Hanns Fischer: Radical Pioneer

by **Athelstan L. J. Beckwith**[a]) and **Keith U. Ingold**[b])

[a]) Research School of Chemistry, Australian National University, Canberra, ACT 0200, Australia
(e-mail: beckwith@rsc.anu.edu.au)
[b]) National Research Council, Ottawa, ON, K1A 0R6, Canada
(e-mail: keith.Ingold@nrc.ca)

For four decades, *Hanns Fischer* played a major and highly innovative role in the development of free radical chemistry. The present article describes the science in several of *Fischer*'s papers. These papers were chosen for analysis because they nicely illustrate *Fischer*'s originality, passion for exactitude, and impact on chemistry, and because they are well-read favorites of the present authors.

Introduction. – *Hanns Fischer* was a towering figure both physically and intellectually. The power of his intellect was clearly reflected by the quality of his publications. They reveal his remarkable capacity for deep and insightful thought, his ability to identify the heart of a problem and the methods for its solution, his capacious and accurate memory, his comprehensive knowledge of chemistry in all its forms, and his ability to relate his own research interests with the wider world of science.

As a speaker at a symposium or a more general meeting, *Fischer* displayed not only his intellectual prowess but also his eminence as a communicator. He had a superb command of language and the ability to express complex ideas in simple terms readily understandable by a non-specialist audience. His listeners quickly became aware of the attractive timbre of his voice, his quiet and disarmingly self-effacing style, his ease, and his friendliness. He had charm.

Blessed with an amiable personality, a quiet wit, diverse interests, and a wide general knowledge, *Fischer* was a genial conversationalist and a good companion. He enjoyed company. When visiting Canberra or Ottawa, he and his wife, *Irmelin*, readily made a wide circle of friends, many of whom were outside academia.

Fischer was a striking figure – tall, strong, well-built, and good-looking. His strength and powers of endurance were perhaps best displayed during the hiking or climbing expeditions that were among his favorite recreations. When walking in the Alps, the Australian high country, or the North American forests, *Fischer* displayed great stamina and energy. He liked to engage in conversation when hiking but his companions usually found they had no breath left for talking.

Fischer was strong but gentle. He was a true liberal, compassionate towards people, caring towards the environment. He loved nature, music, his faith, his choir (he had a fine singing voice), and his vegetable garden. He was a great scientist and a wonderful friend.

Structure and reactivity lie at the heart of modern chemistry. A complete and correct understanding of both allows new molecules with finely tuned properties to be synthesized efficiently. *Hanns Fischer*'s seminal contributions to chemistry include thoughtful examinations of free radical structure by electron spin resonance (ESR) and muon spin rotation (μSR) spectroscopies and his beautifully precise kinetic measurements on a large number of free radical reactions. He delighted in exploring new experimental procedures and then refining these techniques with both mathematical rigor and imagination. *Fischer*'s legacy is enshrined not only in his many ground-breaking research publications but also by his editorship of two mammoth, multi-volume, bibliographic compilations that serve as ready-reference repositories for almost everything we know about the ESR spectra (and hence the conformation and configuration) of free radicals¹) [1], and about the kinetics of the reactions of organic free radicals in solution [2]. Neither of these invaluable reference tools would have been published were it not for *Fischer*'s drive and dedication.

Fischer's research and bibliographic accomplishments have greatly aided and carefully guided the current practice of free radical chemistry. Herein, we summarize some of our favorite *Fischer* publications, favorite because they nicely illustrate his originality, passion for exactitude, and impact on his chosen subject.

Kinetics of the Bimolecular Self-Reactions of Alkyl Radicals. – ESR Spectroscopy was used by *Fischer* from the start of his scientific career to identify and characterize organic free radicals. Much of his early work dealt with high-molecular-weight radicals produced in polymers by ionizing radiation. He studied both the carbon-centered radicals present under anaerobic conditions and the peroxyl radicals present under aerobic conditions. This association of *radicals* and *polymers* was to become *Fischer*'s scientific leitmotif¹). Among *Fischer*'s early publications were also definitive studies on the ESR spectra and structures of a few, prototypical, low-molecular-weight radicals, including cyclohexadienyl and benzyl.

It appears quite likely that *Fischer*'s interest in the kinetics of free radical reactions was actually sparked by his 1967 discovery (with *Bargon*) that, during the thermal decomposition in solution of organic peroxides and azo compounds, the ^{1}H-NMR spectra of the reacting systems often showed lines in emission and/or in enhanced absorption [3]. These abnormal lines became absorption lines of normal intensity at the end of the reactions and the phenomena were christened: *Chemically Induced Dynamic Nuclear Polarization* (*CIDNP*). The anomalous ^{1}H-NMR lines arise from singlet/triplet radical pair sorting that accompanies radical + radical reactions. Sorting occurs because singlet radical pairs generally react rapidly with one another by combination and/or disproportionation (*Eqn. 1*).

$$R^{\uparrow} + R^{\downarrow} \rightarrow R{-}R\ (RH + R_{-H}) \qquad (1)$$

---

¹) For a full list of *Fischer*'s scientific publications, see elsewhere in this issue.

However, triplet radical pairs are repulsive and such radical pairs generally do not react with one another2) (*Eqn. 2*).

$$\mathrm{R}^{\upharpoonright} + \mathrm{R}^{\upharpoonright} \nrightarrow \text{ no reaction} \tag{2}$$

Through the 1960s (and earlier), it was generally accepted that the rate constants for the bimolecular self-reactions of alkyl radicals in the gas phase were equal, at the high pressure limit, to one-quarter of the encounter rate. Such a rate is consistent with the theoretical expectation that all encounters of singlet radical pairs lead to reaction (*Eqn. 1*), whereas the three-fold more frequent encounters of triplet radical pairs do not lead to reaction (*Eqn. 2*). During this same period, rate constants were measured in solution, generally at room temperature, for numerous alkyl radical bimolecular self-reactions [6]. The solvents employed (*e.g.*, cyclohexane, benzene, tetrachloromethane, water, *etc.*) were of relatively low viscosity. The experimental procedures included the Rotating Sector Method, Kinetic ESR Spectroscopy, and Kinetic Absorption Spectroscopy. The various experimental groups agreed that, in solution, all the alkyl radical bimolecular self-reactions that had been examined occurred 'at, or close to the diffusion-controlled limit'. The experimental rate constants, $2k^{\mathrm{R+R}}$, were generally somewhat smaller than the rate constants, k_{diff}, calculated for diffusion-controlled reactions by the *Smoluchowski–Stokes–Einstein* treatment [6]. These results raised the question as to whether theory overestimated k_{diff}, or whether theory was correct (more or less), and the reactions only occurred in one-quarter of the radical/radical encounters, as in the gas phase. This raised the further question as to whether the conversion of a triplet radical pair into a singlet pair by spin inversion would occur during a radical/radical encounter in solution. That is, was spin inversion fast or slow relative to escape from the solvent cage? This was a matter for vigorous debate at that time (see, *e.g.*, [7]).

The final resolution of these very fundamental questions was achieved by *Schuh* and *Fischer* thanks to their meticulous experimental measurements on the bimolecular self-reactions of the *tert*-butyl radical in solution, combination (*Eqn. 5*), and disproportionation (*Eqn. 6*) [8–10].

$$\mathrm{Me_3C\cdot + Me_3C\cdot \xrightarrow{2k_c^{B+B}} Me_3CCMe_3} \tag{5}$$

$$\mathrm{Me_3C\cdot + Me_3C\cdot \xrightarrow{2k_d^{B+B}} Me_3CH + Me_2C{=}CH_2} \tag{6}$$

---

2) Like many formally 'forbidden' processes in the physical sciences, there are 'exceptions that prove the rule' (it is not always recognized that, in this phrase, 'prove' is used as a synonym for 'tests'). In a study of the bimolecular self-reactions of benzoyl radicals (*Eqn. 3*),

$$\mathrm{(PhC{=}O)^{\upharpoonright} + (PhC{=}O)^{\downharpoonright} \rightarrow PhC(O)C(O)Ph} \tag{3}$$

Fischer and co-workers [4] failed to detect the formation of triplet benzil (*Eqn. 4*) by kinetics, *i.e.*,

$$\mathrm{(PhC{=}O)^{\upharpoonright} + (PhC{=}O)^{\upharpoonright} \rightarrow [PhC(O)C(O)Ph]^{\upharpoonright\upharpoonright}} \tag{4}$$

the measured rate constant was equal, within quite a small experimental error, to one-quarter of the calculated rate for a diffusion controlled reaction. They concluded that $k_4/k_3 \ll 0.03$. Both *Reactions 3* and *4* are exothermic. Later, *Lissi* and *de la Fuente* [5] detected chemiluminescence from triplet benzil and reported that $k_4/k_3 = 0.00014$. Chemiluminescence is, of course, a far more sensitive probe for *Reaction 4* than *Fischer*'s kinetic method.

