

Reaction intermediates in organic chemistry — The “big picture”¹

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Abstract: An overview of the discovery of reaction intermediates and associated concepts in physical organic chemistry is presented. Particular attention is paid to chronology of ideas, frequency of occurrence of reaction intermediates in the library of organic reactions used in organic synthesis, and the lexicon of scientific terms used in the language of physical organic chemistry. General logic decision trees are presented for the unique or near unique identification of reaction intermediates based on experimental techniques and common patterns of reactivity documented in the literature over the last century. Contributions made by scientists working in laboratories at Canadian universities and at the National Research Council of Canada are noted throughout.

Key words: physical organic chemistry, mechanistic chemistry, reaction intermediates.

Résumé : On présente une revue de la découverte d'intermédiaires réactionnels et de concepts apparentés en chimie organique physique. On porte une attention particulière à la chronologie des idées, la fréquence de la mention des intermédiaires réactionnels dans les relevés de réactions organiques utilisées en synthèse organique et le lexique des termes scientifiques utilisés dans le langage de la chimie organique physique. On présente des arbres décisionnels logiques et généraux pour l'identification unique ou pratiquement unique d'intermédiaires réactionnels basés sur des techniques expérimentales et sur des patrons communs de réactivité documentés dans la littérature pendant plus d'un siècle. On note partout les contributions faites par les scientifiques travaillant dans les laboratoires des universités canadiennes et dans ceux du Conseil national de recherches du Canada.

Mots clés : chimie organique physique, chimie mécanistique, intermédiaires réactionnels.

[Traduit par la Rédaction]

Introduction

The development of physical organic chemistry concepts is inextricably linked to the discovery and identification of reaction intermediates (1). Once chemists began amassing a library of chemical reactions that made it possible for one chemical structure to be transformed into another, thereby ushering in the vast and unlimited field of organic synthesis, it soon became apparent that patterns of reactivity among common structures emerged as a consequence of such transformations. The central questions of how and why particular products resulted in a given reaction from known substrate structures launched the field of mechanistic chemistry. These questions in turn evolved into others such as “how fast a particular reaction proceeds” and “how can one control the product outcome”. The former launched an era of instrumentation development where various time-resolved techniques were invented to probe the temporal gap between substrate and product(s) of a given reaction. The latter question launched investigations into what parameters were important

and to what degree in determining product outcomes. All of these questions were greatly influenced by ongoing parallel theoretical and experimental developments in the understanding, determination, and verification of chemical structure. Much of the success in structure elucidation and prediction and in time-resolved studies of reaction intermediates may be attributed to the birth of quantum mechanics and spectroscopy, which were the children of the happy marriage between physics and chemistry. Over time a certain “logic” to the understanding of organic reaction transformations emerged. Essentially the whole field of physical organic chemistry can be reduced to an algorithm that attempts to solve the inverse problem of determining the minimum possible set of elementary steps constituting a reaction mechanism that is consistent with experimental observations. It must also satisfy the fundamental condition that the sum of the elementary steps is the overall chemically balanced stoichiometric equation as prescribed by Lavoisier's conservation of mass law. This set of elementary steps may or may not involve transient structures or reaction intermediates between the known substrate structures and identified product structures. Transient structures may be observed directly or inferred indirectly. This inverse problem is akin to the one in algebra of factoring a complex polynomial into its constituent factors, or in number theory of factoring a natural number into its prime factors. However, an important difference between the two related inverse problems is that in mechanistic chemistry the set of “factors” may not be unique and that an iron-clad deductive proof of mechanism

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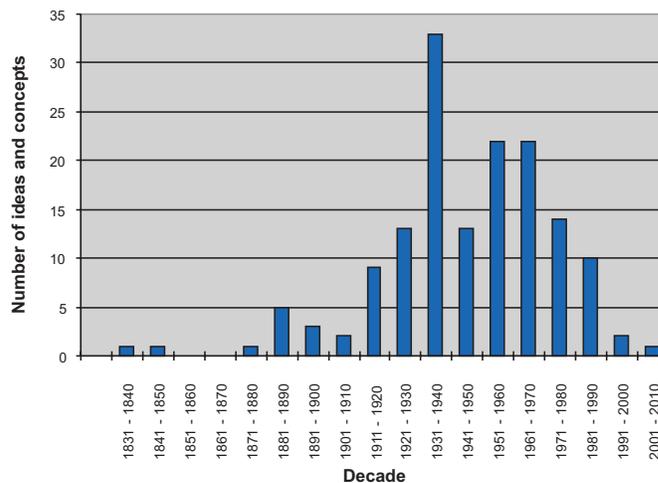
cannot be done. The best one can hope for is consistency among various observations and techniques used. This effectively means that every postulated mechanism, or “set of factors”, is only confirmed by experimental evidence and techniques that are available at the time of discovery, and hence is always open to later revision pending reexamination by new techniques. Laidler in a commentary on the use and misuse of the concept of rate-controlling step states that “reaction mechanism can never be established with a high degree of confidence” (2). In mathematics the analogous proof once confirmed is always true for all time.

This paper outlines key developments in physical organic chemistry and shows how they have impacted studies of reaction intermediates. The approach is to present the “big picture”, tracing both ideas and people in the field so that the reader can get a sense of scale of what has been accomplished as well as take stock of where we are at today in the field and identify new fruitful areas of future research. Particular attention is paid to chronology of ideas, frequency of occurrence of reaction intermediates in the library of organic reactions used in organic synthesis, and the lexicon of scientific terms used in the language of physical organic chemistry. General logic decision trees are presented for the unique or near unique identification of reaction intermediates based on experimental techniques and common patterns of reactivity documented in the literature over the last century. In keeping with the theme of this special issue, contributions made by scientists working in laboratories at Canadian universities and at the National Research Council of Canada are noted throughout.

Chronology of concepts in physical organic chemistry

Figure 1 shows a histogram of the timeline of discovery of key concepts in the field of physical organic chemistry and Table S1 (Supplementary material)² specifies them in a list along with the respective names of scientists who made these contributions. The celebrated ideas are named after particular scientists and the remainder are given special names. It is instructive to point out that when one begins learning about a field of science for the first time one can fast track their study by focusing on the “named things” in that field, since these represent the sign posts of what is important in the subject in question, especially ones that have stood the test of time, usage, and further experimentation by scientists at large. In a number of instances, ideas have been attributed to scientists with established reputations despite them not being the original discoverers. Recent works (3) have documented this phenomenon of incorrect attributions of discovery, priority, and credit of chemical names and eponyms in organic and physical chemistry. Examples relevant to the present compilation (4) include: (i) the Le Châtelier’s principle of equilibria (1884) (5), which was discovered a few months earlier by Jacobus H. van’t Hoff (1884) (6); (ii) the Arrhenius equation (1889) (7) also discovered earlier by van’t Hoff (1884) (6); (iii) the steady-state

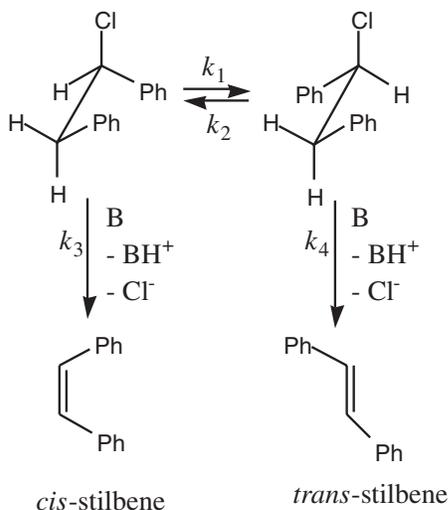
Fig. 1. Histogram showing timeline of discovery of key concepts in physical organic chemistry (growth of ideas and concepts).



approximation in chemical kinetics credited to Max Bodenstein in 1913, which was described earlier in that year by David Leonard Chapman and his student L.K. Underhill (8); (iv) the Michaelis–Menten mechanism of enzyme kinetics (9) (1913), which was first described earlier in 1892–1902 by Adrian J. Brown (10) and by Victor Henri (11) in 1901–1903 following work done in the laboratories of Wilhelm Ostwald in Leipzig and culminating in a doctoral thesis on the enzyme kinetics of diastase; (v) the Orton rearrangement (12) (1902) discovered earlier by Georg Bender (13) in 1866; and (vi) the Curtin–Hammett principle (14) (1954), which was originally formulated in 1907 by Solomon F. Acree (15). The last case has not been discussed before in the literature and deserves further comment here. No references to Acree’s early work are mentioned in any of the well-known papers by Curtin, Hammett, and others including an extensive review of the topic by Seeman (16). Only two citations in the literature appear to mention Acree’s contribution (17, 18). Hammett, in his book, refers to the principle as the “Curtin principle”, but makes the following footnote: “Because Curtin is very generous in attributing credit, this is sometimes referred to as the Curtin–Hammett principle”. Curtin, in turn, in his 1954 paper, published in an obscure journal and likely read by few chemists, refers to a private communication from Hammett in 1950 attributing that the idea originated from Hammett in his comment: “It was pointed out by Professor L.P. Hammett in 1950 that if the transition state theory is accepted and if rotation between the various possible conformations of the starting material is very rapid compared to the rate of the reaction, the relative amounts of products formed from the two critical conformations are completely independent of the relative populations of the conformations and depend only upon the difference in free energy of the transition states.” The chemical reaction referred to in Curtin’s work is the E2-base-catalyzed elimination of halide from 1,2-diphenyl-1-chloroethane to yield *cis*- and *trans*-stilbene (Scheme 1). Curiously, Curtin’s paper

²Supplementary data for this article are available on the Web site or may be purchased from the Depository of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, ON K1A 0S2, Canada. DUD 4039. For more information on obtaining material refer to http://cisti-icist.nrc-cnrc.gc.ca/irm/unpub_e.shtml.

