The Persistent Radical Effect: From Mechanistic Curiosity to Synthetic Tool

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Dedicated to the memory of Professor *Hanns Fischer*

The *Fischer–Ingold* persistent radical effect (PRE) provides a simple conceptual framework to rationalize reactivities in systems involving two radicals with very different self-reaction rate constants; in a limiting, but rather common case, one of these radicals is persistent at room temperature. In these cases, the cross-coupling product is strongly favored. This contribution summarizes some of the work carried out at the University of Ottawa, where the PRE plays a key role in determining product distributions. Much of this work was inspired by the seminal contributions of *Hanns Fischer*.

Introduction. – Radical-combination reactions involving two different radicals can lead to three different combination products, as shown in *Scheme 1*. In fast reactions, we normally expect the cross-combination reaction (forming AB) to reflect statistics as the geometric mean of the self-reaction rate constants (*Eqn. 1*) [1][2].

$$k_{\mathrm{AB}} = 2\sqrt{k_{\mathrm{AA}} k_{\mathrm{BB}}} \qquad (1)$$

However, there are many systems involving radicals with low self-reactivity where this simple relationship does not apply. A case in point involves the reactions of C-centered radicals with nitroxides; the latter do not undergo self-reaction, and thus *Eqn. 1* would predict that the cross-reaction should not take place. In reality, trapping of C-centered radicals by nitroxides is a very fast reaction [3][4]. Whenever a system deviates drastically from the behavior predicted by *Eqn. 1*, the experimental conditions are set for cross-products to be favored by the mechanism now known as the *Fischer–Ingold* persistent radical effect (PRE) [5].

Scheme 1. *Radical-Combination Reactions*

$$\mathrm{A}^{\bullet} + \mathrm{A}^{\bullet} \xrightarrow{k_{\mathrm{AA}}} \mathrm{AA}$$

$$\mathrm{B}^{\bullet} + \mathrm{B}^{\bullet} \xrightarrow{k_{\mathrm{BB}}} \mathrm{BB}$$

$$\mathrm{A}^{\bullet} + \mathrm{B}^{\bullet} \xrightarrow{k_{\mathrm{AB}}} \mathrm{AB}$$

This article presents an account of the work carried out at the University of Ottawa inspired by the ideas on which the *Fischer–Ingold* PRE is based. In the spirit of

Fischer's approach, we started this contribution by setting up the mathematical condition for reaction products to be controlled by the *Fischer–Ingold* PRE.

Physical organic chemistry has greatly benefited from a 1985 discussion between *Fischer* and *Ingold*. *Fischer* was concerned with the apparent photostability of dimethylnitrosamine (=*N*-methyl-*N*-nitrosomethanamine); similarly, the photochemical behavior of methylcobalamine was intriguing, being essentially photostable in the absence of radical traps, but highly unstable in the presence of methyl radical scavengers. If methyl radicals are formed, why is ethane not a significant product?

In his seminal 1986 paper, *Fischer* [5] credits *K. U. Ingold* with the mechanistic suggestion that led to today's understanding of the *Fischer–Ingold* PRE. In a system that generates both transient and persistent radicals, some initial self-termination of the former takes place and 'the concentration of the persistent radical will increase in time to high levels and steer the system toward cross-termination. In effect, the self-termination of the transient species will be suppressed by the slow termination of the persistent species'.

In his characteristic style, *Fischer* took the concepts underlying *Ingold*'s suggestion and developed a full kinetic model for the interpretation of experimental data. In a 2001 review on this kinetic phenomenon and its applications [6], *Fischer* goes further in his acknowledgment of previous, independent descriptions of the effect by *Bachmann* and *Wieselogle* [7], and *Perkins* [8].

The *Fischer–Ingold* PRE has been applied to several systems; some of those examined in our group are presented in this account. More than likely, there are dozens of reactions buried in the literature that could benefit from re-interpretation based on the *Fischer–Ingold* PRE.

