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Kinetic and mechanistic studies of free radical reactions in the 21st century

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Biography: Keith U. Ingold received his B. Sc. degree from University College London and his D. Phil. from Oxford. He holds the position of Distinguished Research Scientist in the Steacie Institute for Molecular Sciences, National Research Council of Canada, and his research has concentrated on the chemistry of free radicals in solution.

The past 50 years has seen an incredible growth in our understanding of free radical reactions in homogeneous gaseous and liquid systems. Fifty years ago, so far as the vast majority of chemists were concerned, radicals were overly reactive species of no practical value or interest since all radical-mediated reactions were presumed to give gunk and tars. This negative view of radical reactions persisted even long after the successful commercialization of the free radical polymerization of vinyl monomers. Half a century ago the prevailing view of an organic or physical organic chemist about any of their colleagues who expressed an interest in research into free radical reactions can best be summarized by a joking remark once made by the father of physical organic chemistry:

"Homolysis, even between consenting adults, is grounds for instant dismissal from this Department"

C. K. Ingold, *ca.* 1955

The idea that radical chain reactions might actually be useful in organic synthesis was regarded with scorn, and the idea that radical chemistry might be important in living organisms was dismissed as utter nonsense.

These fallacious views about radical chemistry were only slowly discarded by "main stream" chemists, biochemists, and the medical profession. This change in outlook is largely due to the perseverance of a few (a very few) physical organic chemists who devoted much of their lives to careful kinetic and reaction product studies of complex chain reactions, particularly polymerizations, chlorinations, and autoxidations. Careful rate measurements under controlled conditions using pure materials and homogeneous systems not only proved to be reproducible, but also yielded overall kinetic rate equations from which overall reaction mechanisms could be deduced and rate-limiting elementary reactions identified. In all free radical chain reactions in homogenous systems the overall rate was found to depend on the rate of chain initiation, R_i or $R_i^{1/2}$, and on the ratio of the rate constants for the rate controlling step of chain propagation, k_p, and the rate constant for chain termination, $2k_t$, (or its square root, $(2k_t)^{1/2}$).

Further understanding of radical chemistry evolved as physical organic chemists turned their attention to measuring the absolute rate constants for individual elementary reactions in homogeneous systems. First came the (accidentally discovered) rotating sector technique which allowed the rate constants for propagation and termination to be measured for a chain reaction which could be photochemically initiated and which exhibited bimolecular chain termination, *i.e.*, which obeyed the overall kinetic rate law, rate a $k_p(R_i/2k_t)^{1/2}$. A couple of decades later, electron spin resonance (ESR) spectroscopy started to be employed to measure the rates of bimolecular radical-radical self-reactions ($R^\cdot + R^\cdot \rightarrow$ products; rate constant $2k_t$). This new ESR technique quickly displaced the rotating sector method because it could be applied both to radicals which did and to those which did not participate in the terminating step of radical chain reactions. Later, ESR methods were developed to measure the rates of unimolecular radical reactions and the rates of radical-molecule reactions.

The measurement of the rate constants for radical-molecule reactions by direct time-resolved monitoring of the decay of the radical or growth of a product, generally using UV-visible absorption spectroscopy, was

first exploited by radiation chemists. The chemistry of the radiolysis of water was well understood to give hydroxyl radicals, hydrogen atoms, and the solvated electron. Pulse radiolysis of aqueous solutions was used to provide specific organic and inorganic radicals which were formed by reaction of the hydroxyl radicals (oxidizing) or the solvated electron (reducing) with particular solutes. Reactions of these radicals with water-soluble substrates were monitored in real time and yielded a wealth of kinetic data.

Although water is nature's favourite solvent it is certainly not the solvent of choice for most organic chemists. The pulse radiolysis kinetic data were therefore of little or no value to synthetic organic chemists no matter how interesting it might be to biochemists and radiation biologists. The development of high powered, pulsed UV lasers some 15-20 years ago opened the door for physical organic chemists to obtain kinetic data for virtually any radical in virtually any homogeneous system. The technique became known as laser flash photolysis (LFP) and it quickly displaced kinetic ESR spectroscopy as the method of choice for free radical kineticists. The loss of a reactant or the appearance of a product is monitored in real time, generally by UV-visible absorption spectroscopy, but occasionally by other techniques such as time-resolved infrared spectroscopy. The explosion of free-radical kinetic data "useful" to synthetic organic chemists is documented in the many volumes of Landolt-Bšrnstein: *Radical Reaction Rates in Liquids*, H. Fischer, ed., Volume II/13, 1984 and Volume II/18, 1995. The "usefulness" of these kinetic data has been pointed out very nicely by D. P. Curran (1988):

> "Since many of the relevant (radical) rate constants required for synthetic planning are known, a chemist can evaluate the possibilities for the success of a given (radical) reaction under a specific set of conditions. This ability to plan is a great asset of radical reactions"

One of the main limitations which retarded the practical application of "known" radical kinetics to "unknown" organic chemical systems was the worry about potential solvent effects on the rates of radical reactions. That there are substantial solvent effects on at least some radical reactions has been known since the early work on free radical chlorination by G. A. Russell (1957) and on alkoxyl radical chemistry by C. Walling (1963). In the last few years, solvent effects have been extensively investigated at the NRC. This recent work can be summarized briefly as follows:

(i) There are generally no solvent effects on the rates of hydrogen atom abstraction from a C-H bond;

(ii) There may be solvent effects on the rates of unimolecular radical scission reactions but these are generally fairly small;

(iii)There are large solvent effects on the rates of hydrogen atom abstraction from O-H bonds (and to a lesser extent, from N-H bonds).