Scheme 1.



does not present a precise mathematical relationship describing the phenomenon, but Hammett does in his book with the following equation given in eq. [1].

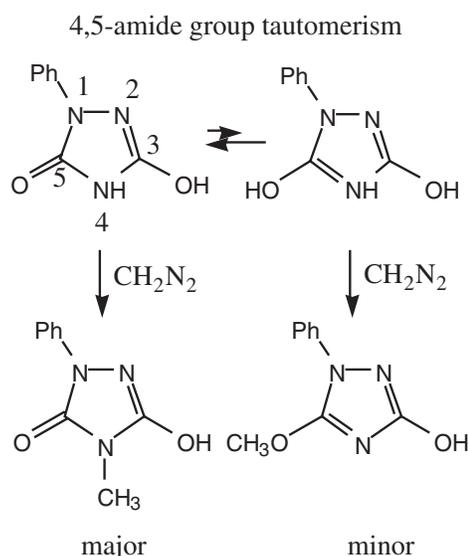
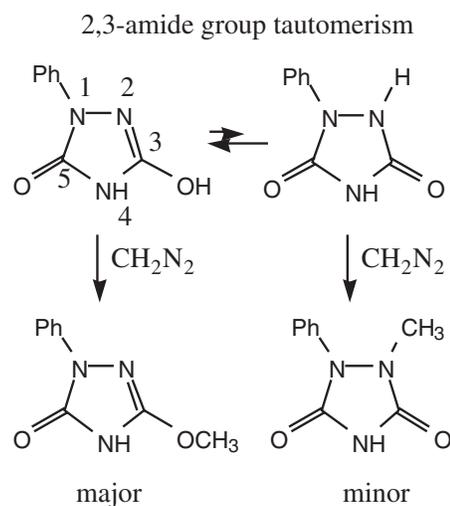
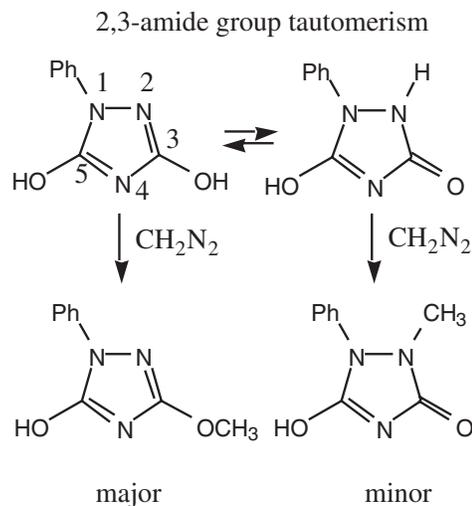
$$[1] \quad \frac{d[\text{trans-stilbene}]/dt}{d[\text{cis-stilbene}]/dt} = \frac{q_{\text{trans}}^{\#}}{q_{\text{cis}}^{\#}}$$

where the q s refer to transition-state partition functions for the elimination steps, which in turn are related to the corresponding rate constants. However, Acree in 1907 studied the oxygen and nitrogen alkylations of tautomeric mixtures of 1-phenyl urazoles with diazomethane in ether solution (Scheme 2). He correctly concluded that “it is perfectly obvious that such reactions ... do not give us decisive evidence in regard to the relative amounts of the enol and keto forms in any given amide group in which the change from one tautomeric form to the other is very rapid in comparison with the reactions between the two forms and the alkylating reagents.” Furthermore, Acree derived an expression, identical in form to the Winstein–Holness equation, for the observed second-order rate constant for the appearance of total product as a function of the relative populations of the urazole enol and keto forms nearly a half-century before Winstein and Holness’s celebrated paper of 1955 (19). The thread of this principle was taken up again nearly 50 years later in 2003 (18) when an experimentally accessible efficiency parameter, defined only in terms of the four relevant rate constants (see eq. [2]), was introduced as a means to gauge the true efficiency of resolution of a chemical system obeying kinetic schemes as shown in Schemes 1 and 2 and having starting materials that are stereochemically related. This parameter was able to account for all experimentally observed cases between and including the limits of complete dynamic kinetic resolution (Acree–Curtin–Hammett conditions) and complete kinetic resolution (anti-Acree–Curtin–Hammett conditions).

$$[2] \quad \epsilon_{\text{DKR}} = \frac{rv + u}{rv + u + 1}$$

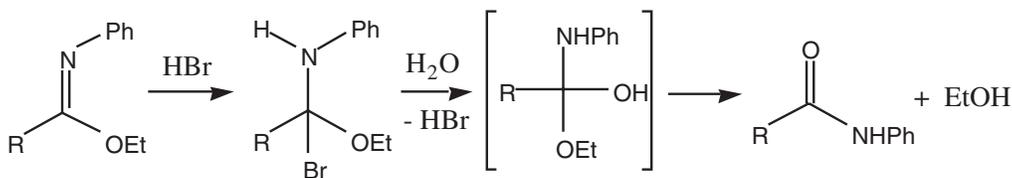
where $r = k_3/k_4$, $u = k_1/k_2$, and $v = k_2/k_3$.

Scheme 2.

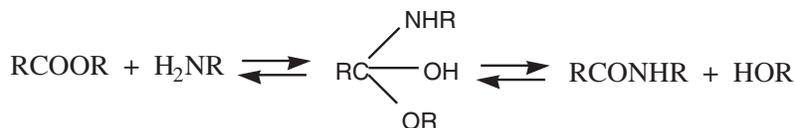


Before the notion of reaction intermediates was even conceived, mathematical laws of chemical kinetics (20) and the concept of catalysis (21) were already established by Jons J.

Scheme 3.



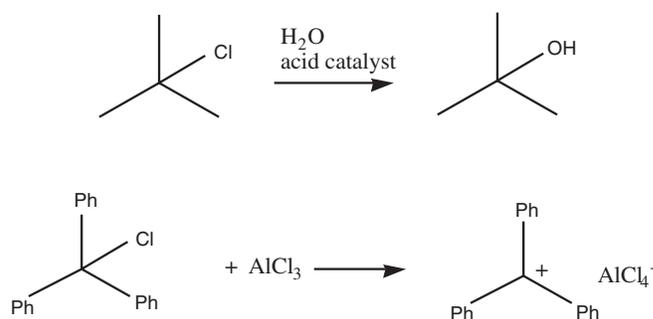
As written by Julius Stieglitz (1899):



Berzelius, Wilhelm Ostwald, and Jacobus H. van't Hoff. Ludwig Wilhelmy carried out the first reported kinetics experiment in 1850 when he examined the acid-catalyzed hydrolysis of cane sugar to invert sugar by polarimetry (22). The concept of the existence of reaction intermediates as chemical species of fleeting lifetimes originated in 1899 when Julius Stieglitz suggested the first mechanism of a chemical reaction when he examined the acid-catalyzed hydration of imidoethers via tetrahedral intermediates (Scheme 3) (23). James Norris in 1901 postulated the existence of carbocations, as it turns out the most extensively studied reaction intermediate class of all, when he examined the solvolysis of tertiary alkyl halides in acidic media (Scheme 4) (24). Almost simultaneously Adolf von Baeyer formulated the carbonium ion theory to account for the chemical behaviour and colour of triphenylmethane dyes such as fuchsine and crystal violet (Scheme 5) (25). A prominent American scientist, Gilbert N. Lewis, in the early part of the last century laid the foundation for a number of concepts that contributed greatly to the study of reaction mechanisms and reaction intermediates: octet rule in bonding (26), electrophilicity and nucleophilicity (27), inductive effect,³ the prediction that radicals could be studied by magnetic methods,⁴ Lewis acids and bases as electron acceptors and donors (27*b*), and the effect of resonance on electronic transitions (28).

Examination of the histogram in Fig. 1 shows the first "golden age" of physical organic chemistry in the 1930s and 1940s when simple reaction mechanisms were systematically categorized by type for the first time and new nomenclatures were introduced by Sir Christopher K. Ingold and his school such as E_{lc} (29), $\text{S}_{\text{N}}1$ and $\text{S}_{\text{N}}2$ (30), $\text{E}1$ and $\text{E}2$ (31), $\text{A}1$ and $\text{A}2$ (32), and $\text{B}1$ and $\text{B}2$ (32). Up to that time about 200 named organic reactions were already known since Wöhler's urea synthesis (33). The earliest attempts to understand reactivity in a systematic way were made by Sir Robert Robinson who formulated the familiar curly arrow notation to symbolize electron flow from electron donor groups to electron acceptor groups in an effort to determine patterns of reactivity in aromatic substitution reactions and to understand electronic effects of substituents on aromatic

Scheme 4.