Schuh and *Fischer* unequivocally demonstrated that, over a range of temperatures in each of twelve solvents, the overall rate constants for *tert*-butyl radical decay, $2(k_c^{B+B} + k_d^{B+B})$, were equal to one-quarter of the diffusion-controlled limit, *i.e.*, were equal to $k_{diff}/4$. This result is very satisfying because it means that, in solvents of normal viscosities, spin inversion is slower than escape of the triplet pair from the solvent cage, and, hence, that gas-phase and solution-phase radical/radical reactions are much more similar than had previously been recognized. *Schuh* and *Fischer*'s work also led to reliable methods for estimating the rate of diffusion of *tert*-butyl radicals in solution. Most importantly, their work led to the development by *Fischer* of a method for measuring the rate constants for radical/molecule reactions *via* the perturbation that the added reactant had on the otherwise 'clean' second-order decay of the radical (see below). Finally, their work ended a second vigorous scientific argument.

The second argument referred to above arose between the practitioners of gas- and solution-phase kinetics, and was about the magnitude of the rate constant for the combination of two *tert*-butyl radicals, $2k_c^{B+B}$. In 1963, *Metcalfe* [11] reported the first absolute determination of this rate constant in the gas phase. At 81 and 115°, she found that $2k_c = 3.2 \times 10^9$ M^{-1} s^{-1} and, taking [11] $k_d/k_c = 3.20$, the overall rate constant for the *tert*-butyl radical self-reaction would be *ca.* 1×10^{10} M^{-1} s^{-1}. A decade later, *Benson* and coworkers [12] [13] absolutely astonished kineticists by presenting gas-phase results from some independent reaction systems which, *when combined with 'known' thermochemistry*, led them to argue that $2k_c^{B+B} = 10^{5.5\pm1.5}$ M^{-1} s^{-1}[3]). Between 1968 and 1973, there were four reports that, in solvents of normal viscosities, $2(k_c^{B+B} + k_d^{B+B})$ lay in the range $0.73-8.1 \times 10^9$ M^{-1} s^{-1} at ambient temperatures [15] [16]. Since the then available data indicated that $2 < k_c/k_d < 8$ in both the gas and liquid phase [13] [17], *Benson*'s 'new' gas-phase rate constant meant that the values of $2(k_c^{B+B} + k_d^{B+B})$ in the gas and liquid phases differed by at least three orders of magnitude!

In 1974, it was demonstrated that the rate constant for the bimolecular self-reaction of the *tert*-butyl radical in solution was equal, within experimental error (±30%), to the bimolecular rate constants for the self-reactions of the ethyl, isopropyl, and cyclopentyl radicals (R) measured simultaneously for B–R pairs in the same experimental systems [18][4]). This established that the *tert*-butyl radical was perfectly 'normal', at least in solution. In this work [18], it was pointed out that *Benson*'s gas-phase value for $2k_c^{B+B}$ ($10^{5.5}$ M^{-1} s^{-1}) depended in a most sensitive manner on the *estimated* heat of formation of the *tert*-butyl radical. Indeed, a 1-kcal/mol change in this heat of formation would change

---

[3]) At this time, there became something of a 'bandwagon' effect with a number of other alkyl radicals being claimed, incorrectly, to undergo their bimolecular self-reactions in the gas phase at rates far below their encounter rates [14].

[4]) *tert*-Butyl (B) and each of the other three alkyl radicals (R) were continuously generated in pairs at exactly equal rates in the cavity of an ESR spectrometer under conditions where radical decay occurred only by the three possible radical/radical reactions: B + B, B + R, R + R. The [B]/[R] ratios were measured. Since $([B]/[R])^2 = 2k^{R+R}/2k^{B+B}$, and since all these ratios were found to be equal to 1.0 ± 0.3, the rate constants for the bimolecular self-reactions of the four alkyl radicals must be essentially equal.

the magnitude of $2k_c^{B+B}$ by a factor of 30! It was suggested [18] that *Benson*'s value of 8.7 kcal/mol for this heat of formation was in error – which it was⁵).

Although the work just described [18] proved that simple alkyl radicals reacted with one another at essentially identical rates, it did not prove that this rate was equal to the diffusion-controlled limit, or to one-quarter (or some other fraction) of this limit. Arguments between gas- and liquid-phase kineticists continued. They finally ceased after publication of *Schuh* and *Fischer*'s precise experimental study and penetrating analysis of the factors that control the rate [8] [9] and products [10] of the bimolecular self-reaction of the *tert*-butyl radical in solution. One major feature of this monumental work was the application of ESR spectroscopy to generate kinetic data that were far more precise than any previous measurements. This was achieved by the following experimental innovations:

a) Photo-generation of the *tert*-butyl radicals using a much improved optical arrangement. This gave significantly higher concentrations of the radical than had been previously achieved. The light was brought to a sharp focus outside the ESR cavity because this permitted a very fast 'cut-off' of the light by a sectored disc rotating at the focus (allowing the radicals to decay during the dark period).

b) The choice of di(*tert*-butyl) ketone as the photolyzable source of the *tert*-butyl radicals (*Eqn. 7*). This reaction has a high quantum yield (0.71) and, at temperatures above 0° where decarbonylation is fast, it provides a 'clean' and efficient source of *tert*-butyl radicals.

$$(\mathrm{Me_3C})_2\mathrm{C{=}O} \xrightarrow{h\nu} \mathrm{Me_3C}\cdot + \mathrm{Me_3C\dot{C}{=}O} \xrightarrow{\text{fast}} \mathrm{Me_3C}\cdot + \mathrm{CO} \qquad (7)$$

c) The use of a flow system to avoid over-consumption of the ketone.

d) The use of a homogeneous distribution of light over the surface of a flat ESR cell to reduce inhomogeneous radical concentrations.

e) The direct measurement of the baseline signal at zero radical concentration (only estimated in all earlier work.) This was achieved by rapidly shifting the magnetic field from the on-resonance position used to collect and average many decay traces, to an off-resonance position, and collecting and averaging the same number of baseline signals before returning to the resonance position and repeating the entire procedure. Typically, 15,000 decay traces and 15,000 background signals were averaged.

f) Among the twelve solvents employed were six *n*-alkanes (C_7H_{16} to $C_{16}H_{34}$) which would 'solvate' the *tert*-butyl radical to equal extents. Thus, any dependence of the rate or products on alkane could only be attributed to differences in the bulk or micro viscosities of the alkanes. Once the alkane solvent systems were thoroughly understood, the kinetic data in polarizable (benzene) and polar (acetonitrile, various alcohols) solvents could be (and were) properly interpreted.

g) Measurements were made over a sufficiently wide temperature range (*e.g.*, 294–365 K for *n*-C_7H_{16}, 299–366 K for *n*-$C_{16}H_{34}$) that accurate activation enthalpies

---

⁵) The currently accepted heat of formation for *tert*-butyl is 12.3 ± 0.4 kcal/mol [19], a value that brings *Benson*'s gas-phase data into line with all the liquid-phase work. Later gas-phase measurements also gave much more reasonable rate constants for $\mathrm{Me_3C^{\bullet}} + \mathrm{Me_3C^{\bullet}}$, see, *e.g.*, [20].

could be determined for *tert*-butyl radical bimolecular decay – and then be compared with the activation enthalpies for the bulk viscosities of the solvents.

h) The *tert*-butyl radical concentration under steady illumination, [B(0)], was also measured in the same experimental set-up while the effluent from the ESR cell was collected. This effluent was subsequently analyzed to obtain the absolute concentrations (*i.e.*, yields) of the three principal organic products, 2,2,3,3-tetramethylbutane (*Eqn. 5*), isobutane, and isobutene, the concentrations of these last two hydrocarbons being equal to each other, as expected (*Eqn. 6*). The absolute yields of the products formed in time, *t*, were then employed to calculate the rate constants for the bimolecular self-reaction of *tert*-butyl radicals *via* the expression:

$$2(k_c^{B+B} + k_d^{B+B}) \times [B(0)]^2 \times t = [Me_3CCMe_3] + ([Me_3CH] + [Me_2C{=}CH_2])$$

Rate constants obtained by steady irradiation and chemical analyses were found to be in excellent agreement with those calculated from the decay traces obtained with intermittent irradiation, further supporting the reliability of both procedures. These product data were extensive and stimulated *Schuh* and *Fischer* [10] to propose a most elegant explanation for the factors controlling disproportionation/combination ratios, *i.e.*, $2k_d^{B+B}/2k_c^{B+B}$ (see below).

