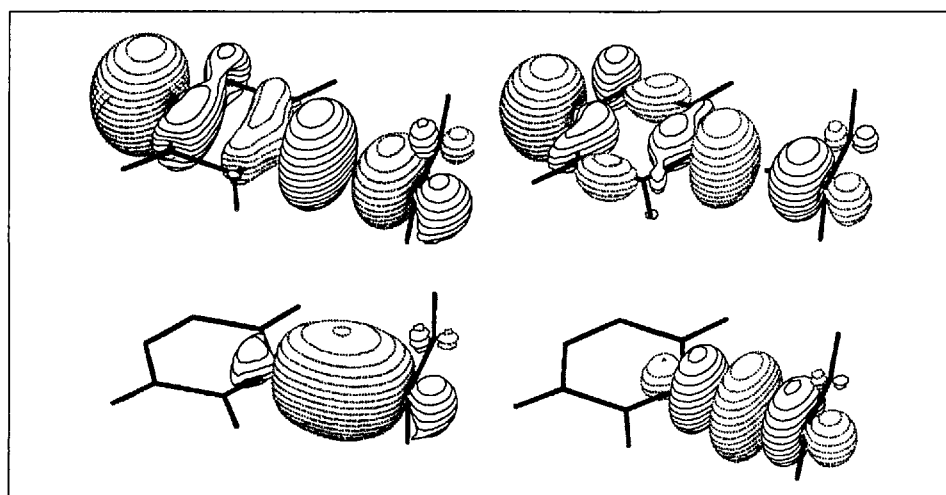


Fig. 8. The most important molecular orbitals from the abstraction of hydrogen from methanol by the 2,5-dihydropyridine biradical from a CASSCF(4x4) calculation.

using state-of-the-art methods to characterize reactive intermediates. For organic species, high-level *ab initio* calculations – up to CCSD(T) with triple- ζ basis sets – produce results with chemical accuracy. For organometallic complexes found in catalysis, DFT and QM-MM calculations describe the full ligand sphere of the complexes of interest.

Conclusion

For the theoretical and experimental study of reactive intermediates, a common palette of tools provides valuable insights in a wide range of chemical phenomena. While homogeneous catalysis, high-temperature chemistry of hydrocarbons, and DNA cleavage may seem, at first sight, to share little common ground, the emphasis on reactive intermediates proves to be the unifying theme that binds the several areas together. In all cases, the ‘snapshot’ of a transient event leads to new mechanistic insights, which then feed back into the engineering of desirable properties into new chemical products and processes.

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