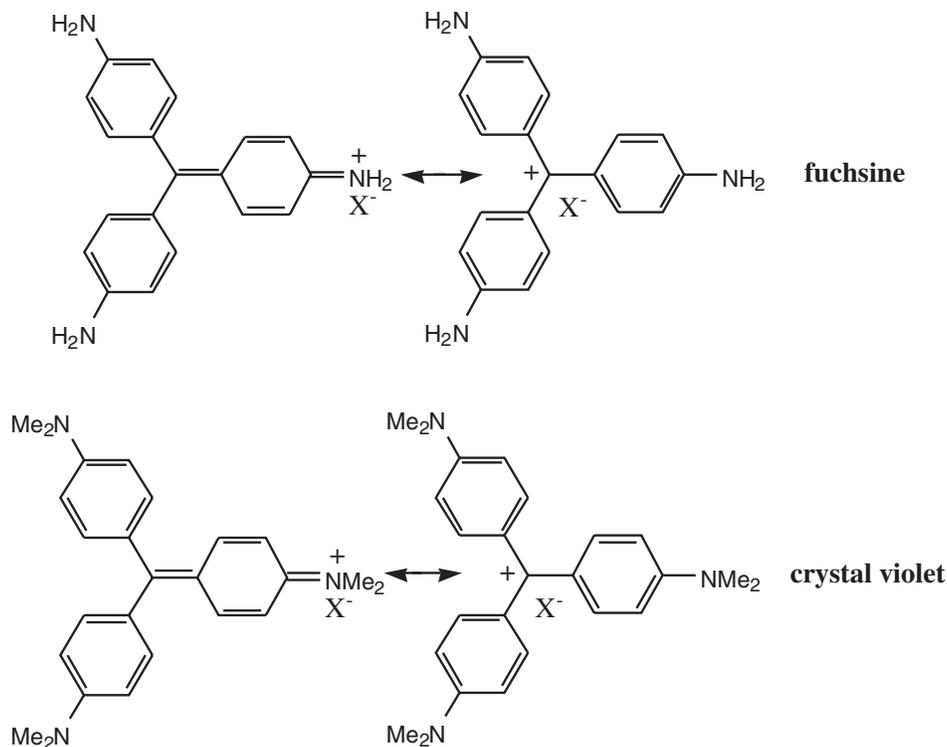
rings (34), and by Arnold F. Holleman who introduced the concept of directing groups in such reactions (35). Both Robinson and Ingold formulated the electronic theory of organic chemistry (36) though a bitter controversy over priority developed between them (37). The next major advances to be put forward during this period were by Johannes Brønsted (38), who introduced a linear double logarithmic correlation between rate constants and acid strength for acid- and base-catalyzed proton transfer reactions, by Louis Hammett (39), who introduced the general concept of linear free energy relationships and the quantitative partitioning of substituent effects via substituent constants, and by Henry Eyring (40), who introduced transition-state theory that linked measurable kinetic and thermodynamic parameters to explain the dynamics of bond-making and bond-breaking processes in elementary steps of a reaction mechanism. In a short time after the discovery of deuterium by Harold Urey in 1932 (41) powerful techniques for probing the nature of such transition states, particularly those pertaining to the rate-determining step, emerged; namely the determination of isotope effects on rate constants and equilibrium constants (42), isotopic labelling experiments (43), and isotopic exchange experiments (44). All of these advances helped to rationalize chemical reactions and gave chemists the confidence to predict product outcomes for new reactions that had yet to be carried out.

In the second golden age of physical organic chemistry in the 1950s and 1960s, attention shifted to the United States

³See ref. 20*a*, p. 139.

⁴See ref. 20*a*, p. 80, 148.

Scheme 5.



where the following people figured prominently in further developing ideas in the field: Paul D. Bartlett (Harvard), Ronald Breslow (Columbia), William von Eggers Doering (Columbia), George S. Hammond (Iowa State, Cal Tech), William P. Jencks (Brandeis), George A. Olah (USC), C. Garner Swain (MIT), Robert W. Taft, Jr. (Pennsylvania State, UC Irvine), Frank H. Westheimer (Harvard), and Saul Winstein (UCLA). Though Canadian university students of chemistry have heard of Winstein's name in connection with several concepts in physical organic chemistry as attested by the many things named after him, very few, if any, know that he was born and raised in Montreal, Quebec before embarking on a doctoral degree at Cal Tech under Howard J. Lucas and launching his legendary career at UCLA (45).

In this time period the invention of time-resolved techniques (46) for probing fast reactions resulted in an explosion of research on monitoring the temporal behaviours of a wide variety of transients in various media whose lifetimes are in the submillisecond to picosecond time domains. This second golden age was characterized by technological advances in instrumentation, which made it possible to probe the earliest stages of chemical processes in a reaction mechanism. The strength of these methods led mainly by flash photolysis provided direct observation of reaction intermediates by various kinetic and spectroscopic means. Both kinetic decay (or growth) curves and spectra of transients could thus be obtained. The invention of lasers by physicists and other electronic equipment by engineers and skilled technicians to rapidly convert optical signals into electrical signals and to capture, digitize, and store kinetic waveforms for subsequent analysis helped to propel this technique to the forefront of research. Modern day physical organic

chemists ought to therefore give these scientists the credit and respect that they so rightly deserve. The main condition for making the chemistry work by this method was the fact that targeted transients had to be generated by some photochemical reaction. Other techniques based on rapid mixing of solutions such as stopped-flow (46) or on applying sudden perturbations of temperature on solutions, commonly called the T-jump technique (46), also contributed to the study of reaction intermediates, but to a lesser extent. Virtually every kind of spectroscopy has been modified to become time-resolved in one way or another. Another useful technique pioneered by George C. Pimentel (47) to probe reaction intermediates is that of generating them in noble gas matrices at low temperatures and inferring their structure by IR, microwave, or UV spectroscopy in conjunction with theoretical calculations of their geometries at various levels of theory. IR spectroscopy is particularly useful since observed spectra can be directly compared with vibrational frequencies calculated from analyses of corresponding geometry optimized structures.

In recent years emphasis has shifted to the syntheses of thermodynamically and (or) kinetically stable analogs of reaction intermediates, essentially putting them in a bottle. This has led to a number of chemical curiosities (see Table S6 in the Supplementary materials).² Success can be achieved by judicious choice of substituents so as to impart stabilization by electronic and (or) steric effects or by generating them in exotic media that stabilize their structures such as "magic acid" (48), or by caging the intermediates in highly restricting media such as zeolite supercages (49). Another new frontier that is being examined is the probing of organometallic intermediate structures in important carbon-

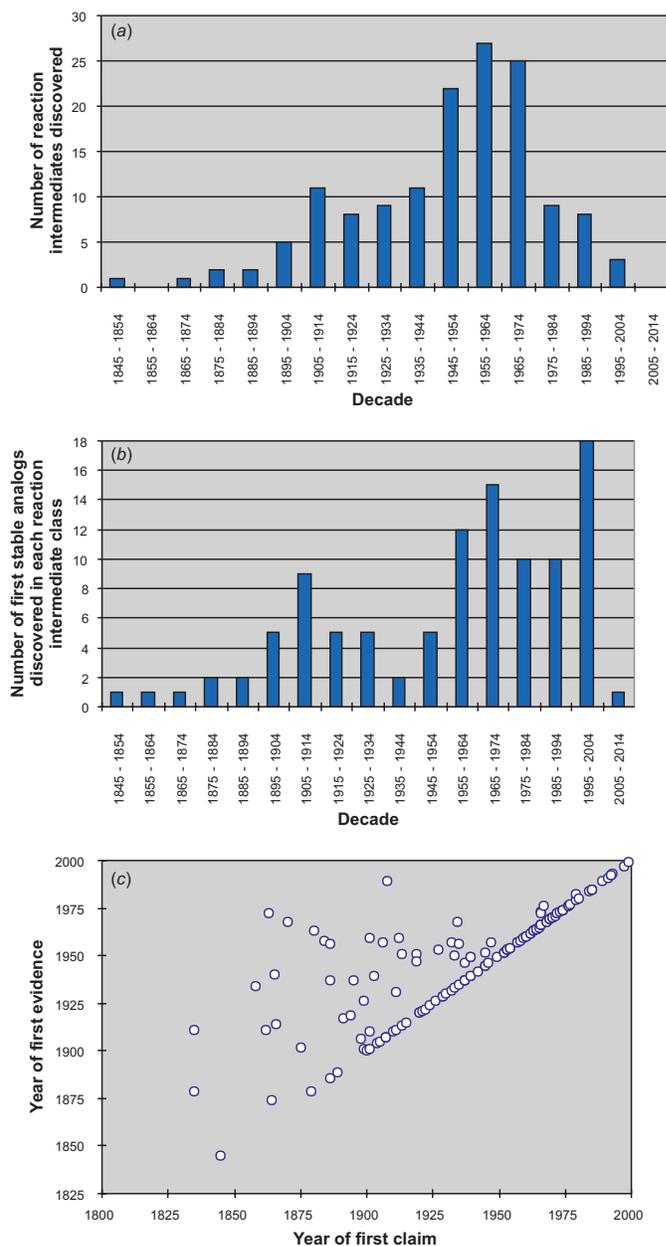
carbon bond-forming reactions that utilize organometallic catalysts, particularly those containing palladium and other transition metals (50).

Table S2 (Supplementary material)² summarizes important coined terms used in physical organic chemistry and reaction intermediate studies. It is instructive to point out here that a very effective way for a scientist to carve out their scientific niche and get attention for their work is to coin a particular word or phrase that over time will end up being synonymous with the discovery that they have made or the concept that they initiated and their persona. Perusal of this list shows some well-known coined name – scientist associations as well as some surprises, which even the seasoned practitioner in the field may learn about for the first time. The true measure of worth and recognition of an idea or concept is when other scientists use that idea or concept in their own work and even go further by building on top of it.