In the six *n*-alkane solvents at any one temperature, the magnitude of $2(k_c^{B+B} + k_d^{B+B})$ increased with a decrease in the solvent's viscosity and, in any one solvent, this rate constant increased with temperature. In each of these solvents, the activation enthalpies for the bimolecular decay of the *tert*-butyl radicals (measured by both the intermittent illumination method and by the steady illumination/product method) were in surprisingly close agreement with the enthalpies of activation of the bulk (dynamic) viscosities. This provided the first fully trustworthy evidence that solvent viscosity was the dominant factor determining the rates of *tert*-butyl radical self-reactions in liquids. However, measurements in the different alkanes at temperatures where their viscosities were equal yielded rate constants that increased with increasing length of the *n*-alkane chain. Thus, a factor other than bulk viscosity must also play a significant role in this reaction. This factor was identified as microfriction [9]. In non-associating solvents, the magnitude of the microfriction factor depends on the radii of the solute (*tert*-butyl) and solvent molecules and on the temperature. The *tert*-butyl radical's diffusion constants (incorporating microfrictional effects as well as bulk viscosities) were estimated using isobutane as a model (because of their similar sizes and shapes). Following this procedure, it was found that, in all six alkane solvents and at all temperatures, the measured rate constants were equal to one-quarter of the calculated diffusion-controlled rate constants. It was concluded that all singlet encounters of two *tert*-butyl radicals in alkane solvents led to reaction, and that triplet radical pairs did not react with one another. It was also concluded that there could be no *tert*-butyl radical/alkane complexes because, if complexes had been formed, the radical's diffusion constants would be smaller than the calculated values, and this would mean that the measured reaction rates would be smaller than (rather than equal to) the calculated values.

Schuh and *Fischer* [9] went on to show that, over wide temperature ranges, the experimental rate constants for the *tert*-butyl radical bimolecular self-reaction were also equal (within the error limits) to one-quarter of the calculated rate constants for diffusion-controlled reactions in benzene, acetonitrile, octamethylcyclotetrasiloxane, *tert*-butyl alcohol, 3-methylpentan-3-ol, and a highly viscous 1:2 molar mixture of *tert*-butyl alcohol and pinacol. Thus, alkyl radical/solvent complexes are not formed in any of these solvents, the reactions involve only singlet radical pairs, and, over nearly three orders of magnitude in $2(k_c^{B+B}+k_d^{B+B})$, the reaction is entirely diffusion-controlled[6]).

The firm identification by *Schuh* and *Fischer* of the factors determining the rates of the bimolecular self-reaction of *tert*-butyl (and other alkyl and allyl) radicals was accompanied by their clarification of the factors that determined disproportionation/combination product ratios (*Eqns. 5* and *6*) [10]:

$$([Me_3CH]+[Me_2C{=}CH_2])/2[Me_3CCMe_3]=P_d/P_c$$

In the gas phase, $P_d/P_c \approx 2.8$ and is independent of temperature [10]. However, in liquids, P_d/P_c is larger, and, in any particular solvent, this ratio decreases with an increase in temperature. For example, at 25° and 87° the values of P_d/P_c are 5.4 and 4.1 in *n*-octane, and 6.9 and 5.0 in *n*-hexadecane, respectively [10]. Much more dramatic changes in this ratio were found in solvents that are mobile at elevated temperatures but very viscous at low temperatures, *e.g.*, P_d/P_c is 23.5 and 5.5 in a *tert*-butyl alcohol/pinacol 1:2 mixture at $-8.5°$ and 88.5°, and it is 23.5 and 4.7 in 3-methylpentan-3-ol at $-28.5°$ and 98°, respectively [10]. This solvent viscosity effect on the product ratio was ascribed to the anisotropy of reorientational motions of the singlet pair of radicals during their encounter, but prior to their mutual reaction – which, of course, always occurs. This reorientation within the solvent cage allows unreactive (initial) configurations of the singlet radical pair to evolve into configurations favorable for disproportionation or for combination. The *tert*-butyl radical is only slightly nonplanar[7]), and it undergoes rapid pyramidal inversion, the barrier to inversion being only 0.45 kcal/mol [22]. The *tert*-butyl radical has the shape, therefore, of an oblate spheroid, and the rates of reorientation about its principal axes will depend differently on the viscosity of the surrounding medium. This leads to viscosity-dependent probabilities for disproportionation and combination reactions of singlet radical pairs that are formed in unreactive configurations. Reorientation by rotation around an axis perpendicular to the plane of the radical (*i.e.*, about an axis coincident with the unpaired electron's 2p orbital) leaves the solvent shell nearly unchanged. However, reorientation around either of the other two principal axes (*i.e.*, a 'coin-flipping' reorientation) requires substantial amounts of the surrounding fluid to be displaced. Hence, 'coin-flipping' reorientation will be much more strongly retarded in viscous solvents than reorientation by rotation about the 2p orbital axis. *Schuh* and *Fischer* [10] suggested that the *tert*-butyl radical should be considered to posses two reactive zones, the central carbon zone, C, and the nine hydrogen atoms, zone H, together with many non-reactive

---

[6]) Subsequently, *Fischer* and co-workers demonstrated that the same holds true for benzoyl radicals [4], but see *Footnote 2*, and for benzyl radicals [21].

[7]) The angle between the plane of the methyl C-atoms and a C–C bond in the minimum energy structure is 11.5° [22].

zones, N. Formation of the combination product requires a CC configuration of the two radicals, while formation of the disproportionation products requires a CH configuration. Non-reactive configurations, CN, where N is on or near the rim of the disk of the second *tert*-butyl radical, can be transformed into a reactive CH configuration by the almost unhindered rotation of this *tert*-butyl about its 2p orbital axis, CN → CH. However, transformation of this same non-reactive CN configuration into a reactive CC configuration requires the second *tert*-butyl radical to undergo a 'coin-flip' rotation that will be strongly coupled to the viscosity of the solvent. For this reason, the probability of forming the coupled product, Me_3CCMe_3, decreases as the viscosity of the solvent increases, with a consequent increase with viscosity of the P_d/P_c ratio – as is observed.

In all of these magnificent studies, the *tert*-butyl radical concentration *perfectly* followed second-order decay kinetics in unreactive solvents. *Fischer* recognized that small perturbations of these second-order decays caused by a simultaneous pseudo-first-order reaction of a small fraction of the *tert*-butyl radicals should be both observable and kinetically quantifiable. This led to further very careful optimization of the experimental system, plus the monitoring of 100,000 to 200,000 individual decays, to obtain traces virtually free of noise. Pseudo-first-order perturbations to the 'perfect' second-order decay traces found in methylcyclopentane were recorded upon the addition of 0.12–0.62M $CHCl_3$ at temperatures from 0° to 50° [23]. Analyses of these perturbations yielded first-order rates that were converted to second-order rate constants for the global reaction of *tert*-butyl radicals with $CHCl_3$, a reaction that includes both H-atom and Cl-atom abstraction, *e.g.*, at 30° $(k_H + k_{Cl}) = 360\ \text{M}^{-1}\ \text{s}^{-1}$, with $k_H/k_{Cl} = 1.4$ [23]. In a similar manner, the rate constants for H-atom abstraction by *tert*-butyl radicals from toluene (neat) and ring-substituted toluenes were measured, *e.g.*, 14.4 $\text{M}^{-1}\ \text{s}^{-1}$ for toluene at 48° [24]. Rate constants for the addition of *tert*-butyl radicals to numerous olefins, including polymerizable olefins, soon followed, *e.g.*, 16,500 $\text{M}^{-1}\ \text{s}^{-1}$ for vinyl chloride and 460,000 $\text{M}^{-1}\ \text{s}^{-1}$ for 2-vinylpyridine, both at 30° [25][8]). All of the *Fischer*'s studies in this area have been very nicely summarized in [26]. The radical addition work appears to have re-awakened *Fischer*'s interest in radical polymerization kinetics. This interest quickly led *Fischer* into the new and exciting field of 'Living' Free Radical Polymerization. Here, his rigorous physical chemistry and mathematics, exemplified by his earlier treatment of the phenomenon now called the 'Persistent Radical Effect' [27], allowed him to make many major contributions.

Muonium Radical Chemistry. – Muonium, the atom formed by the combination of a positive muon with an electron, $\mu^+ + e^- \rightarrow Mu$, can be considered as a light radioactive isotope of the H-atom. It has 1/9 the mass of H· and a lifetime of 2.2 μs. A relatively simple technique for detecting muonium is muon spin rotation (μSR). In this technique, a beam of spin-polarized muons is stopped in a target, and positrons from the spontaneous decay of μ^+ in a given direction are counted as a function of the time spent by the

---

[8]) *Fischer*'s analysis [23] of 'perturbed' radical/radical bimolecular self-reaction kinetics has indicated that this method could be used to determine second-order rate constants for radical/molecule reactions that lay between 0.1 and $5 \times 10^5\ \text{M}^{-1}\ \text{s}^{-1}$, and first-order rate constants for radical rearrangements and fragmentations that lay between 1 and $5 \times 10^4\ \text{s}^{-1}$.

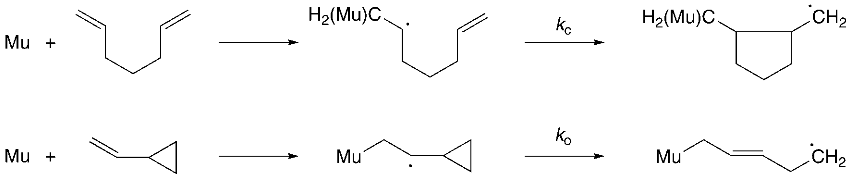
muons in the target. By analysis of the μSR histograms, muonium had been identified as early as 1966 in inert gases [28] and by 1967 in solids [29]. However, it eluded detection in various liquids for another decade. Muonium's successful detection in carefully degassed water was reported in 1976 [30]. This success was entirely due to *Hanns Fischer*'s recognition that earlier attempts to detect muonium in solution had failed because oxygen had not been rigorously excluded from the samples [31]. *Fischer* realized that muonium would undergo a fast chemical reaction with oxygen (by analogy with H·), and that the presence of paramagnetic oxygen would also lead to spin relaxation *via Heisenberg* spin exchange.