The authors of this contribution both had the opportunity of meeting *Hanns Fischer*. One of us met him over 25 years ago and had abundant opportunity to interact with him and admire his profound (and precise) understanding of reaction kinetics and his encyclopaedic knowledge of radical chemistry. His love for kinetics also led *Fischer* to a leadership role in *Landolt–Börnstein* compilation in radical kinetics to which one of us contributed [9][10]. The other author met *Fischer* at the 2003 IUPAC conference in Ottawa, Canada. During the student poster session, *Fischer* was determined to convince us that the system we were investigating (and described herein) was merely radical trapping, and was not, in fact, a true representation of the PRE. It was a wonderful opportunity for a young graduate student to engage in a spirited yet friendly discussion about kinetics with a true master. Therefore, to honor that conversation, we refer to the system as 'inspired by' the concepts behind the PRE.

Persistent Carbon-Centered Radicals. – In general, tertiary, secondary, and even primary benzyl radicals are considered to be *stabilized but transient* radicals: while the parent benzyl C–H bonds are weaker than in the corresponding alkanes, C-centered benzyl radicals are usually very short-lived (undergoing self-termination reactions close to the diffusion-controlled limit) and display high reactivities towards O_2.

Recently, the *Scaiano* group investigated several lactones and cyano-substituted compounds as potential antioxidants (for corresponding radicals, see *Fig. 1*) [11–15]. These molecules all behaved as excellent H-donors, as their benzyl C–H bonds were readily abstracted by *tert*-butoxy radicals with rate constants of the order of *ca.* 10^7

$\mathrm{M}^{-1}\mathrm{s}^{-1}$. However, the resulting C-centered radicals were remarkably long-lived, with half-lives in the hundreds of microseconds, and they displayed a greatly attenuated reactivity towards O_2 (*i.e.*, essentially negligible on the time scale of laser flash photolysis).

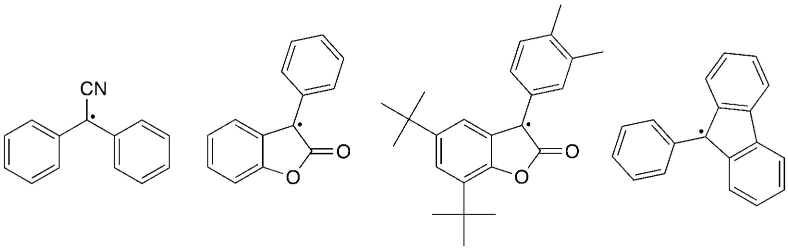
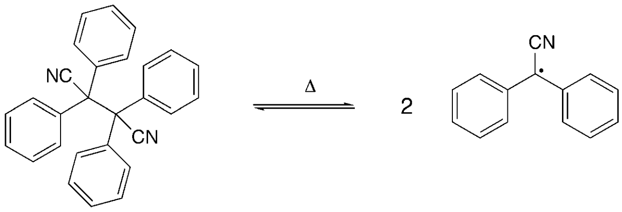


Fig. 1. *Persistent carbon-centered radicals investigated at the University of Ottawa*

Geometry-optimization calculations revealed that these radicals are generally planar, and spin-distribution calculations showed that the heteroatoms contribute significantly to the overall spin density, in some cases as much as 25%. Therefore, it was proposed that there are essentially five factors which influence radical persistence and electrophilic attack by O_2: *1*) resonance stabilization, *2*) unpaired-spin delocalization on a heteroatom, *3*) favorable stereoelectronic effects (*e.g.*, planarity), *4*) the presence of electron-withdrawing groups, and *5*) steric effects. This list is not in order of importance nor is it a checklist: it is the combination of some or all of these criteria which render a C-centered radical persistent and/or unreactive towards O_2.

Encouraged by these results, dimers of these persistent C-centered radicals were prepared from their corresponding monomers (*Scheme 2*) [11]. The UV/VIS spectra revealed that, in toluene solution, they are in thermal equilibrium with the radical species, with bond dissociation energies of 15–26 kcal/mol for the central C–C bond. Ultimately, this characteristic was responsible for the feasibility of clean organic synthesis by exploiting the kinetic phenomenon of the PRE [12].