Chronology of discovery of reaction intermediates

Figures 2a and 2b show timelines of discovery of reaction intermediates and of stable analogs. Original references, including reviews, and schemes depicting reactions for all of these intermediates are compiled in the extensive database of Tables S5 and S6 (Supplementary material).² The histogram in Fig. 2a shows that the greatest number of intermediates were discovered during the second golden age of physical organic chemistry (mid-1940s to mid-1970s) that coincided with the advent of time-resolved techniques. Table 1 gives a detailed list of this chronology from Frey's nitroxide radical salt (1845) to Thomas Tidwell's basketenes (2000). Figure 2b shows the timeline of discovery of stable analogs of reaction intermediates, where it is observed that most of the advances have been made in the last 40 years particularly between 1995 and 2004. Figure 2c shows the correlation between first claim and first evidence of intermediate identification by experimental means. Not surprisingly the correlation is worse from the mid-19th century to the mid-20th century and improves markedly from about 1950 to the present day. During the early years, many intermediates were conjectured with little experimental evidence. Several years had to pass before their identities were finally confirmed, again largely thanks to technological advances that had to be developed in order for this to happen. Notable intermediates with extended time gaps between claim and discovery include: (i) the dication intermediate in the benzidine rearrangement confirmed by George Olah in 1972, 109 years after A.W. Hofmann's discovery of the rearrangement reaction in 1863; (ii) oxirene in Wolff rearrangement confirmed by Imre G. Csizmadia and Otto P. Strausz in 1968, 98 years after Marcellin Berthelot's first claim in 1870, which was later proven false, for the oxidation of propyne in the presence of chromic acid; (iii) Wallach intermediate confirmed by George Olah in 1963 in magic acid, 83 years after Otto Wallach's discovery of the rearrangement of aromatic azo-*N*-oxides; (iv) ynols confirmed by Robin Hochstrasser, Jakob Wirz, and A. Jerry Kresge in 1989, 81 years after Hermann Staudinger's confirmation that the ketene structure is not that of a hydroxyacetylene and 69 years after Charles D. Hurd's conjecture of the keteno–ynol tautomerism; (v) ketyl radicals

Fig. 2. (a) Histogram showing the timeline of discovery of reaction intermediates. See Table S5² for specific structures and references. (b) Histogram showing the timeline of discovery of the first stable analogs of reaction intermediates in each class by direct synthesis. See Table S6 in the Supplementary material² for specific structures and references. (c) Graph showing the correlation between first claim and first evidence of intermediate identification by experimental means.



confirmed by Wilhelm Schlenk in 1911, 76 years after A. Laurent's observation of coloured solutions of aromatic ketones upon exposure to sodium metal in 1835; (vi) acetoxy radicals confirmed in 1934, 76 years after B.C. Brodie's discovery of benzoyl peroxide in 1858; (vii) episulfonium ions confirmed by Reynold C. Fuson in 1940, 75 years after A. Cahours's synthesis of thiirane from dimethylsulfide and 1,2-dibromoethane in 1865; (viii) phenyl cation confirmed by Edward S. Lewis in 1954, 74 years after the discovery of

Table 1. Chronology of discovery of reaction intermediates.

Year	Reaction intermediate discovered (scientists) ^a
1845	Fremy's nitroxide radical
1874	Sulfonium ions (A. von Oefele, C. Schoeller, A. Cahours)
1879	Radical cations (A. Laurent, C. Wurster, H. Wieland)
1879	Wurster salts
1886	Janovsky complex
1889	Meisenheimer–Jackson complexes
1900	Gomberg radical
1901	Carbocations (J. Stieglitz, J.F. Norris, A. Baeyer)
1901	Piloty's nitroxide radical
1902	Enols (E. Erlenmeyer, A. Lapworth)
1904	Thiele biradical
1905	Ketenes (H. Staudinger)
1906	Phosphonium ions (A. Michaelis, A.E. Arbuzov)
1907	Chichibabin biradical
1907	<i>o</i> -Quinodimethanes (R. Willstaetter)
1910	Carbanions (V. Grignard, W. Schlenk)
1910	Niementowski's nitroxide radical
1911	Ketyl radicals (A. Laurent, W. Schlenk)
1911	Carbenes (A. Geuther, H. Staudinger, J. Hine)
1911	<i>o</i> - and <i>p</i> -Quinonemethides (H. Staudinger)
1913	2,4- and 2,5-Cyclohexadienones (H. McCombie)
1914	Radical anions (M. Berthelot, W. Schlenk)
1915	Schlenk–Brauns biradical
1917	Nitrenes (F. Tiemann, H. Staudinger)
1919	Phosphonium ylides (A. Michaelis, H. Staudinger)
1920	Hydronium ions (L.S. Bagster, G. Cooling, M. Volmer)
1920	Hydrazyl radicals
1921	Pyridine ylides (W. Scheider)
1922	Sulfimine ylides (F. Mann, W.J. Pope)
1924	Flavylium salts (R. Robinson)
1926	Tetrahedral intermediates (J. Stieglitz, F. Swarts)
1926	Kenyon–Banfield radical
1929	Gas-phase alkyl radicals (F. Paneth)
1929	Ammonium ylides (C.K. Ingold)
1930	Sulfonium ylides (C.K. Ingold)
1931	Halonium ions (A. McKenzie, R. Kuhn, C.K. Ingold)
1932	Iminium ions (T.D. Stewart, W.E. Bradley)
1933	Solution-phase alkyl radicals (M.S. Kharasch)
1934	Acetoxy radicals (B.C. Brodie, D.H. Hey, W.A. Waters)
1935	Norrish type I and II biradicals
1937	Benzyl radicals (A. Michaelis, M.S. Kharasch)
1937	Aryl radicals (E. Bamberger, O. Kuehling, W.A. Waters)
1937	Acylium ions (L.P. Hammett, M. Bender)
1937	Acylammonium ions
1937	Meerwein salts
1939	Benzoyl radicals (J.F. Norris, H.H. Glazebrook, T.G. Pearson)
1939	Müller–Neuhoff biradical
1939	Mercurinium ions (H.J. Lucas)
1940	Episulfonium ions (A. Cahours, R.C. Fuson)
1942	Acetoxonium ions (S. Winstein)
1945	Phosphinyl radicals (M.S. Kharasch)
1945	Excited-state triplet ketones (G.N. Lewis, M. Kasha)
1946	Nitronium ions (C.K. Ingold, R.J. Gillespie)
1946	Aziridinium ions (J.S. Fruton, M. Bergmann)
1947	<i>p</i> -Quinodimethanes (W. Schlenk, M. Szwarc)
1949	Bridged carbocations (C.L. Wilson, S. Winstein)

Table 1 (continued).

Year	Reaction intermediate discovered (scientists) ^a
1949	Nonclassical ions (C.L. Wilson, S. Winstein)
1949	Phenonium ions (D.J. Cram, S. Winstein)
1950	Germynes (P. Royen, R. Schwarz, S.N. Glarum, C.A. Kraus)
1951	Nitrenium ions (J. Stieglitz, C.K. Ingold)
1951	Metallocenes (F. Hein, P.L. Pauson, G. Wilkinson, R.B. Woodward)
1952	Aromatic π complexes (M.J.S. Dewar, H.C. Brown)
1952	Metal carbenoids (P. Yates)
1952	Nitrosonium ions (C.K. Ingold)
1952	Methoxonium ions (S. Winstein)
1953	Benzynes (W.E. Bachmann, H.T. Clarke, J.D. Roberts)
1953	Aromatic σ complexes (M. Kilpatrick, G.A. Olah, H.C. Brown)
1953	Doering–Zeiss intermediate
1953	Peroxy radicals
1953	Phenoxy radicals (E. Muller, C.D. Cook)
1954	Phosphonium betaines (G. Wittig)
1954	Tropylium ions (W.v.E. Doering)
1956	Nitrilium ions (E. Beckmann, F. Klages, W. Grill, I. Ugi)
1956	Wheland intermediate (H.C. Brown, G.A. Olah)
1957	Aminyl radicals (H. Wieland)
1957	Koelsch radical
1957	Silyl radicals (F.C. Whitmore, R.N. Haszeldine)
1957	Cyclopropenyl cations (R. Breslow)
1957	Flavinium salts (A. Robertson, W.B. Whalley)
1958	Phenyl cation (T. Sandmeyer, E.S. Lewis)
1958	1,3-Dioxolenium ions (H. Meerwein)
1959	Pyrylium salts (A. Werner, A.T. Balaban)
1959	Nitroxyl radicals (H. Wieland, K.H. Meyer, O.L. Lebedev)
1959	Phosphoranyl radicals (C. Walling)
1960	Thiocarbonyl ylide (G. Wittig)
1960	Vinyl cations (C.A. Grob, P.E. Peterson)
1960	Wanzlich carbenes
1962	Nitrile ylide (R. Huisgen)
1962	Carbonyl oxide (Criegee zwitterion) (R. Criegee, P.D. Bartlett)
1963	Wallach intermediate (O. Wallach, E. Bunzel, G.A. Olah)
1963	1,3-Dipole traps (R. Huisgen)
1963	Dinitrenes (A.M. Trozzolo, E. Wasserman)
1963	Verdazyl radicals (R. Kuhn)
1964	Violenes (S. Hünig)
1964	Thiophenoxy radicals (U. Schmidt)
1964	Phenylselanyl radicals (U. Schmidt)
1964	Fischer carbene
1964	Vinylidene carbenes (H.D. Hartzler, W.J. le Noble)
1964	Iminoxyl radicals (J.R. Thomas)
1965	Phosphinoyl radicals
1966	Dications in magic acid (G.A. Olah)
1966	Acyl radicals (H.G. Kuivila, E.J. Walsh, Jr.)
1966	Stannyl radicals
1966	Silylenes (P.P. Gaspar)
1968	Oxirene (M. Berthelot, W. Madelung, I.G. Csizmadia, O. Strausz)
1968	Vinylidenes (G.H. Coleman, R.D. Maxwell, M.S. Newman, P.J. Stang)
1968	Allene oxides (J.K. Crandall)