The potential utility of muonium in free radical chemical kinetics was immediately apparent to *Fischer*. Initial studies involved a comparison of the reactivities of Mu and H· with various inorganic compounds in water [32]. These were quickly followed by the first direct observation of the radicals formed by the addition of muonium to carefully degassed organic liquids such as 2,3-dimethylbut-2-ene, penta-1,3-diene, benzene, and acetone [33], *e.g.*,

$$\mathrm{Mu} + \mathrm{Me_2C} = \mathrm{CMe_2} \rightarrow \mathrm{Me_2(Mu)}\dot{\mathrm{C}}\mathrm{Me_2}$$

This early and very successful work on the reaction of muonium with unsaturated organic compounds provides yet another example of *Hanns Fischer*'s lifelong enthusiasm for kinetic studies on the additions of radicals to alkenes. One manifestation of this enthusiasm was his use of Mu to generate alkyl radicals that underwent unimolecular rearrangements on the μSR time scale (microseconds). Rate constants for numerous radical cyclizations, k_c, and numerous radical ring openings, k_o, were determined over a range of temperatures [34][35] (for examples, see *Scheme 1*).

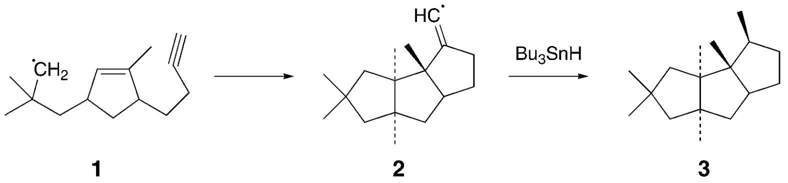
Scheme 1



The rate constants measured for the two reactions shown above using muonium, *viz.*, $k_c = 4.7 \times 10^5\ \mathrm{M^{-1}\,s^{-1}}$ at 338 K with $E_a = 22.2 \pm 2.5$ kJ/mol, $\log(A/\mathrm{s^{-1}}) = 9.1 \pm 0.3$ [35], and $k_o = 5.6 \times 10^6\ \mathrm{M^{-1}\,s^{-1}}$ at 273 K [36], are in excellent agreement with values obtained by the present authors using more conventional, non-muonium-substituted radicals, *viz.*, $k_c = 6.4 \times 10^5\ \mathrm{M^{-1}\,s^{-1}}$ at 338 K (extrapolated) with $E_a = 26.8 \pm 1.3$ kJ/mol, $\log(A/\mathrm{s^{-1}}) = 9.8 \pm 0.3$, by kinetic ESR spectroscopy [36], and $k_o = 7.0 \times 10^6\ \mathrm{M^{-1}\,s^{-1}}$ at 273 K by the tin hydride ($\mathrm{Ph_3SnH}$) method [37]. These and other agreements were, and still are, extremely gratifying because they serve to confirm the validities of all the experimental techniques employed to obtain alkyl radical unimolecular rearrangement rate constants for use in radical-clock [38] measurements of the rate constants for bimolecular radical + molecule reactions.

Radical Reactivity. – While *Fischer* was perfecting his analytical and experimental techniques for the accurate determination of absolute rate data by kinetic ESR spectroscopy and muon spectroscopy, significant developments had occurred in other areas of free radical chemistry. For example, it had become firmly established that free radicals were involved in a number of biological processes both beneficial and deleterious [39]. Equally dramatic was the impact that free radical chemistry was having on organic synthesis. It had earlier been observed that some radical chain processes, such as the reduction of alkyl halides by trialkylstannanes [40], are very chemoselective and proceed under mild conditions in good yield with substrates bearing a variety of unprotected functional groups [41]. This high chemoselectivity made the use of protecting groups unnecessary, and thus bestowed a distinct advantage for stannane-mediated radical chemistry over some other organic synthetic methods [42]. The later recognition that suitably constituted halides, when exposed to these conditions, can undergo highly efficient rearrangements [43] also attracted the attention of synthetic organic chemists, an interest that was further aroused by the recognition that a series of consecutive radical rearrangements (tandem or cascade reactions) can afford complex products in a highly regio- and stereoselective fashion, often in one experimental step [44]. In a typical early example, the highly stereoselective synthesis (*Scheme 2*) of (±)-hirsutene (**3**) involves the rearrangement **1** → **2** of the radical **1** generated by the reaction of the analogous iodide with Bu_3SnH [44a].

Scheme 2



This interest in the utility of free radical reactions for the synthesis of complex organic compounds revealed the difficulty of choosing the optimum experimental conditions, a problem arising from the relative paucity of information concerning the factors that control the rates and the chemo-, regio-, and stereoselectivities of radical processes. *Tedder* [45] and *Giese* [46] were among a number of workers who addressed this question with respect to radical addition reactions. Although they formulated some qualitative rules, the general conclusion was that a 'complex interplay of polar, steric, and bond-strength effects' determines the outcome of reactions involving the formation or fission of C–C bonds [45]. Meanwhile, the study of radical cyclizations had shown that the strain energy generated in the formation of the required transition structure is a significant factor for intramolecular additions [47].

A useful contribution to the design of optimum experimental conditions for conducting radical cyclizations and other rearrangements had already been made by *Walling et al.* [43a] who showed that, for Bu_3SnH-mediated processes, the relative yields of rearranged (YH) and unrearranged (RH) products are given by the approximate expression,

$$[\mathrm{YH}]_{\mathrm{final}}/[\mathrm{RH}]_{\mathrm{final}} \approx k_{\mathrm{Y}}/k_{\mathrm{RH}}\ [\mathrm{Bu_3SnH}]_{\mathrm{mean}} \tag{8}$$

where k_{Y} and k_{RH} are the respective rate constants for the two competing rate-controlling processes, namely, the rearrangement (*Eqn. 9*) and the reaction of the unrearranged radical with stannane (*Eqn. 11*). The rate expression (*Eqn. 8*) indicates that high yields of rearrangement product are favored when [$\mathrm{Bu_3SnH}$] is small and $k_{\mathrm{Y}}/k_{\mathrm{RH}}$ is relatively large.

$$\mathrm{R}\cdot \xrightarrow{k_{\mathrm{Y}}} \mathrm{Y}\cdot \tag{9}$$

$$\mathrm{Y}\cdot + \mathrm{Bu_3SnH} \rightarrow \mathrm{YH} + \mathrm{Bu_3Sn}\cdot \tag{10}$$

$$\mathrm{R}\cdot + \mathrm{Bu_3SnH} \xrightarrow{k_{\mathrm{RH}}} \mathrm{RH} + \mathrm{Bu_3Sn}\cdot \tag{11}$$

Accurate values of the relative rate constants ($k_{\mathrm{Y}}/k_{\mathrm{RH}}$) of the two reactions are readily obtained by substitution of experimental values of $[\mathrm{YH}]_{\mathrm{f}}$ into the integrated rate equation (*Eqn. 12*), where $\mathrm{S_0}$ and $\mathrm{S_f}$ are the initial and final concentrations of stannane, respectively, and where $r = k_{\mathrm{Y}}/k_{\mathrm{RH}}$ [48]. Hence, if the absolute value of either of k_{RH} or k_{Y} is already available, then the value of the other can be determined from the relative yields of the rearranged and unrearranged products from reactions carried out under carefully controlled conditions. This approach provides the basis for the concept of radical clocks [38].

$$[\mathrm{YH}]_{\mathrm{f}} = r\ \ln(\mathrm{S_0} + r)/\ln(\mathrm{S_f} + r) \tag{12}$$

Although the above kinetic expressions were first developed for reactions involving trialkylstannanes, they are equally applicable to all radical chain processes in which a unimolecular process competes with a bimolecular process, and are, therefore, very useful for choosing the best experimental conditions for organic synthetic work provided values of the appropriate rate constants are available.

In the summary [26] of his earlier work on the development of advanced experimental techniques for the determination of radical kinetic data, *Fischer* made it quite clear that he was aware that the outcomes of many synthetically important radical reactions depend on the careful choice of the experimental reaction conditions based on a knowledge of relevant rate constants and the factors controlling them. As he said '*their design and applications can greatly profit from the advanced knowledge of radical reaction rate constants*' [26]. The same is true of radical polymerization.