Scheme 2. *Dimers prepared from the persistent carbon-centered radicals are in thermal equilibrium with the radical species*

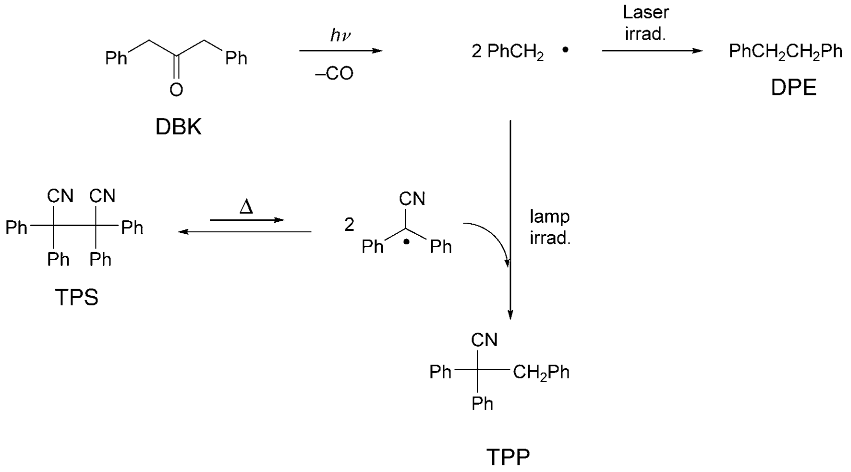


Organic Synthesis by Means of the PRE. – Armed with these remarkable dimers of persistent C-centered radicals, and inspired by the operation of the PRE, we anticipated that the introduction of a new species capable of reacting with the radicals would lead to new products.

Although the PRE is normally examined in systems where two different radicals are generated simultaneously, frequently from a single precursor, we devised a novel synthetic method wherein the persistent and transient radicals were independently controlled: persistent radicals were produced thermally from their corresponding dimers while transient radicals were generated *in situ* photochemically. In a contribution dedicated to *Hanns Fischer*, we described a 'radical buffer', with the persistent radicals trapping the transient radicals to form the cross-reaction product, while the dimer (through the equilibrium of *Scheme 2*) keeps the supply of radicals available [16].

In our new system, transient benzyl radicals were generated photochemically *via* steady-state UV-B photolysis of dibenzyl ketone (DBK) at *ca.* 50°, in the presence of the 2,2,3,3-tetraphenylbutanedinitrile dimer (TPS). We obtained a simple, yet effective one-pot synthesis of 2,2,3-triphenylpropanenitrile (TPP), as illustrated in *Scheme 3* and *Fig. 2,a*. Thus we were able to achieve C–C bond formation through independent control of persistent and transient radicals.

Scheme 3. *Organic Synthesis by Means of the Persistent-Radical Effect* (PRE)[a])



[a]) Benzyl radicals are produced photochemically from DBK, while diphenylcyanomethyl radicals are generated thermally from the dimer TPS. Under pulsed laser conditions, the self-reaction product DPE dominates. In contrast, under steady-state lamp irradiation, the cross-product TPP dominates.

Under the conditions of 308-nm *laser* excitation, the reaction products were instead dominated by the decarbonylated product of dibenzyl ketone, 1,2-diphenylethane (DPE) with only small amounts of TPP formed (*Scheme 3*, *Fig. 2,b*). Subsequent experiments revealed that the conditions of time-resolved photolysis favor radical recombination, in spite of the presence of the equilibrium concentration of the diphenylcyanomethyl radical.