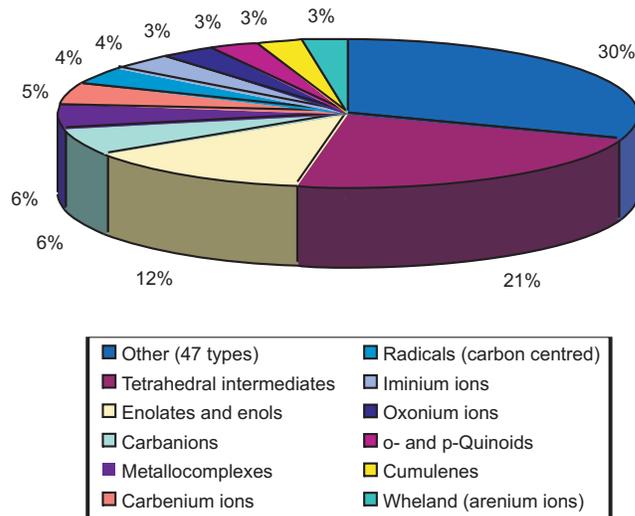
Table 1 (concluded).

Year	Reaction intermediate discovered (scientists) ^a
1968	Trinitrenes (E. Wasserman)
1969	Azomethines
1969	<i>N</i> -Alkoxy- <i>N</i> -alkylamino radicals
1969	Thiirenium ions (G. Modena)
1970	Carbonyl ylide (D.R. Arnold)
1970	Phosphinothioyl radicals
1970	Transition-metal vinyl cation complexes (H.C. Clark, R.J. Puddephatt)
1971	Nicholas cation
1972	Dication in benzidine rearrangement (A. Hofmann, G.A. Olah)
1972	Transition metal vinylidene complexes (O.S. Mills, A.D. Redhouse, R.B. King)
1972	Amido radicals
1972	Transition-metal keteniminium complexes
1973	Oxenium ions (R.A. Abramovitch)
1973	Transition-metal carbyne complexes (E.O. Fischer)
1974	Carbynes (O.P. Strausz)
1974	Propadienones (R.F.C. Brown)
1974	Schrock carbene
1976	Thionitroxide radicals (J.E. Bennett, W.C. Danen)
1976	Thioaminy radicals (W.C. Danen)
1976	Transition-metal ketenyl complexes (F.R. Kreissl)
1976	Transition-metal vinylidenecarbene (allenylidene) complexes (E.O. Fischer)
1977	Transition-metal silene complexes
1979	Butatrienones (R.F.C. Brown)
1980	2,4- and 2,5-Cyclohexadienimines
1982	Ketene zwitterions (R. Gompper, U. Wolf, J. Pacansky, J.C. Scaiano)
1984	Trapping of carbenes via ylide formation (J.C. Scaiano , M.S. Platz)
1985	Bertrand carbene
1985	<i>N</i> -Thiosulfonamidyl radicals (Y. Miura)
1985	Distonic radical cation (L. Radom)
1989	Ynols (H. Staudinger, C.D. Hurd, R. Hochstrasser, J. Wirz, A.J. Kresge)
1989	Oxonium ylides (W. Kirmse)
1991	Arduengo carbene
1992	Iminopropadienones (C. Wentrup)
1992	Trimethylsilyl substituted bisketenes (T.T. Tidwell)
1993	Silylium ions (C.A. Reed)
1997	Allenylketenes (T.T. Tidwell)
1999	Phosphenium ions (M.K. Denk)

Note: See Table S5 in the Supplementary material² for references.

^aBolded entries represent contributions by scientists working in Canadian universities or at the National Research Council of Canada.

the Sandmeyer reaction in 1884; (ix) nitrilium ions confirmed by F. Klages, Ivar Ugi, and A. Hassner between 1956 and 1966, 70–80 years after the discovery of the Beckmann rearrangement of 1886; (x) pyrylium ions confirmed by A. Balaban's synthesis of pyrylium salts in 1959, 58 years after Alfred Werner's initial observations in 1901; (xi) benzyl radicals confirmed by Morris S. Kharasch in 1937, 51 years after August Michaelis's synthesis of tribenzylarsine from benzyl chloride and arsenic trichloride in 1886; and (xii)

Fig. 3. Pie chart showing the frequency of occurrence of reaction intermediate types in named organic reactions that constitute the library of reactions used in organic synthesis.

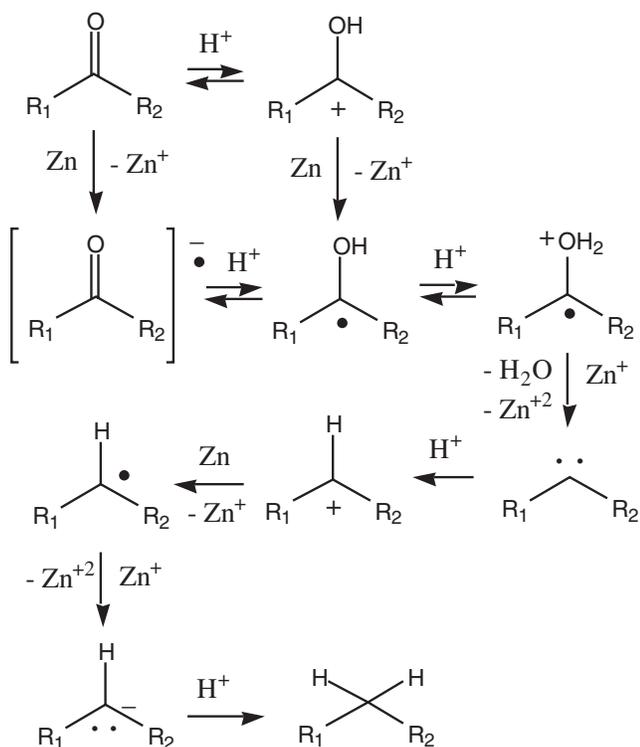
carbenes confirmed by Hermann Staudinger in 1911 in the thermal and photochemical Wolff rearrangement of diazoketones and by Jack Hine in 1950 in the haloform hydrolysis reaction under basic conditions 49 and 88 years, respectively, after A. Geuther's conjecture of their existence in the hydrolysis of chloroform in base in 1862.

Reaction intermediates in organic synthesis

Figure 3 illustrates the frequencies of occurrence of each of the major classes of intermediates in the library of organic reactions used in synthesis and Table S3 (Supplementary material)² lists the specific reactions corresponding to each intermediate type. Organic reactions may be classified succinctly according to the following types: carbon–carbon and non-carbon–carbon bond-forming reactions (includes additions, cyclizations, and couplings), condensations, multicomponent reactions, oxidations and reductions with respect to the substrate of interest, rearrangements, substitutions, and fragmentations or eliminations. The first four reaction types figure prominently in skeletal building, or *aufbau* type, reactions, which are the most important class of organic reaction in synthesis. The documentation of carbon–carbon bond-forming reactions dates back to the early part of the 19th century with Faraday's electrochemical synthesis of hydrocarbons from carbon monoxide, carbonic acid, and hydrogen in 1834 (51), Robert Kane's aldol condensation in 1838 (52), and Strecker's synthesis of α -cyanoamines from aldehydes, hydrocyanic acid, and ammonia in 1850 (53). The top five most frequently appearing intermediates in organic reactions based on a library of 435 reactions (4, 54) are: tetrahedral intermediates (21%), enols and enolates (12%), carbanions (6%), metallocomplexes (6%), and carbenium ions (5%).

The ease or difficulty in elucidating reaction mechanisms depends on the reaction type. Tetrahedral intermediates, enols, enolates, and carbanions figure heavily in skeletal building reactions. It is fairly straightforward to write out reasonable reaction mechanisms for organic reactions involving these

Scheme 6.