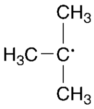
The experimental techniques that *Fischer* had already perfected were highly suitable for obtaining the required kinetic information, as they gave results that were of unprecedented precision, could be applied to a wide variety of substrates and reactants, could cover a wide range of rate constants, could be conducted in a large number of different solvents, and were applicable over a wide range of temperature, and hence afforded reliable *Arrhenius* parameters. In the course of his earlier work, he had already obtained accurate absolute kinetic data for a variety of reactions including atom transfers [49], radical rearrangements [34][35][50], and C–C bond fissions [51]. He then decided to focus his attention on the kinetic characteristics of radical additions to alkenes, a reaction that was not only of long-standing personal interest but also of great significance in organic synthesis and in free radical polymerizations.

Despite the extensive work already conducted on radical additions, the mechanistic conclusions were essentially qualitative. *Giese*'s rules [46] were useful for predicting the regioselectivity and relative rates of reactions involving a radical addition step but they were not sufficiently quantitative to guide the choice of the optimum reaction times and temperatures required for advanced synthetic work. *Fischer* recognized that a systematic and extensive compilation of accurate absolute rate constants covering a wide range of radicals and alkenes would be needed to disentangle the 'complex interplay of steric, polar, and bond-strength terms' [45]. Accordingly, he set out to amass a large and comprehensive set of accurate rate constants and *Arrhenius* parameters using mainly the advanced techniques already developed in his own laboratories.

The first such case study involved the precise measurement of the absolute rate constants and their temperature dependencies for the reactions of *tert*-butyl radicals with 24 alkenes and several other compounds in isopropanol solution [25] [52]. *Fischer* first chose a set of 13 monosubstituted and 1,1-disubstituted alkenes in which the nature of the substituents was expected to minimize steric factors and should thus allow polar effects to be more clearly revealed [25]. This expectation was realized. In accord with the nucleophilic nature of the *tert*-butyl radical, there was a very wide spread of rate constants at 300 K. These (in M^{-1} s^{-1} and statistically corrected for symmetric alkenes) ranged from 1.5×10^2 for (*tert*-butyl)ethylene, through 1.3×10^3 for ethylene, 1.6×10^4 for chloroethylene, to 3.5×10^5 for 1,1-dichloroethylene [25], and up to 2.4×10^6 M^{-1} s^{-1} for acrylonitrile [52]. Furthermore, the observation that there was little variation in the values of the frequency factor indicated that the wide range of rate constants mainly reflected differences in activation energies. *Fischer* concluded that the effect exerted by substituents at the new radical center is predominantly polar, a view supported by an approximately linear relationship between the electron affinities of the alkenes and the experimental activation energies (and log (k/M^{-1} s^{-1})). Steric hindrance to addition was clearly apparent for alkenes substituted at both the 1 and 2 positions. For example, the rate constants (M^{-1} s^{-1}, statistically corrected for symmetric alkenes) for *tert*-butyl addition to (*Z*)-but-2-ene and but-1-ene were 31 and 1.1×10^3, respectively, and they were 1.3×10^3 for (*Z*)-CHCl=CHCl, 3.6×10^3 for (*E*)-CHCl=CHCl, 1.7×10^4 for CHCl=CCl_2, and 1.1×10^3 for $\text{CCl}_2\text{=CCl}_2$. Indeed, the first Cl-atom at the C-atom to which the *tert*-butyl radical adds produces an increase in the activation energy of *ca.* 8 kJ/mol, and there is an additional 12 kJ/mol produced by the second Cl-atom on this C-atom.

Fischer also studied the kinetics of the addition of *tert*-butyl radicals to a series of 20 alkynes [53]. The rate constants for monosubstituted alkynes ranged from 2.2 M^{-1} s^{-1} for (*tert*-butyl)acetylene to 2.2×10^5 M^{-1} s^{-1} for ethyl propiolate, again indicating a strong polar effect. The alkynes reacted with *tert*-butyl radicals rather more slowly than the analogous alkenes. Although the additions to alkynes have larger frequency factors than the additions to their alkene analogues, this rate-enhancing factor is more than compensated for by higher activation energies.

In addition, *Fischer* and his co-workers studied the kinetics for the additions to a variety of unsaturated substrates of a wide range of nucleophilic, electrophilic and ambiphilic radicals including: methyl (**5**) [54], benzyl (**6**) [55], cumyl (**7**) [55], 2-hydroxy-2-propyl (**8**) [56], cyanomethyl (**9**) [57], hydroxymethyl (**10**) [58], 2-(*tert*-butoxycarbonyl)-2-propyl (**11**) [57], 2-cyano-2-propyl (**12**) [59], (*tert*-butoxycarbonyl)methyl (**13**) [53] [57], and (trifluoroacetyl)methyl radicals (**14**) [60], and the cyclic malonyl radical (**15**) [61]. The combined results cover more than 200 separate reactions and were usually conducted over a range of temperatures. This body of work constituted a monumental experimental endeavor. Indeed, the data reported for *tert*-butyl alone required the measurement of more than 500 individual rate constants [26].


$(CH_3)_3C^\bullet$

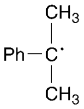
4

$H_3C^\bullet$

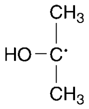
5

$Ph{-}CH_2^\bullet$

6


$Ph{-}C^\bullet(CH_3)_2$

7


$HO{-}C^\bullet(CH_3)_2$

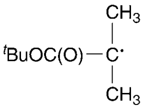
8

$NC{-}CH_2^\bullet$

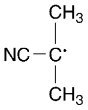
9

$HO{-}CH_2^\bullet$

10


$^tBuOC(O){-}C^\bullet(CH_3)_2$

11


$NC{-}C^\bullet(CH_3)_2$

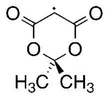
12

$^tBuOC(O){-}CH_2^\bullet$

13

$CF_3CO{-}CH_2^\bullet$

14



15

Having collected this impressive array of experimental rate constants and *Arrhenius* parameters, *Fischer* was then fully equipped to address his long standing goal of defining how enthalpic effects, polar charge transfer contributions, and steric substituent effects define the rates and outcomes of radical addition reactions. He was joined in this endeavor by *Leo Radom* who complemented the experimental approach with advanced theoretical calculations. Their joint work culminated in the publication of a very significant article – '*Factors Controlling the Addition of Carbon-Centered Radicals to Alkenes – An Experimental and Theoretical Perspective*' [62]. This remarkable paper covers a range of topics including an overview of existing rules and concepts for radical addition reactions, experimental techniques, theoretical procedures, an extensive analysis of the experimental results in the light of theoretical concepts, and a synopsis and perspective including rules and guidelines that give new insights into the factors controlling these reactions and that provide unprecedented predictive utility.

A key feature of this paper is the compilation in tabular form of a large number of rate constants and activation parameters representative of those determined by *Fischer* in the preceding decade. The tables include kinetic data for the addition reactions of some eleven different radicals with more than 20 substituted alkenes. The rate constants span an extraordinary breadth of about nine orders of magnitude. They are an invaluable resource for anyone seeking guidance on the design of the optimum experimental conditions for a preparative radical addition reaction.

They also provided *Fischer* with a unique and extensive set of reliable kinetic data against which he could test the validity of existing concepts of radical reactivity. He found that by and large the trends in reaction rates associated with changing the radical and alkene substituents for relatively simple systems conformed to the earlier qualitative rules and guidelines [45] [46]. For example, the regioselective addition of radicals to the least substituted terminus of an alkene and the general decrease in the rate of addition for tertiary radicals as compared with primary accord with the prevailing views of steric hindrance and the use of steric substituent parameters [45] [46]. Also, in very general terms, the data showed that activation energies (E_a) decreased with increasing exothermicity (H_r) in accord with the *Evans–Polanyi–Semenov* relation (*Eqn. 13*) where α is a proportionality constant.

$$E_a = \text{const} + \alpha H_r \tag{13}$$

Even so, further examination of the experimental data revealed some interesting new kinetic features of radical addition reactions. First, it showed that the nature of the solvent and the steric bulk of substituents at the new radical center have only minor effects on reaction rates. Second, when allowance was made for the possible effect of experimental errors, it was possible to recognize significant systematic trends in the values of the frequency factors. The values of $\log(A/\text{M}^{-1}\ \text{s}^{-1})$ for all of the reactions studied centered around 8.5 for primary radical adducts, 8.0 for secondary radicals, 7.5 for tertiary radicals, and 7.0 for polymeric radicals, in accord with the view that the loss of internal rotational freedom accompanying the formation of the transition state structure increases in the order primary $<$ secondary $<$ tertiary. Accordingly, *Fischer* was able to accept these as standard values for $\log(A/\text{M}^{-1}\ \text{s}^{-1})$ and hence to calculate corrected activation energies.

In light of the recognition that frequency factors vary systematically and predictably with the nature of the radical, and that reaction rates are affected to only a minor degree by the choice of solvent, or by steric hindrance by substituents on the attacking radical or on the C-atom that becomes the new radical center, *Fischer* realized that any further advance in understanding the combined effect of bond strength and polar factors on the rates of radical addition reactions would require consideration of activation barriers in the light of modern theoretical principles.