It is interesting to compare the results from laser and lamp irradiation. The fact that pulsed laser irradiation tends to favor the formation of the recombination product DPE reflects the thermal and light-intensity dependence of the supply of the two radicals. In general, cross-reaction can only dominate if the condition of *Eqn. 2* is fulfilled, where $T^•$

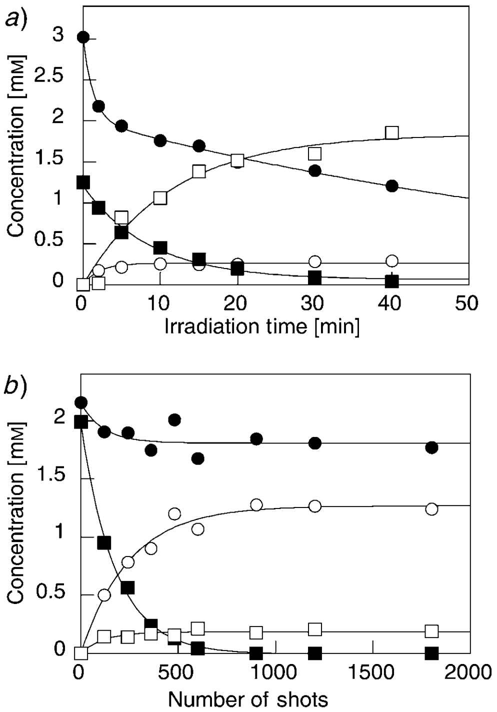


Fig. 2. a) *Lamp photolysis of 3.0 mM TPS and 1.2 mM DBK.* b) *Pulsed laser photolysis of 2.0 mM TPS and 2.0 mM DBK.* Both irradiations were performed at room temperature in deareated toluene and followed by GC/MS: TPS (●), DBK (■), DPE (○), and TPP (□). Reproduced with permission from the copyright owner.

and $P^\bullet$ represent the transient and persistent radicals, respectively. Radical concentrations generated by pulsed lasers can easily be four orders of magnitude higher than those achieved under lamp illumination. Therefore, generation of radical intermediates *via* steady-state photolysis is more likely to fulfill this requirement.

$$k_{TP}[T^\bullet][P^\bullet] \gg k_{TT}[T^\bullet]^2; \quad i.e., \quad k_{TP}[P^\bullet] \gg k_{TT}[T^\bullet] \tag{2}$$

In typical examples of the PRE, k_{PP} is near zero, and the radical $P^\bullet$ is truly 'persistent'; however, we found that this is not a necessity, as long as $k_{PP} \ll k_{TT}$. As well, this example differs somewhat from others in that the two radicals are not formed from a single precursor, and are not produced in a stoichiometric ratio.

The mechanism for the PRE has been described as 'self-adjusting'; in fact, the mechanism of *Scheme 3* also has this characteristic, except that the origin of the concentration adjustment is different – in this case, the concentration of persistent radical is supplied by the dissociation equilibrium for the dimer P–P. As well, the mechanism of *Scheme 3* does not allow the concentration of $P^\bullet$ to grow to any arbitrary value, but rather it is capped by the equilibrium constant. In effect, P–P is a 'dormant' source of radical $P^\bullet$; however, it is possible to adjust the concentration by changing the temperature. Therefore, the combination of a thermal and a photochemical source for the two radicals allows for virtually independent control of the supply of the two radicals.

In summary, though radical-coupling reactions have gained a reputation for yielding complex mixtures of products, it is possible to circumvent this issue if we require the radical intermediates to be *disciplined*. In other words, it is possible to obtain clean organic syntheses with some knowledge and control of the kinetic parameters defining the radical–radical or radical–molecule reactions.

Bond-Dissociation Energies Relevant to Living Radical Polymerization. – In the 1980's, *Rizzardo* and co-workers [17] [18] established that vinyl-radical polymerization could be controlled by reversible capping with nitroxides, reflecting the weak C–O bond formed in the capping reaction. The 1994 report by *Georges et al.* [19] [20] discussing the preparation of low-polydispersity polystyrene by living radical polymerization regulated by nitroxides has stimulated a widespread research effort in this area. The now well-established mechanism for this polymerization is shown in *Scheme 4*. A number of initiators mimicking the polymer-chain end, *i.e.*, **I**–**V** (*Fig. 3*), have been reported by us and by others [21]. These initiators produce the radicals in the correct stoichiometric ratios and facilitate using the algorithms developed by *Fischer*.