species in carbon–carbon and non-carbon–carbon bond-forming reactions, condensations, and multicomponent reactions. Historically, substitution reactions and their associated mechanistic types (SN1, SN2, E1, E1cb, E2, and electrophilic and nucleophilic aromatic), as noted previously, are the best characterized. The elucidation of rearrangement reactions, on the other hand, is less straightforward and is strongly connected to the identification of specific reaction intermediates. Studies of carbenium ions and other cationic intermediates in acid-catalyzed reactions are particularly noteworthy in this regard such as the Wagner–Meerwein rearrangement. Generally, this class of reactions is the most challenging to elucidate and are often the subject of mechanistic puzzles. Labelling experiments are particularly helpful in decoding molecular reorganization processes. Oxidation and reduction reactions with respect to the substrate of interest are the least well-characterized mechanistically in terms of acquiring spectroscopic and kinetic data. This may be due to the fact that many of them occur in heterogeneous media, involve metals or organometallic species, or are surface reactions where traditional methods employed successfully in homogeneous phases may not be adequate to handle the complexities of kinetic treatments, in particular. It is probably in this class of reactions where mechanistic chemists may find it fruitful to explore uncharted territory, particularly with respect to inventing improved redox catalysts for industrial processes and understanding redox cascades in biological processes such as photosynthesis and nitrogen fixation that involve metal-containing enzymes. However, organometallic esters have been reasonably characterized for simple oxidation reactions such as the Criegee glycol cleavage (cyclic lead ester), Hooker oxidation (cyclic manganate es-

ter), Jones oxidation (chromate ester), Lemieux–Johnson oxidation of olefins to 1,2-diols (cyclic osmate ester), Lemieux–Johnson oxidative cleavage of olefins to aldehydes (cyclic osmate ester), permanganate oxidation of olefins to 1,2-diols (cyclic manganate ester), Sarett procedure (chromate ester), Sharpless oxyamination (cyclic osmate ester and cyclic osmate amide), and Sharpless–Jacobsen dihydroxylation (cyclic osmate esters). Ozonides are also well-documented as intermediates in the Harries ozonolysis reaction. Browsing through Table S3² shows that reduction reactions may involve carbanion, carbene, radical, radical anions, or ylide intermediates. It is interesting to note that the Clemmensen reduction of ketone groups to methylene groups in acidic media potentially proceeds by the greatest number of intermediate types of any reaction. As shown in Scheme 6, the four-electron redox reaction can be postulated to proceed successively via radical anion, ketyl radical, carbene, carbenium ion, carbon centered radical, and finally carbanion intermediates. Table S4 (Supplementary material)² lists those named organic reactions that do not proceed via reaction intermediates and thus occur by concerted processes involving either asynchronous or synchronous bond-forming and bond-breaking processes in the transition states.

Identification of reaction intermediates — The underlying logic of it all

In determining the identity of a reaction intermediate in a thermal or photochemical transformation there are a number of steps that need to be followed. The first thing is to precisely determine the structures of the starting substrate structures as well as the final product structures, including their distribution. At this stage, comparison of product and reactant structures can lead to educated guesses as to the possible structures of transient species. This kind of analysis was the basis of understanding rearrangement reactions such as the Wagner–Meerwein rearrangement where carbocation intermediates were postulated, or the Wolff and Curtius rearrangements where carbene and nitrene intermediates were conjectured. Julius Stieglitz, James F. Norris, and Frank C. Whitmore were the first to successfully use this technique in predicting likely transient species in such reactions (23, 24, 55). Astute chemists know that often it is the minor products of a reaction that give the most important clues as to the kind of mechanism that may be operative and the speciation of the suspect transient. Examples include liberated gases such as nitrogen (eliminated in Bamford–Stevens oxidation of hydrazones via carbenes, Curtius rearrangement via nitrenes, cyclopropanation with diazomethane via carbenes, diimide reduction via radicals, 1,3-dipolar additions of 1,2-diazoles to olefins, Gatterman reaction via arylum ions or aryl radicals, Gomberg–Bachmann and Meerwein arylation reactions via aryl cations, McFadyen–Stevens reaction via nitrenes, radical dehalogenation via radicals, Sandmeyer reaction via arylum ions or aryl radicals, Schiemann reaction via arylum ions or aryl radicals, Schmidt rearrangement via nitrenes, Staudinger reaction via nitrenes, Tiffeneau–Demjanov reaction via ring expansion, von Richter reaction via carbanions, Wharton reaction via tetrahedral intermediates, Wolff rearrangement reaction via carbenes, and Wolff–Kishner re-

duction via carbanions, iminium ions, and tetrahedral intermediates), hydrogen (eliminated in Chichibabin reaction via carbanions, Corey–Bakshi–Shibata reduction via ylides, Corey–Chaykovsky epoxidation reaction via carbanions, Gribble reduction of diarylketones via tetrahedral intermediates, Wadsworth–Horner–Emmons reaction via carbanions, and Williamson ether synthesis via alkoxides), carbon dioxide (decarboxylations in Borodin–Hunsdiecker reaction via acetoxy radicals, Corey–Winter reaction via carbenes and ylides, Dakin–West reaction via tetrahedral intermediates, diimide reduction via radicals, Eschweiler–Clarke reaction via iminium ions, Hofmann–Martius rearrangement via nitrenes, Hooker oxidation via enols, Kochi reaction via carbenium ions, Leuckart reaction via tetrahedral intermediates, Lossen rearrangement via nitrenes, malonates, and acetoacetates via tetrahedral intermediates, Perkin rearrangement via tetrahedral intermediates, and Schmidt rearrangement via nitrenes), ethylene (eliminated in ring-closing metathesis reactions via organometallic intermediates), hydrogen sulfide (eliminated in Willgerodt–Kindler reaction via tetrahedral intermediates and thiirenium ions), and sulfur dioxide (Ramberg–Bäckland rearrangement via carbanions). Products arising from recombination of fragments generated in a reaction are a signature of radicaloid processes such as 1,2-diphenylethane (dibenzyl), which arises by recombination of benzyl radicals.

There are a number of techniques that can be used to probe or interrogate a reaction between reactants and products. These fall into two main categories: indirect or direct methods. Under indirect methods we have: trapping or quenching kinetic and spectroscopic experiments, which introduce one or more chemical species that react noncompetitively or competitively with the generated intermediate, isolation of the trapped products from the quenching method, isotopic labelling studies, and pH – rate profile behaviour. Under direct methods we have: kinetic and spectroscopic time-resolved techniques that estimate the lifetimes and spectral properties of transient species, direct isolation or “freezing out” of intermediates in restricting media, and direct synthesis of thermodynamically and (or) kinetically stable analogs.

In the quenching technique one aims to use probe molecules that are unique or near-unique traps for the particular transient investigated, rather than promiscuous ones. One key assumption that needs to be experimentally verified is that the trapping agents should not undergo secondary reactions under the prescribed experimental conditions. Examples of specific traps are azide ion for carbenium ions; whereas, examples of promiscuous traps are oxygen that can quench excited state triplet species by triplet–triplet annihilation and carbon centred radicals to give peroxy radicals, and pyridine that can quench ketenes to ketene zwitterions and carbenes to pyridine–carbene ylides. However, specific quenching may not be so simple and often the strategy is to use a combination of trapping agents and then to look for consistency in their kinetic and spectroscopic behaviour. If an intermediate is suspected to be electrophilic then nucleophilic traps are selected, as in the case of cationic transients that are quenched by nucleophilic species with electron-donating groups, lone pairs of electrons, or negatively charged atoms. If an intermediate is suspected to be

nucleophilic then electrophilic traps are chosen, as in the case of anionic transients that are quenched by electrophilic species with electron-withdrawing groups, electron-accepting centres, or positively charged atoms. Table 2 summarizes sets of quenchers that have been used to identify various reaction intermediate families. Sometimes trapping agents lead to secondary transients that themselves degrade. The probe technique to “see” spectroscopically invisible transients is particularly important here (56). For example, carbenes absorbing in the UV may be quenched by pyridine to yield coloured carbene ylides absorbing in the visible range, which in turn may be trapped with dimethoxycarbonylacetylene (Scheme 7). Transient ketenes may be first quenched by pyridine to produce ketene zwitterions. These adducts can conceivably undergo further trapping reactions with 1,4-dipolarophiles by analogy with pyridine carbene ylides that can be trapped with 1,3-dipolarophiles (Scheme 8) (57).

Isolation of the final products from quenching experiments can further corroborate structural assignments of the investigated transient species. Stereochemical aspects are often very helpful in this regard. Notable examples are the establishment of the connection between the Walden inversion rule and the S_N2 mechanism (58) and the trapping of singlet vs. triplet carbenes by olefins to give cyclopropane derivatives (59). The trapping of transients to yield stable isolable compounds such as transition-metal complexes has also been of great value. Ernst O. Fischer’s pioneering work in trapping carbenes, carbynes, and ketenes using tungsten, molybdenum, and chromium carbonyls are good examples of this technique (60).

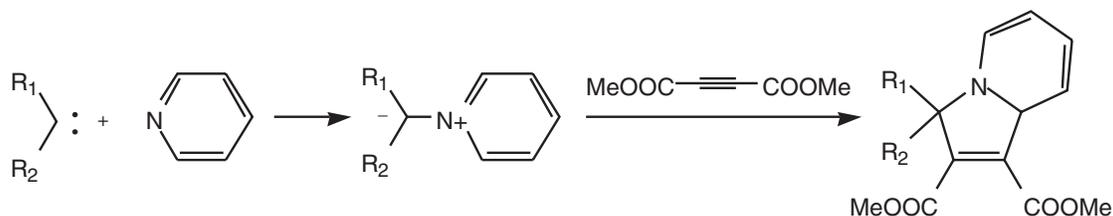
Deuterium and C13 labelling studies, including the measurement of kinetic primary and secondary isotope effects, can inform which bonds are being made and broken in particular steps in the proposed mechanism, particularly the rate-determining step. Scrambling of isotopic labels usually infers the presence of a symmetrical intermediate. For example, oxirenes have been inferred as possible intermediates in the Wolff rearrangement of diazoketones to carbenes and then ketenes (61), and thiirenium ions have been inferred in the cyclization–elimination reaction of thioalkoxy substituted vinyl sulfonates (62). If it is suspected that the transient structure has ionizable groups then the acquisition of pH – rate profiles are particularly useful, since their shapes reveal important kinetic and thermodynamic parameters. Enols are particularly noteworthy. Also, the form of buffer catalysis gives insights about whether general or specific acid- or base-catalysis mechanisms are operative. An important point to keep in mind is that such experiments need to be conducted in aqueous media so that meaningful kinetic and thermodynamic parameters can be determined, as well as their dependencies on acid or base concentration. Also, for meaningful comparisons to be made between related chemical structures of any reaction intermediate class, it is best to conduct experiments in a uniform medium under a standard set of conditions. For example, aqueous solution at an ionic strength of 0.1 mol/L NaCl or NaClO₄ at 25 °C and 1 atm (1 atm = 101.325 kPa).