For this purpose, *Fischer* and *Radom* chose the state correlation diagram (SCD) approach that had been developed by *Shaik* and *Pross* [63] from earlier work based on the valence bond description of chemical reactivity[9]). *Fischer* and *Radom*'s calculations led them to conclude that: *1*) when polar effects are small or absent the reaction barrier should decrease with increasing exothermicity (H_r) as in the *Evans–Polanyi–Semenov* relation (*Eqn. 13*), *2*) the barrier should decrease with decreasing singlet-triplet energy gap, Δ_{ST}, and *3*) polar effects are expected to increase with decreasing energy of either of the charge transfer (CT) configurations, namely $E_i(\text{R}) - E_{ea}(\text{A})$ and/or $E_i(\text{A}) - E_{ea}(\text{R})$, of the reactants reduced by the *Coulomb* interaction, C (see below), where E_i = ionization energy, E_{ea} = electron affinity, R represents the radical and A represents the alkene. Hence, radicals should exhibit nucleophilic behavior if $E_i(\text{R}) - E_{ea}(\text{A})$ is sufficiently small and electrophilic behavior if $E_i(\text{A}) - E_{ea}(\text{R})$ is sufficiently small.

First, it was necessary, however, to determine which of the various theoretical methods would best model kinetic data. Accordingly, *Fischer* and *Radom* reviewed the available procedures and compared the results produced by various levels of theory with

---

[9]) A model state correlation diagram is shown in [62].

reliable experimental data. In general, they found that the CBS-RAD level with the 6-31G(2) basis set performed best and gave reasonably good agreement with experimental values of reaction barriers and reaction enthalpies. Although the theoretical values for reaction enthalpies were systematically *ca.* 7% less than experiment, they are useful because of the difficulty of obtaining reliable experimental values. There are some other reaction properties that are difficult to determine accurately or are inaccessible by experiment. For example, the direction and extent of charge transfer in the transition-state structure that have been obtained by calculation are likely to be more reliable than those available from experimental data. The geometry of a transition structure cannot be experimentally determined, but it can be straightforwardly accessed by *ab initio* calculations. The results show that there is not much difference between values afforded by the various levels of theory for the angle of approach and the C−C distance.

Fischer then set out to rationalize his results in the light of the above theoretical concepts focusing mainly on factors affecting the magnitude of the activation energy. In some simple cases, *e.g.*, the addition of methyl (**5**), and benzyl (**6**) radicals to a variety of alkenes, a plot of activation energies, E_a, against the reaction enthalpies, H_r, conformed reasonably well to a linear *Evans–Polanyi–Semenov* relationship (*Eqn. 14*).

$$E_a = 50 + 0.22 H_r \tag{14}$$

Reasonable linear correlations between E_a and H_r were also found for reactions of the cumyl radical (**7**), and for the reactions of the more strongly nucleophilic radicals **4**, **8**, and **10** but not for those of the strongly electrophilic radicals **14** and **15**. A significant trend was observed in these plots of E_a against H_r. For the donor-substituted radicals **4**, **8**, and **10**, both the intercept and the gradients were much larger than the 0.22 given in *Eqn. 14* for **5** and **6**, whereas, for the electrophilic radicals **9**, **11**, **12** and **13**, the gradients were smaller. For the highly electrophilic radicals **14** and **15**, the gradients were negative. These correlations indicated a general influence of reaction enthalpy, H_r, on the activation energy, E_a, but they did not allow the specification of a dependence that would be valid for all alkenes and radicals. *Fischer*, therefore, examined possible correlations of activation energies with charge transfer energies. A plot of E_a for the nucleophilic radicals hydroxymethyl (**10**), *tert*-butyl (**4**), and 2-hydroxy-2-propyl (**8**) against the relative energies of the charge transfer configuration R^+A^- (measured by $E_i(R) - E_{ea}(A)$) showed considerable scatter but there was a distinct trend about the regression line given by E_a [kJ mol^{-1}] $= -63.0 + 10.1(E_i(R) - E_{ea}(A))$ [eV]. Even the weakly nucleophilic radicals methyl (**5**) and benzyl (**6**) and the electron-acceptor substituted radicals showed similar behavior, but, for the electrophilic cyclomalonyl (**15**) and trifluoroacetonyl (**14**) radicals, it was the plot of E_a against the alternative CT configuration R^+A^- that showed a trend toward a linear regression line.

In light of these observations, *Fischer* and *Radom* decided that it would not be possible to devise a simple linear correlation for the prediction of all radical addition reaction rates. However, they did come to one important conclusion, namely, that any polar effects, as distinct from steric factors, can only serve to decrease the reaction barriers predicted from values of H_r *via Eqn. 14.*

The validity of this conclusion was demonstrated by a plot of the activation energy *vs.* reaction enthalpy for nearly all of the reactions studied experimentally by *Fischer* (>200); it comprised a highly dispersed set of points with no clearly defined lower boundary. There was, however, a quite well defined upper boundary that closely conformed to the line described by *Eqn. 14*. The fact that most data points lay below this line indicated that only reactions of *tert*-butyl, benzyl, and related non-polar radicals have the activation energies expected on the basis of *Eqn. 14*. For all other addition reactions involving either nucleophilic or electrophilic species, the values of E_a are lower than these. *Fischer* concluded, therefore, that enthalpic effects are indeed described by a relation similar to *Eqn. 14* but that polar effects should also be included. This was done by the inclusion of appropriate polar factors, F_n and F_e, as indicated in *Eqn. 15*.

$$E_a = (50 + 0.22H_r)F_nF_e \tag{15}$$

The nucleophilic factor, F_n, depends on $E_i(R) - E_{ea}(A) - C_n$ and an interaction parameter, γ_n, and the electrophilic factor, F_e, on $E_i(A) - E_{ea}(R) - C_e$ and γ_e. The values of the various terms and factors could then be determined through matching appropriate heuristic functions to selected experimental data. To test the validity of this approach, the experimental activation energies for the 206 reactions tabulated earlier in the paper were plotted against values calculated from *Eqn. 15* with a unified set of polar *Coulomb* and interaction parameters[10]). The 206 data points correspond closely to the linear regression $E_{calc} = E_{exp}$ with a standard deviation of 2.4 kJ mol^{-1}, thus confirming the widespread applicability of the method. In a further test of its utility for the prediction of rate constants, the new general relation, *Eqn. 15*, with estimated reaction enthalpies was used to calculate the values of 27 rate constants that had previously been independently determined. The agreement between calculation and experiment was remarkably good.

In the final section of the paper, *Fischer* and *Radom* discuss the applicability of their advanced procedures for reactions involving 1,1-disubstituted and 1,1,2-trisubstituted alkenes as they relate to aspects of homopolymerizations and copolymerizations, and to reactions involving additions to dienes, alkynes, and arenes. In most cases, the same general principles apply. However, they are not satisfactory for radical additions to alkynes in that these processes have higher frequency factors (on average, $\log(A/\text{M}^{-1}\,\text{s}^{-1}) = 9.2$ [25]) and higher activation energies than the analogous additions to alkenes of methyl [54b], *tert*-butyl [25], and (*tert*-butoxycarbonyl)methyl radicals [25]. *Fischer* tentatively suggested that the higher $\log A$ values (indicating lower entropy loss in the transition state) could be attributed to the linear alkyne structure, and that the higher E_a values could be attributed to the smaller electron affinities, and larger ionization and triplet energies of alkynes compared with alkenes. The implication is that the parameters of an *Evans–Polanyi–Semenov* relation for alkynes would be smaller than those for alkenes (*Eqn. 14*).

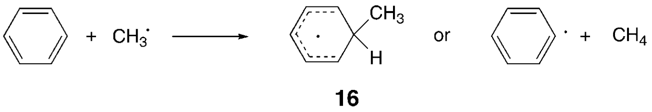
---

[10]) A list of appropriate values of C_n, γ_n, C_e, and γ_e is given in a footnote to [62].

In summary, this is a very significant paper that is remarkable not only for the wealth of useful and reliable kinetic data that it contains but also, and more importantly, because it outlines a new rationalization of radical addition rates. As the Authors point out, their work provides a model for the development of similar approaches to many other types of radical reactions.

Methyl Affinities. – The last of our favorite *Fischer* papers [54b] is the very personal choice of one of us (*A. L. J. B.*) who had the occasion many years ago during his Ph.D. candidature to refer frequently to the work of *Michael Szwarc* on the reactions of methyl radicals with benzene and other aromatic compounds. Earlier, there had been considerable discussion about the intimate mechanisms of organic free radical processes. Following the success of earlier work on electrophilic aromatic substitution in defining the effect of electronic and other factors on the mechanisms and outcomes of such reactions, it was reasonable to expect that similar studies of homolytic aromatic substitution would be equally fruitful. However, unlike their ionic counterparts, reactions of arenes with various radical precursors frequently gave mixtures that were either intractable or very difficult to analyze, and hence failed to support reliable mechanistic conclusions. A key question was whether the intermediate step involved H-atom abstraction from the arene to afford an aryl radical intermediate or radical addition to give a cyclohexadienyl intermediate, *e.g.*, in the case of methyl radical attack on benzene was the intermediate a cyclohexadienyl radical (**16**) or the phenyl radical (*Scheme 3*).