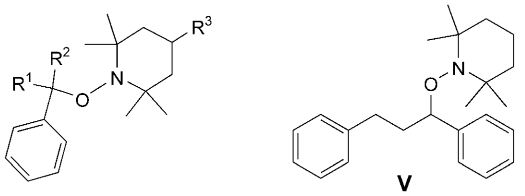
Scheme 4. *Living Radical Polymerization of Styrene.* St = styrene unit.

$$\text{Initiator} \longrightarrow 2\,\text{R}^\bullet$$

$$\text{R}^\bullet + \text{C}_6\text{H}_5\text{CH=CH}_2 \longrightarrow \text{RSt}_1^\bullet$$

$$\text{RSt}_n^\bullet + \text{C}_6\text{H}_5\text{CH=CH}_2 \longrightarrow \text{RSt}_{n+1}^\bullet$$

$$\text{RSt}_n^\bullet + \text{TEMPO} \underset{\substack{\text{reversible}\\ \text{capping}}}{\rightleftarrows} \text{RSt}_n\text{-TEMPO}$$



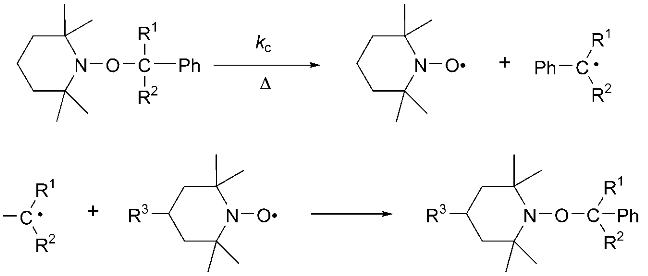
V

I $R^1 = R^2 = R^3 = H$
II $R^1 = R^3 = H, R^2 = Me$
III $R^1 = R^2 = Me, R^3 = H$
IV $R^1 = R^2 = H, R^3 = OH$

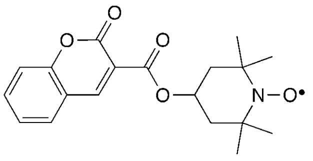
Fig. 3. *Alkoxyamine initiators for 'living' radical polymerization*

The mechanism of *Scheme 4* is an excellent example of the operation of the *Fischer–Ingold* persistent-radical effect and can be interpreted with *Fischer*'s mechanism. A key parameter for such an analysis is the strength of the weak O–C alkoxyamine bond responsible for the reversible capping reaction in *Scheme 4*. We have been interested in measuring these bond-dissociation energies (BDEs) in model compounds, as well as in the nitroxide-capped polymer. Analysis of data aimed at BDE determinations is again inspired by the treatment that *Fischer* developed. *Scheme 5* illustrates the approach that we have used to determine these critical BDE values. An alkoxyamine is thermally decomposed at temperatures around 100°, leading to TEMPO (=2,2,6,6-tetramethylpiperidin-1-yloxy) and a benzyl radical, *e.g.*, in the case of **II** (R^1 = H and R^2 = Me). In the case of a nitroxide-capped polymer, R^1 is H and R^2 is a polymer-chain segment.

Scheme 5. *Modelling the Uncapping/Capping Reactions in living radical polymerization*



We have studied the system using several combinations of R^1, R^2, and R^3. When the label R^3 is not a H-atom (*e.g.*, R^3 = OH or oxo), the system is examined on the basis of chromatographic analytical techniques. In an interesting example, we were able to examine the system of *Scheme 5* using a fluorescent label as R^3 at TEMPO, with a technique that we describe as 'pre-fluorescent' probes [22]. This coumarin-derived probe **CU–T•** is shown in *Fig. 4*. In this case, the fluorescence of the coumarin chromophore is quenched intramolecularly by the paramagnetic TEMPO moiety. When the polymer chain (*e.g.*, R^2 = 'polystyrenyl') is trapped in the second step of *Scheme 5*, the probe is converted to a diamagnetic alkoxyamine, and the fluorescence is restored: indeed, another example where the cross-combination product dominates.