The determination of rate laws for the dependence of observed rate constants on concentrations of various species gives important information about the molecularity and

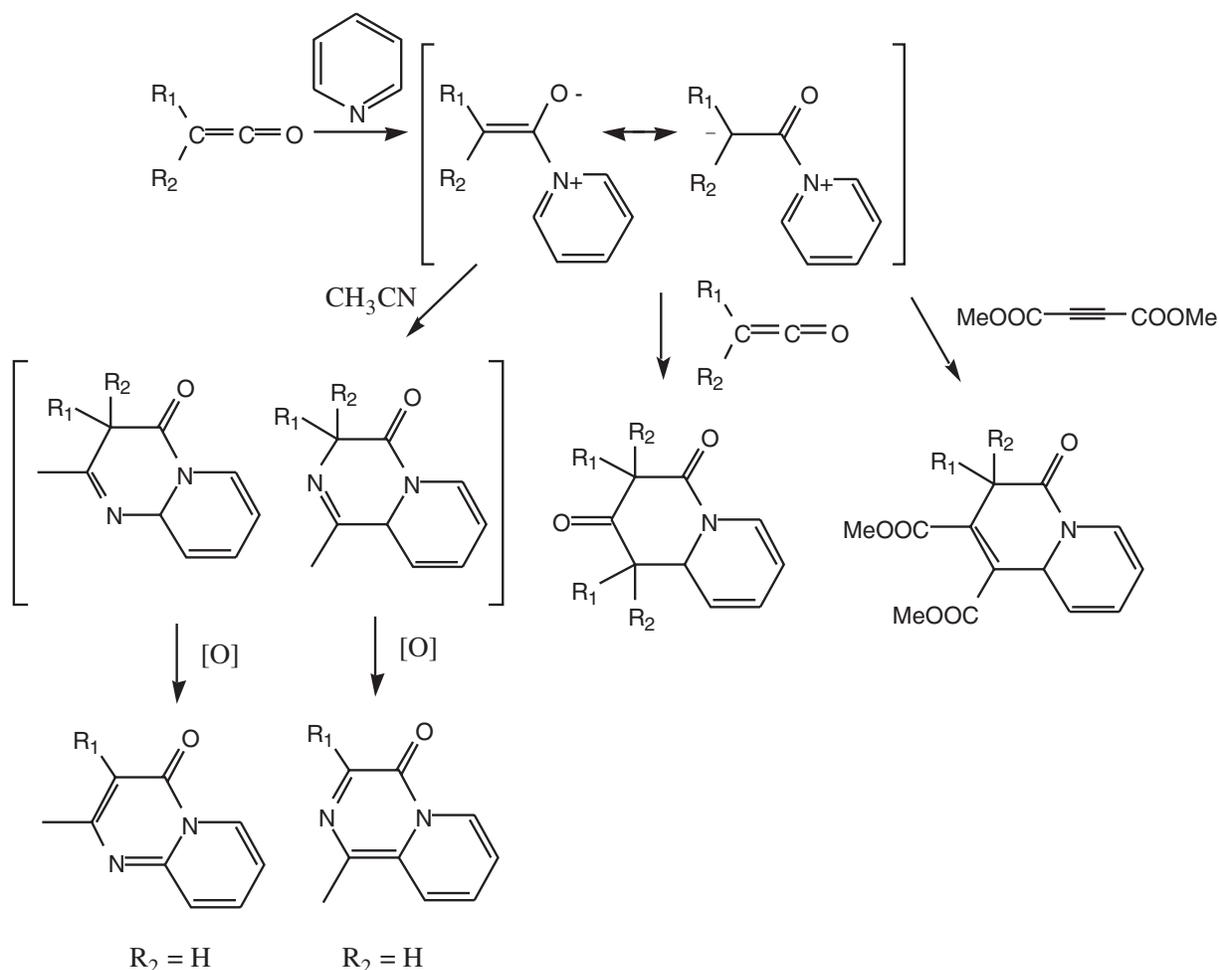
Table 2. List of quenchers used for each reaction intermediate group.

Reaction intermediate group	Quenchers used
Carbenes	Alcohols Diazocompounds Halogen donors (e.g., carbon tetrachloride, chloroform) Hydrogen donors (e.g., <i>n</i> -hexane, methanol, isopropanol, isooctane, trialkyltin hydride) Imines Ketones (e.g., Michler's ketone, acetone) Maleic acid, dimethyl ester Nitriles (e.g., acetonitrile) Olefins Oxygen Pyridine 2,2,6,6-Tetramethylpiperidine- <i>N</i> -oxide (TEMPO) Thioketones (e.g., adamantanethione) Thiols Triethylamine
Carbocations	Alcohols (e.g., methanol, ethanol, hexafluoroisopropanol, trifluoroethanol) Azide ion 1,3,5-Trimethoxybenzene
1,3-Dipoles	Hydrogen donors (e.g., <i>n</i> -hexane, methanol, isopropanol, isooctane, trialkyltin hydride) Olefins
Excited state triplets	Aromatics (e.g., azulene, xylenes, 1,4-dimethoxybenzene, 9,10-dibromoanthracene) Diethylsulfide Iodine Methyl viologen Olefins (e.g., acrylonitrile, styrene, methylmethacrylate, vinylacetate, 1,1-diphenylethene) Oxygen Peroxy compounds (e.g., di- <i>tert</i> -butylperoxide, benzoyl peroxide) Phenols 2,2,6,6-Tetramethylpiperidine- <i>N</i> -oxide (TEMPO) Triethylamine Nitrous oxide Di- <i>tert</i> -butylnitroxide
Ketenes	Alcohols Primary and secondary amines Pyridine 2,2,6,6-Tetramethylpiperidine- <i>N</i> -oxide (TEMPO) Water
Nitrenes	Nitriles (e.g., acetonitrile)
Radicals	Alcohols Chloranil 1,4-Cyclohexadiene 2,3-Dichloro-5,6-dicyanobenzoquinone (DDQ) Halogen donors (e.g., carbon tetrachloride, chloroform) Hydrogen donors (e.g., <i>n</i> -hexane, methanol, isopropanol, isooctane, trialkyltin hydride) Ni(acac) ₂ , Fe(acac) ₃ Nitrones Nitroso compounds Olefins Oxygen 2,2,6,6-Tetramethylpiperidine- <i>N</i> -oxide (TEMPO) Tetracyanoethylene (TCNE) Tetracyano- <i>p</i> -quinodimethane (TCNQ) Thiols

Scheme 7.



Scheme 8.



structure of the rate-limiting transition state. Limiting or asymptotic approximations with respect to relative rate constant magnitudes and (or) concentrations of catalyst, quencher, or reactant such as preequilibrium and steady-state approximations are especially useful in verifying rate law behaviours under simplified experimental conditions.

Direct methods are the most convincing in identifying transients, but comparisons of results with known reactions and with other indirect methods previously described are still necessary to obtain a complete story. Time-resolved techniques such as flash photolysis, pulse radiolysis, stopped-flow, and temperature jump allow both detailed kinetic and spectroscopic measurements to be made. In flash photolysis, pulse radiolysis, and temperature-jump techniques, chemical systems are suddenly perturbed by excita-

tion pulses of light, electron beams, or heat, which results in the generation of the transient in solution. The stopped-flow technique involves rapid mixing of two solutions containing substrates. A thermal reaction proceeds giving rise to corresponding transient species once these solutions come into contact with one another. In all cases, once a transient is generated the optical density of the reaction solution is altered and the temporal dependence of this optical density change is monitored. The reaction solution is said to be "probed" by some spectroscopic means such as by UV-vis, IR, EPR, or NMR. Characteristic kinetic behaviours with respect to quenching experiments, such as magnitude of quenching rate constants, order of reaction, dependence of observed rate constants on catalyst concentration, and mathematical forms of the disappearance of substrate and appear-

ance of product as functions of time, and characteristic spectroscopic absorption markers, such as unique absorption bands, help to eliminate false candidates and narrow down the possibilities. The key condition to “catch” or view a transient is that the time resolution of the apparatus used must be smaller than the expected lifetime of the transient. Time resolutions range from several seconds in standard UV spectrophotometric devices to picoseconds in laser flash photolysis apparatuses. Obvious chemical constraints in using these techniques are the kinds of chemical reactions and precursors that are available to generate the appropriate intermediates. Photoreactions are necessary if flash photolysis is to be used and thermal reactions are necessary if T-jump or stopped flow is to be used. Often the choice of precursor is dictated by the suspected identity of the transient. Again, the library of known reactions is of great value in this selection.

Generation of intermediates in highly restricting media such as low-temperature noble gas matrices or organic glasses, or at room temperature in zeolites where the possibility of further reaction is severely impeded is also a powerful way of directly viewing transient species. Transients may be generated photochemically from appropriate precursors that are themselves trapped in a restricting matrix, or by flash vacuum pyrolysis of a substrate in the gas phase where the target intermediate is first generated and then subsequently trapped at 10 K in an argon matrix deposited on a KBr window using a cryostat apparatus. Once trapped, the spectrum of a transient may be obtained and its structure inferred from difference spectra in which the background spectrum of the matrix medium is subtracted out. Often such studies are done in conjunction with computational studies to determine their theoretically predicted IR, UV, or microwave spectra and to compare these with the experimental ones. Matching of spectra constitutes corroborative evidence for transient identification.