Scheme 3



Both *D. H. Hey* and *W. A. Waters* had obtained results favoring the intermediacy of cyclohexadienyl radicals, but the most compelling evidence came from *Szwarc* and his colleagues who during the 1950s and early 60s developed a straightforward experimental technique involving the accurate analysis of the relative amounts of carbon dioxide and methane evolved, when acetyl peroxide and an arene or a related unsaturated compound was heated in isooctane (2,2,4-trimethylpentane). From the results, they were able to determine the relative rates of attack of methyl radials on the substrate (*Eqn. 16*) and the solvent (*Eqn. 17*), and hence obtain values of $k_{\mathrm{add}}/k_{\mathrm{H}}$, the so-called methyl affinities [64][11]). In a series of papers published over a period of about eight years, they amassed a set of *ca.* 200 methyl affinities and used the same method to obtain similar relative rate data for ethyl, propyl, cyclopropyl, and trifluoromethyl radicals.

$$(\mathrm{CH_3CO_2})_2 \rightarrow 2\ \mathrm{CH_3CO_2}\cdot \rightarrow 2\ \mathrm{CH_3}\cdot + 2\ \mathrm{CO_2}$$

$$\mathrm{CH_3}\cdot + \mathrm{C_6H_6} \xrightarrow{k_{\mathrm{add}}} \mathrm{C_7H_9}\cdot \text{ (methylcyclohexadienyl radical)} \tag{16}$$

---

[11]) A complete list of *Szwarc*'s papers on methyl affinities is included in [54b].

$$CH_3\cdot + C_8H_{18} \xrightarrow{k_H} CH_4 + C_8H_{17}\cdot \tag{17}$$

Other workers similarly obtained additional methyl affinities. Unfortunately, despite the potential value of this extensive resource of kinetic data, *Szwarc*'s work has been infrequently cited and has received neither the acknowledgment nor the applications it deserves. Indeed, the methodology has attracted some criticism from time to time.

In the course of his earlier work on methyl radicals [54a], *Fischer* found that his results were in excellent agreement with the relevant methyl affinities and thus confirmed the reliability and accuracy of the data, and hence of the reliability of *Szwarc*'s method. Accordingly, he set about converting the extensive list of methyl affinities into absolute rate constants. All that was necessary was to calibrate values of k_{add}/k_H from *Szwarc*'s data with values of k_H determined under comparable experimental conditions.

Fischer's approach involved photolysis of dicumyl peroxide, a reaction that affords methyl radicals *via* the rapid β-fission of the first formed cumyloxyl radicals. The peroxide photolysis was conducted in isooctane and was monitored at various temperatures by kinetic ESR spectroscopy using an instrument with good time resolution (10 ms minimum response time). In this way, *Fischer* was able to determine rate constants for the bimolecular self-termination of methyl radicals (k_{term}) and for the decay of cumyloxyl radicals as well as the *Arrhenius* parameters for these reactions. When the experiments were carried out in the presence of an arene or alkene, the value of k_{term} could be used as a standard against which rate constants, k_{add}, for the first-order consumption of methyl by its addition to the unsaturated compound could be measured.

In the course of the above experiments, the rate constants for the H-atom abstraction (*Eqn. 17*) were also determined but, because of side reactions, they lacked the precision that *Hanns Fischer* always insisted upon. This difficulty was overcome by using the *Arrhenius* parameters for the addition to calculate values of k_{add} at the temperatures used by *Szwarc* (mainly 332, 338, and 358 K). These values were then substituted into relevant values of the methyl affinity (k_{add}/k_H) to obtain k_H. From a number of such determinations, *Fischer* determined the temperature dependence of k_H (*Eqn. 18*).

$$\log(k_H/\mathrm{M}^{-1}\ \mathrm{s}^{-1}) = 8.08 - 33.30\ [\mathrm{kJ/mol}]/2.303RT \tag{18}$$

Substitution of the value of k_H at the relevant temperature into methyl affinities from *Szwarc*'s extensive compilation allowed *Fischer* to determine the absolute values of k_{add}. All of *Szwarc*'s methyl affinities and other relative rate data determined by the *Szwarc* method were thus converted into absolute values. In his paper [54b], *Fischer* records the rate constants and, in some cases, other kinetic data, for the addition of methyl radicals to more than 250 unsaturated compounds including alkenes, alkynes, allenes, conjugated dienes, benzenes, condensed aromatic compounds, quinones, and heterocycles.

In the course of this work, *Fischer* noted that the characteristics of the new values of k_{add} concurred with the trends identified from his own major kinetic survey, namely, that the frequency factors for the addition of methyl radicals to mono-substituted and 1,1-disubstituted alkenes are close to the mean of $\log(A/\mathrm{M}^{-1}\ \mathrm{s}^{-1}) = 8.6$. This indicated that the variation in the rate constants for alkenes with this type of substitution pattern arises from variations in the activation energies, which are governed mainly by enthalpic or polar effects of the substituents.

In summary, this paper is highly significant because the kinetic data it contains supplement the extensive tabulation of such information available in *Fischer*'s review of radical addition reactions [62]. Also, it provides for the first time an extensive set of reliable absolute rate constants for radical addition reactions to arenes, heteroarenes, and related compounds that will be very useful for those intending to employ radical methodology for synthesis in this area.

Conclusions. – When facing the difficult task of selecting our favorite papers from *Fischer*'s extensive publication list, we were greatly tempted to include his article somewhat enigmatically entitled '*Unusual Selectivities of Radical Reactions by Internal Suppression of Fast Modes*' [27]. In fact, what this paper does contain is an analysis of the factors that control the rates and outcomes of reactions involving the intermediacy of persistent radicals, and it thus provides a theoretical approach for understanding the basis of living radical polymerization, an area of much current attention. However, inclusion of '*Unusual Selectivities*' would necessarily have required an extensive discussion of *Fischer*'s later and very important contributions to this area [65], and this we considered to be beyond the intended scope of this paper. As it stands, our collection of favorite papers demonstrates well the salient features of *Fischer*'s work – the development of new experimental techniques, meticulous experimentation, rigorous and innovative theoretical analysis, and an uncanny knack for choosing research topics later found to be of great theoretical and practical significance. He was indeed a great radical pioneer.

REFERENCES

[1] H. Fischer, 'Magnetic Properties of Free Radicals', Landolt-Börnstein Neue Serie: II/1, 1965; II/9a–9d, 1977–1979; II/17a–17h, 1984–1990.

[2] H. Fischer, 'Radical Reaction Rates in Liquids', Landolt-Börnstein Neue Serie: II/13a–13e, 1980–1983; II/18a–18e2, 1994–1997.

[3] J. Bargon, H. Fischer, U. Johnson, *Z. Naturforsch., A* **1967**, *22*, 1551; J. Bargon, H. Fischer, *Z. Naturforsch., A* **1967**, *22*, 1556; J. Bargon, H. Fischer, *Z. Naturforsch., A* **1968**, *23*, 2109; H. Fischer, J. Bargon, *Acc. Chem. Res.* **1969**, *2*, 110.

[4] C. Huggenberger, J. Lipscher, H. Fischer, *J. Phys. Chem.* **1980**, *84*, 3467.

[5] E. Lissi, J. de la Fuente, *J. Chem. Soc., Perkin Trans. 2* **1986**, 819.

[6] K. U. Ingold, in 'Free Radicals', Ed. J. K. Kochi, John Wiley & Sons, New York, 1973, Vol. 1, p. 37.

[7] E. L. Allred, R. L. Smith, *J. Am. Chem. Soc.* **1969**, *91*, 6766; P. S. Engel, P. D. Bartlett, *J. Am. Chem. Soc.* **1970**, *92*, 5883; S. A. Weiner, *J. Am. Chem. Soc.* **1971**, *93*, 425; T. Koenig, H. Fischer, in 'Free Radicals', Ed. J. K. Kochi, John Wiley & Sons, New York, 1973, Vol 1, p. 157.

[8] H. Schuh, H. Fischer, *Int. J. Chem. Kinet.* **1976**, *8*, 341.

[9] H.-H. Schuh, H. Fischer, *Helv. Chim. Acta* **1978**, *61*, 2130.

[10] H.-H. Schuh, H. Fischer, *Helv. Chim. Acta* **1978**, *61*, 2463.

[11] E. L. Metcalfe, *J. Chem. Soc.* **1963**, 3560.

[12] D. F. McMillen, D. M. Golden, S. W. Benson, *J. Am. Chem. Soc.* **1972**, *94*, 4403.

[13] R. Hiatt, S. W. Benson, *Int. J. Chem. Kinet.* **1973**, *5*, 385.

[14] R. M. Marshall, J. H. Purnell, *J. Chem. Soc., Chem. Commun.* **1972**, 764; D. C. Montague, *Int. J. Chem. Kinet.* **1973**, *5*, 513.

[15] D. J. Carlsson, K. U. Ingold, *J. Am. Chem. Soc.* **1968**, *90*, 7047; S. A. Weiner, G. S. Hammond, *J. Am. Chem. Soc.* **1969**, *91*, 986; G. B. Watts, K. U. Ingold, *J. Am. Chem. Soc.* **1972**, *94*, 491.