CU–T•

Fig. 4. *Structure of coumarin–TEMPO* (**CU–T•**), *a 'pre-fluorescent' probe*

By studying the decomposition kinetics over a temperature range, it is possible to determine activation energies for C–O bond cleavage, and from them the corresponding BDEs. The *Table* shows the values obtained for various alkoxyamine derivatives.

Thus, structures with substitution patters resembling polystyrene, or polystyrene itself, all form alkoxyamines with bond dissociation energies of *ca.* 117 kJ/mol, values

Table. *Bond Dissociation Energies for the C–O Bond of Alkoxyamines Relevant to Living Radical Polymerization* [21–23]

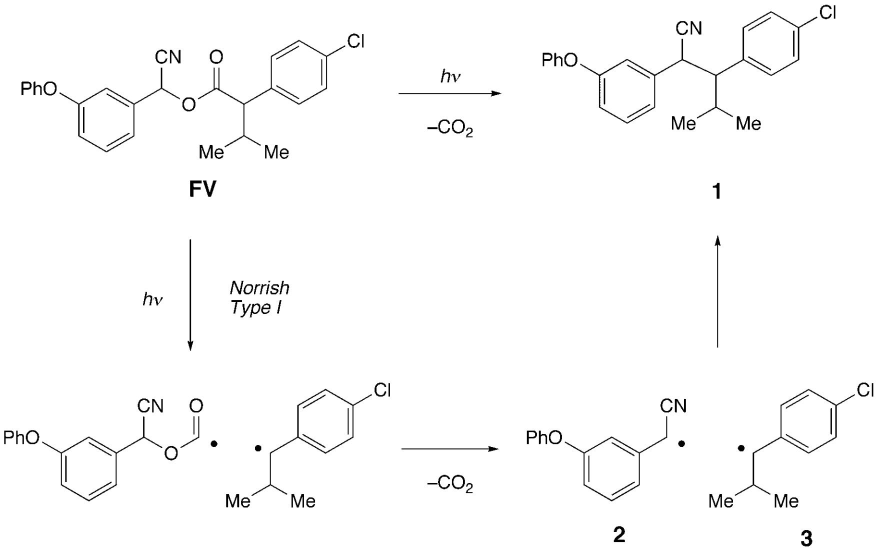
Molecule or C-centered group	BDE [kJ/mol]	Method
I	128.7	product studies
II	118.7	product studies
III	102.8	product studies
IV	131.3	product studies
V	117.0	product studies
'Polystyrenyl'	116.6	pre-fluorescent probe

low enough that thermal decapping occurs readily at temperatures around or above 100°.

Photodecomposition of Fenvalerate. – Another interesting example of the PRE arose when we were examining the photodecomposition of the pesticide fenvalerate (**FV**; *Scheme 6*) [24]. Fenvalerate is a member of the pyrethroid family that finds ample use in agriculture as a potent insecticide. Steady-state UV-C photolysis of solutions of **FV** ($4 \cdot 10^{-3}$ M) in MeCN or H_2O (with 8% MeOH) gave rise to the decarboxylation product **1** as a mixture of two diastereoisomers, with trace amounts of other decomposition products.

The product distribution in aqueous solution was explained by the homolytic *Norrish*-type-I bond breaking of the CO−CH^{i}Pr followed by rapid decarboxylation of the primary oxycarbonyl radical [25]. In this fashion, two C-centered benzyl radicals are generated as a consequence of the same bond-breaking event. Recombination of this

Scheme 6. *Photodecomposition of the Pesticide Fenvalerate* (**FV**)



radical pair yields the decarboxylation compounds **1** with little or no memory effect, leading to a complete loss of the configuration of the starting **FV**.