Point (i) means that radical reactivities, insofar as hydrogen abstraction (and addition) reactions are concerned, are not influenced by the solvent. Point (iii) means that O-H containing substrates (*e.g.*, phenols, hydroperoxides, *etc.*) have their reactivities towards radicals influenced by the solvent. This influence was shown to be due to deactivation of the substrate, XOH, when it can act as a hydrogen bond donor to a hydrogen bond accepting (HBA) solvent, S. To a first approximation, the hydrogen bonded XOH, *i.e.*, XOH—S, is unreactive towards radicals, all of the hydrogen atom abstraction from the substrate actually occurring from "free" XOH, *i.e.*, non-hydrogen bonded XOH. This is a kinetic solvent effect, KSE, on the molecular reactant, XOH. Therefore, it was predicted that the KSE should be dependent on the ability of XOH to participate as a hydrogen bond donor to HBA solvents but should be independent of the reactivity or nature of the radical which does the hydrogen atom abstraction. This prediction, which is the first new and unifying principle for organic free radical chemistry to have been proposed in the last twenty years, has been dramatically confirmed for hydrogen abstraction from phenol by the highly reactive cumyloxyl radical, $PhCMe_2O\cdot$, and by the very unreactive diphenyl picrylhydrazyl radical, DPPH, $Ph_2N{\cdot}NC_6H_2(NO_2)_3$-2,4,6. In the same solvent, the cumyloxyl radical abstracts the phenolic hydrogen atom from phenol ten billion (10^{10}) times faster than DPPH. However, a change in solvent which reduces the rate of the cumyloxyl radical's reaction by a factor of 100, *e.g.*, as occurs on changing from CCl_4 as solvent to ethyl acetate as solvent, also reduces the rate of the DPPH reaction by the same factor of 100. Thus, it is now, at last, possible to predict the rate constant for hydrogen abstraction from phenol by any radical, Z·, in any solvent provided only that one single rate constant in one solvent has been measured for the Z· + PhOH reaction.

This new principle allows the quantitative prediction of free radical kinetics for hydroxylic substrates. Combined with the knowledge that there are generally no (or only very small) solvent effects on hydrogen

atom abstraction from C-H bonds (or radical additions to C=C bonds) this new principle has, quite simply, made the measurement of the kinetics of free radical reactions in homogeneous solution a subject no longer worthy of further basic scientific research. Even as late as 1994 it looked as though the subject of homogeneous free radical kinetics was infinite (*i.e.*, it lay in a flat universe) with a measurement being required (or, at least, worth a paper) for all radical-molecule reactions in all solvents. In 1995 it became obvious that homogeneous free radical kinetics was a very finite subject (*i.e.*, it lies in a very sharply curved universe). A few hundred, or at most a few thousand, rate constants for radical-molecule reactions in homogeneous solution are all that are ever likely to require measurement - and many of these rate constants have already been measured! Any and all other radical-molecule kinetic data which might be required in any solvent will be easy to predict with relatively high precision (probably generally better than a factor of 2-3).

If there really are no more worthwhile scientific goals for free radical kineticists in homogeneous systems, what direction should we expect this discipline to take in the 21st century? Obviously, forefront kinetic research on free radicals will abandon studies in homogeneous systems. Instead, it will tackle the currently daunting challenge of making reproducible rate measurements in heterogeneous systems and will concentrate on those systems which are of great interest and importance to organic chemistry, to biochemistry and to medicinal chemistry. One of the challenges is that many very important heterogeneous systems are, themselves, inherently somewhat irreproducible, *e.g.*, cells in culture, isolated organs and whole animals. Indeed, even such an apparently simple reaction as the autoxidation of linoleic acid dispersed in water in sodium dodecylsulfate micelles and inhibited by various phenolic antioxidants has been found to give different relative antioxidant activities in different laboratories! This particular problem of kinetic irreproducibility should be a simple matter to resolve. Nevertheless, it does serve to illustrate the kinds of difficulties the measurement of radical kinetics in heterogeneous systems is likely to encounter before inter-laboratory consensus as to the "truth" is achieved.

Undoubtedly, novel instrumentation and new applications for existing instruments will play a major role in heterogeneous radical kinetics. For example, there is a need to be able to monitor the movement of neutral and charged free radicals across the lipid/aqueous interface of biomimetic systems, *e.g.*, phospholipid vesicles, and biological supramolecular assemblies, *e.g.*, low density lipoprotein (LDL) particles. Similarly, there is a need to monitor the rates and products of radical induced chemical change within single phospholipid vesicles and single LDL particles because so much valuable information becomes "scrambled" (averaged) when all the lipid particles are not only assumed to be identical but also are assumed to talk to one another (chemically speaking) as readily as if the overall systems were actually homogeneous.

In short, my vision of physical organic chemistry in the 21st century (insofar as free radical kinetics is concerned) is that it will continue (as in the past) to be applied to solve mechanistic questions regarding chemical processes of scientific interest and of fundamental importance in all areas of organic chemistry, biochemistry, and medicinal chemistry. The free radical kineticists of the 21st century will use new instruments, and old instruments in novel ways. They will develop theoretical models for even the most complex heterogeneous systems and subject these models to rigorous experimental verification. They will ensure that their branch of physical organic chemistry remains vibrant in itself and relevant and important to 21st century chemists. The challenges are exciting, the goals are worthy, and the value of the scientific knowledge to be gained is incalculable. Let's get started!