[16] E. J. Hamilton Jr., H. Fischer, *J. Phys. Chem.* **1973**, *77*, 722.

[17] M. J. Gibian, R. C. Corley, *Chem. Rev.* **1973**, *73*, 441.

[18] D. Griller, K. U. Ingold, *Int. J. Chem. Kinet.* **1974**, *6*, 453.

[19] S. J. Blanksby, G. B. Ellison, *Acc. Chem. Res.* **2003**, *36*, 255.

[20] D. A. Parkes, C. P. Quinn, *J. Chem. Soc., Faraday Trans. 1* **1976**, *72*, 1952; K. Y. Choo, P. C. Beadle, L. W. Piszkiewicz, D. M. Golden, *Int. J. Chem. Kinet.* **1976**, *8*, 45.

[21] M. Lehni, H. Schuh, H. Fischer, *Int. J. Chem. Kinet.* **1979**, *11*, 705.

[22] D. Griller, K. U. Ingold, P. J. Krusic, H. Fischer, *J. Am. Chem. Soc.* **1978**, *100*, 6750.

[23] H. R. Dütsch, H. Fischer, *Int. J. Chem. Kinet.* **1981**, *13*, 527.

[24] H. R. Dütsch, H. Fischer, *Int. J. Chem. Kinet.* **1982**, *14*, 195.

[25] K. Münger, H. Fischer, *Int. J. Chem. Kinet.* **1985**, *17*, 809.

[26] H. Fischer, H. Paul, *Acc. Chem. Res.* **1987**, *20*, 200.

[27] H. Fischer, *J. Am. Chem. Soc.* **1986**, *108*, 3925.

[28] R. M. Mobley, J. M. Bailey, W. E. Cleland, V. W. Hughes, J. F. Rothberg, *J. Chem. Phys.* **1966**, *44*, 4354.

[29] G. G. Myasishcheva, Y. V. Obukhov, V. S. Roganov, V. G. Firsov, *Zh. Exper. Teor. Fiz.* **1967**, *53*, 451; English transl. *Sov. Phys. JETP* **1968**, *26*, 298.

[30] P. W. Percival, H. Fischer, M. Camari, F. N. Gygax, W. Rüegg, A. Schenck, H. Shilling, H. Graf, *Chem, Phys. Lett.* **1976**, *39*, 333.

[31] H. Fischer, private communication to *K. U. I.*, 1975.

[32] P. W. Percival, E. Roduner, H. Fischer, M. Camani, F. N. Gygax, A. Schenck, *Chem. Phys. Lett.* **1977**, *47*, 11.

[33] E. Roduner, P. W. Percival, D. G. Fleming, J. Hochmann, H. Fischer, *Chem. Phys. Lett.* **1978**, *57*, 37.

[34] P. Burkhard, E. Roduner, J. Hochmann, H. Fischer, *J. Phys. Chem.* **1984**, *88*, 773.

[35] P. Burkhard, E. Roduner, H. Fischer, *Int. J. Chem. Kinet.* **1985**, *17*, 83.

[36] Y. Maeda, K. U. Ingold, *J. Am. Chem. Soc.* **1979**, *101*, 4975.

[37] A. L. J. Beckwith, G. Moad, *J. Chem. Soc., Perkin Trans. 2* **1980**, 1473.

[38] D. Griller, K. U. Ingold, *Acc. Chem. Res.* **1980**, *13*, 317.

[39] B. Halliwell, J. M .C. Gutteridge, 'Free Radicals in Biology and Medicine', Oxford University Press, Oxford, 1986.

[40] H. G. Kuivila, *Acc. Chem. Res.* **1968**, *1*, 299; H. G. Kuivila, *J. Am. Chem. Soc.* **1962**, *84*, 3584; L. W. Menapace, H. G. Kuivila, *J. Am. Chem. Soc.* **1964**, *86*, 3047.

[41] B. Giese, J. Dupuis, *Tetrahedron Lett.* **1984**, *25*, 1349; D. G. Norman, C. B. Reese, *Synthesis* **1983**, 304; B. Giese, 'Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds', 1st edn. Pergamon Press, Oxford, 1986.

[42] D. P. Curran, in 'Comprehensive Organic Synthesis', Eds. B. M. Trost, I. M. Fleming, M. G. Semmelhack, Pergamon, Oxford, 1991, Vol. 4, p. 715.

[43] a) C. Walling, J. H. Cooley, A. A. Ponaras, E. J. Racah, *J. Am. Chem. Soc.* **1966**, *88,* 5361; b) A. L. J. Beckwith, K. U. Ingold, in 'Rearrangements in Ground and Excited States', Ed. P. de Mayo, Academic Press, New York, 1980, Vol. l, p. 161.

[44] a) D. P. Curran, D. M. Rakiewicz, *Tetrahedron* **1985**, *41*, 3943; b) D. P. Curran, S.-C. Kuo, *J. Am. Chem. Soc.* **1986**, *108*, 1106; 'Comprehensive Organic Synthesis', Eds. B. M. Trost, I. M. Fleming, M. G. Semmelhack, Pergamon, Oxford, 1991, Vol. 4, p. 779.

[45] J. M. Tedder, *Angew. Chem.* **1982**, *94*, 433; J. M. Tedder, J. C. Walton, *Tetrahedron* **1980**, *36*, 701; *Adv. Phys. Org. Chem.* **1978**, *16*, 51; J. M. Tedder, J. C. Walton, *Acc. Chem. Res*, **1976**, *9*, 183.

[46] B. Giese, *Angew. Chem., Int. Ed.* **1983**, *22*, 753.

[47] A. L. J. Beckwith, C. H. Schiesser, *Tetrahedron Lett.* **1985**, *26*, 373; A. L. J. Beckwith, C. H. Schiesser, *Tetrahedron* **1985**, *41*, 3925; D. C. Spellmeyer, K. N. Houk, *J. Org. Chem.* **1987**, *52*, 959.

[48] A. L. J. Beckwith, G. Phillipou, *J. Chem. Soc., Chem. Commun.* **1973**, 280.

[49] H.-R. Dütsch, H. Fischer, *Int. J. Chem. Kinet.* **1981**, *13*, 527; H. R. Dütsch, H. Fischer, *Int. J. Chem. Kinet.* **1982**, *14*, 195.

[50] E. J. Hamilton Jr., H. Fischer, *Helv. Chim. Acta* **1973**, *56*, 795; H. Itzel, H. Fischer, *Helv. Chim. Acta* **1976**, *59*, 880.

[51] L.-M. Wu, H. Fischer, *Helv. Chim. Acta* **1983**, *66*, 138.

[52] F. Jent, H. Paul, E. Roduner, M. Heming, H. Fischer, *Int. J. Chem. Kinet.* **1986**, *18*, 1113.

[53] H. Rubin, H. Fischer, *Helv. Chim. Acta* **1996**, *79*, 1670.

[54] a) T. Zytowski, H. Fischer, *J. Am. Chem. Soc.* **1996**, *118*, 437; b) T. Zytowski, H. Fischer, *J. Am. Chem. Soc.* **1997**, *119*, 12869.

[55] M. Walbiner, J. Q. Wu, H. Fischer, *Helv. Chim. Acta* **1995**, *78*, 910.

[56] K. Hèberger, H. Fischer, *Int. J. Chem. Kinetic.* **1993**, *25*, 913; R. Martschke, R. D. Farley, H. Fischer, *Helv. Chim. Acta* **1997**, *80*, 1363.

[57] J. Q. Wu, I. Beranek, H. Fischer, *Helv. Chim. Acta* **1995**, *78*, 194.

[58] J. Q. Wu, H. Fischer *Int. J. Chem. Kinet.* **1995**, *27*, 167.

[59] K. Hèberger, H. Fischer, *Int. J. Chem. Kinet.* **1993**, *25*, 249.

[60] T. Zytowski, B. Knühl, H. Fischer, *Helv. Chim. Acta* **2000**, *83*, 658.

[61] M. Weber, H. Fischer, *Helv. Chim. Acta* **1998**, *81*, 770.

[62] H. Fischer, L. Radom, *Angew. Chem., Int. Ed.* **2001**, *40*, 1340.

[63] A. Pross, S. S. Shaik, *Acc. Chem. Res.* **1983**, *16*, 363; S. Shaik, A. Shurki, *Angew. Chem., Int. Ed.* **1999**, *38*, 586.

[64] M. Levy, M. Szwarc, *J. Chem. Phys.* **1954**, *22*, 1621; M. Szwarc, J. H. Binks, in 'Theoretical Organic Chemistry; Kekule Symposium', Butterworth, London, 1959, p. 262; M. Szwarc, in 'The Transition State', Special Publication No. 16, Chemical Society, London, 1959, p. 91.

[65] H. Fischer, *Chem. Rev.* **2001**, *101*, 3587; M. Souaille, H. Fischer, *Macromolecules* **2002**, *35*, 248.

Received April 25, 2006