Since the benzyl-radical intermediates were detectable by nanosecond laser-flash photolysis work, we could presume that a significant fraction, if not all, of the radical recombination occurs following the separation of the initial radical pair, as solvent-cage events are too fast to be detected with nanosecond techniques. Therefore, something other than geminate radical recombination was controlling product formation.

Direct detection of the proposed benzyl radicals **2** and **3** was possible by time-resolved spectroscopic techniques. *Fig. 5* shows the transient absorption spectrum recorded for **FV** in deaerated MeCN after 266-nm laser excitation, conducted under dynamic flow to avoid interference from the photogenerated products. The spectrum shown in *Fig. 5* contains at least two different transients. The peak at 340 nm decaying on the order of *ca.* 1–3 μs (depending on radical concentration) was attributed to the 1-(4-chlorophenyl)-2-methylpropyl radical (**3**). The second transient at 440 nm, following independent generation, was assigned to the radical **2**. Like the persistent C-centered radicals discussed previously, radical **2** was much longer-lived, with a lifetime of *ca.* 37 μs, suggesting that recombination of **2** is remarkably slow. Furthermore, on the time scale of our experiments (tens of microseconds), **2** is unreactive toward O_2 (typical reactive radicals have lifetimes of less than 100 ns in an O_2 atmosphere). Therefore, the properties of **2** provide the ideal conditions for product control by the persistent radical effect. During steady-state irradiation of **FV**, radicals **2** and **3** are generated at the same rate. Of course, since **2** undergoes little or no recombination, it accumulates at the rate of two radicals per self-termination event of radical **3**. As a result, the cross-reaction between **2** and **3** soon takes over as the dominant reaction path for radical **3**, leading to the selective formation of **1** as the primary product.

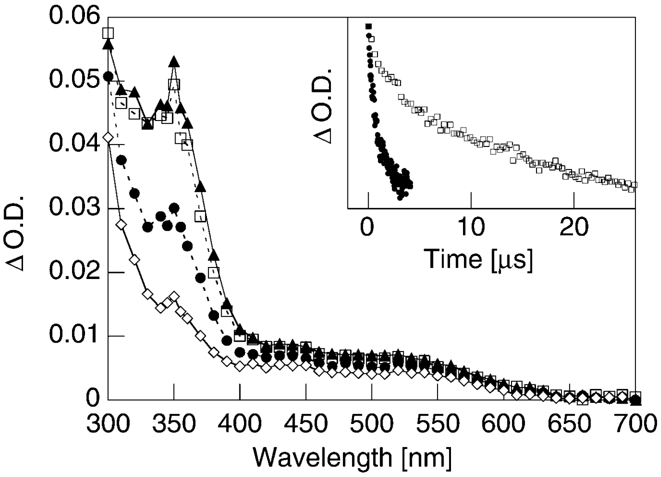


Fig. 5. *Transient absorption spectra from* **FV** *in MeCN following 266-nm laser excitation*. Time windows 0.012 μs (△), 0.15 μs (□), 0.63 μs (●), 1.5 μs (○). Inset: Normalized kinetic traces taken at 350 nm (●) and 440 nm (□).

Along with the previous examples of organic synthesis and living radical polymerization, it is remarkable that the simple kinetic phenomenon of the PRE is also responsible for the initial photoproduct in the photodecomposition of fenvalerate (**FV**).

Conclusions. – The *Fischer–Ingold* persistent-radical effect (PRE) provides a mechanistic understanding for many systems where radical–radical reactions lead almost exclusively to radical cross-combination products. Systems where transient and persistent radicals are produced stoichiometrically in a 1:1 ratio lend themselves to detailed kinetic analysis by using the algorithms developed by *Fischer*. Beyond this, the simple concepts underlying this effect can be used qualitatively to interpret mechanisms, or as in one of the examples described above, to design chemical synthesis. Indeed, when these concepts apply, very clean product formation can result, in contrast with the somewhat unjustified reputation of radical reactions to give complex product mixtures.

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