The most direct method is the synthesis of a thermodynamically stable analog, effectively bottling the intermediate as a *bona fide* isolable compound. This allows the complete characterization of the structure by conventional means such as boiling point, melting point, ^1H and ^{13}C NMR, IR, and UV spectroscopy, mass spectrometry, and X-ray crystallography. To make this strategy work, all available knowledge gained from previous methodologies is used. Thermodynamic stability is influenced by such factors as increased steric crowding, counterbalancing electronic effects by judicious choice of substituents, and topology. Highly stable analogs of reaction intermediates as summarized in Table S6 (Supplementary material)² have been found by using one or more of these strategies. Often such chemical curiosities have been discovered by accident rather than by design.

Like most of the thinking done in an empirical science, chemistry relies heavily on comparing new results with the growing empirically derived database or library of past re-

sults. The common paradigm is to select special reactions or conditions as “standards”, which can be used as yardsticks or comparators for other reactions or conditions.⁵ This, for example, is the basis of the linear free energy relationship analysis and compilation of various substituent constants advanced by Hammett, Taft, and others. Substituent effect experiments fine-tune our understanding of the nature of the rate-determining step, which involves a key intermediate. Such questions as charge distribution in the rate-determining transition state, its position along the reaction coordinate relative to reactants and immediate products, and degree of proton transfer, if applicable, may be answered. Also, changes in curvature of Brønsted and Hammett plots and pH – rate profiles may be interpreted as changes in rate-determining step occurring if downward bends (concave down curvature) are observed or as changes in reaction mechanism occurring if upward bends (concave up curvature) are observed.

Naturally, as the database of knowledge increases, comparisons between new and known reactions become more reliable and hence one’s guesses as to the identity of reaction intermediates improve markedly. In terms of the decision trees shown in Figs. 4a–4d, one need not start at the top and work their way down, but begin somewhere in the middle and quickly gravitate to the likely transient structure in a few iterations of experimentation.

If one knew nothing about a suspected transient at all or had no precedent of analogous reactions to go by in the identification process, then the multiplicity assignment of the transient becomes the uppermost question in the decision tree. Overall, the key concept is to corroborate evidence from various methods so that a consistent picture is built for transient identification, keeping in mind the caveat given in the introduction that *definitive* proof is not possible, but *corroborative* proof is. It may be argued that corroborative proof may evolve into definitive proof the longer the evidence stands the test of time and further experimentation by ever more techniques. Corroboration of experimental results with theoretical computational studies of possible stable geometries and energetics of chemical species from reactants to products, including intervening intermediate structures with associated transition states in each step, is also a very useful strategy. The aim is to map out a complete energy reaction coordinate profile or surface showing the number of sequential elementary steps, the number of relevant transition states, the number of possible intermediates, the structures of all chemical species, and the energy differences between one structure and the next. Relationships such as the ones shown in eq. [3] become useful. The determination of reaction energy barriers and relative thermodynamic stabilities of reactants and products is important in identifying kinetic and thermodynamic control processes, particularly when they operate synergistically or antagonistically

⁵Unfortunately, nucleophilicity, which is a ubiquitous chemical phenomenon, continues to be poorly described in pure quantitative terms from a theoretical point of view. No one universal standard reaction or set of standard reactions have been found to describe nucleophilicity adequately for all chemical structures or reaction types. Practically all existing scales break down at some point. The best that has been accomplished is to use entirely empirical approaches such as the ones advanced by Mayr and co-workers (63) based on extensive families of correlations. On the other hand, proton and electron transfer reactions are both rigorously described in theoretical and quantitative terms. In such reactions protons or electrons are either consumed or produced regardless of the chemical structures of reactants and products involved. This commonality greatly simplifies comparisons between reactions.

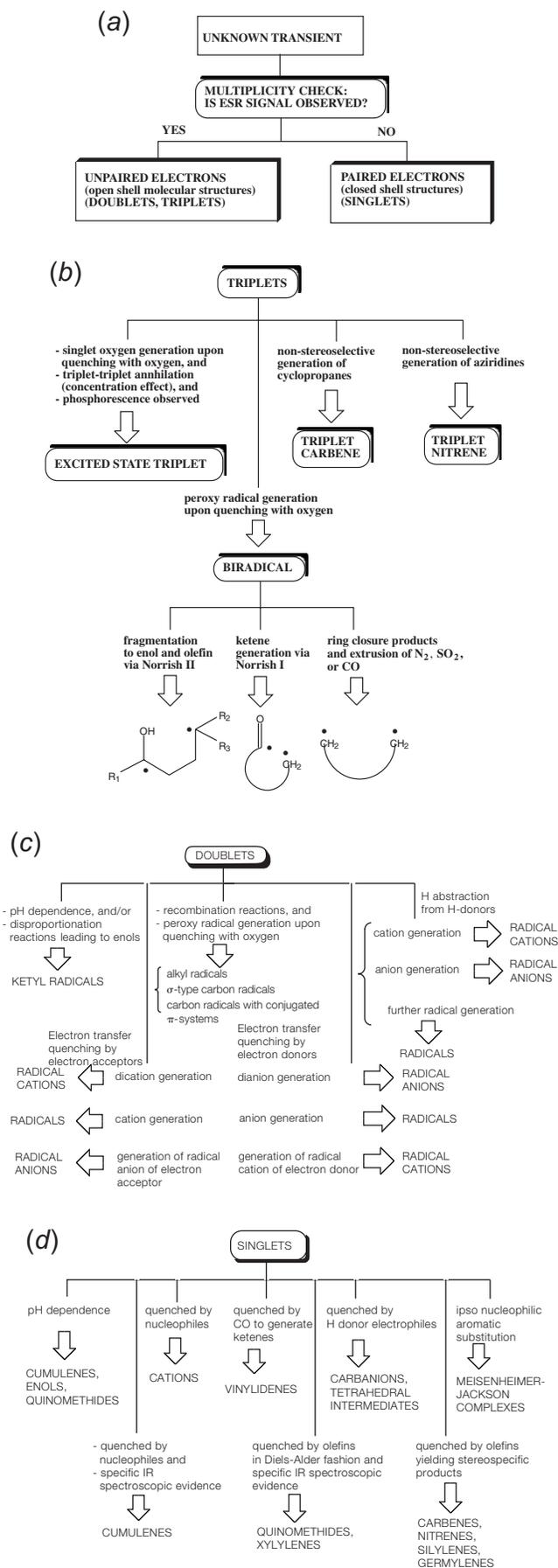
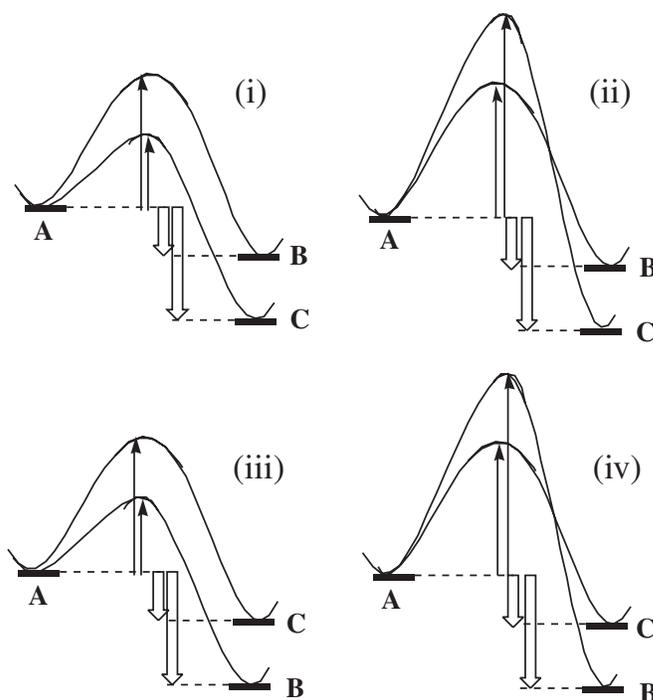


Fig. 4. (a) Decision tree showing the main separation of reaction intermediates according to multiplicity. (b) Decision tree for the identification reaction intermediates that have a triplet multiplicity. (c) Decision tree for the identification reaction intermediates that have a doublet multiplicity. (d) Decision tree for the identification reaction intermediates that have a singlet multiplicity.

Fig. 5. Kinetic and thermodynamic control processes for reaction scheme $A \rightarrow B + C$. (i) Product C is both a thermodynamically and kinetically controlled product (synergistic); (ii) product C is a thermodynamically controlled product and product B is a kinetically controlled product (antagonistic); (iii) product B is both a thermodynamically and kinetically controlled product (synergistic); (iv) product B is a thermodynamically controlled product and product C is a kinetically controlled product (antagonistic).



(see Fig. 5). Complimentary agreement between experiment and theory is particularly satisfying in such analyses.

$$[3] \quad \frac{\text{Number of elementary steps in mechanism}}{\text{Number of transition states in mechanism}} = \frac{\text{Number of reaction intermediates in mechanism}}{\text{Number of elementary steps in mechanism} - 1}$$

Within the realm of experimentation, probably the strongest evidence that can be obtained for the identity of a particular transient is if it can be generated from different precursors and by different techniques and if it can be shown that its spectroscopic and kinetic behaviours are the same irrespective of its origin or method of generation.

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