Radical versus Polar Mechanisms. The Sonochemical Addition of Phosphonate Esters to Imines

Cathy Hubert, Aurelio Munoz,
Bernard Garrigues, and Jean-Louis Luche*

Laboratoire AMPERES, Université P. Sabatier, Bat. 2R1, 118, route de Narbonne, 31062 Toulouse Cedex, France

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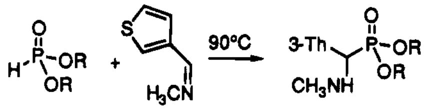
The notion of composite reaction mechanisms, i.e., the coexistence of polar and radical (or SET) pathways leading to the same reaction products, has been evoked by several authors in recent literature.[1] In this work, relevant recent findings are described, with the addition of phosphonate esters to an imine as a model reaction, under thermal and sonochemical conditions.[2]



1 **2** **3** Eq. (1)

Under heating (0.2 M solution of each reactant in toluene), diethyl phosphonate **1a** added to imine **2** (eq 1, R = C_2H_5) after a 60 min induction period to give 37% of aminophosphonate **3a** in 2 h. In contrast, sonication[3] initiated an immediate addition, leading to improved yields.[5] Since the rules of sonochemistry postulate that in homogeneous solutions, free radical, but not ionic or polar, processes are enhanced by the cavitational effects,[6] reaction (1) was studied with a double purpose. First, relating a sonochemical reaction to the aforementioned rules should lead to a better definition of their validity domain. Second, this reaction is generally considered to occur via polar or concerted pathways,[2a,b,7] despite the known examples of free radical reactivity of phosphines and phosphonic acid derivatives.[8,9] Results of this study are shown in Table 1.

Table 1. Yield of Ester 3a under Various Conditions

entry	condns^a	reaction time (min) 15	30	60	120
1	stirring	0	0	<5	37
2	sonication	12	32	67	82
3	stirring, AIBN	12	26	43	68
4	sonication, 1 equiv of NaN_3^{b}	0	0	0	0
5	stirring, AIBN, then 1 equiv of NaN_3^{c}	12	12	12	12
6	stirring, 1 equiv of NEt_3^{d,e}				10
7	sonication, 1 equiv of NEt_3^{e,f}		20		

^{a} Deoxygenation (30 min argon bubbling before irradiation) decreases the yields unsignificantly (<5%). Temperature is 90 °C in all the cases. ^{b} An identical result is obtained in the presence of 1 equiv of Bu_4NCl as a phase transfer agent. ^{c} Added after 15 min reaction. ^{d} 15% with DBU. ^{e} 10−15% of secondary products is observed in the ^{31}P NMR spectra. ^{f} 11% with DBU.

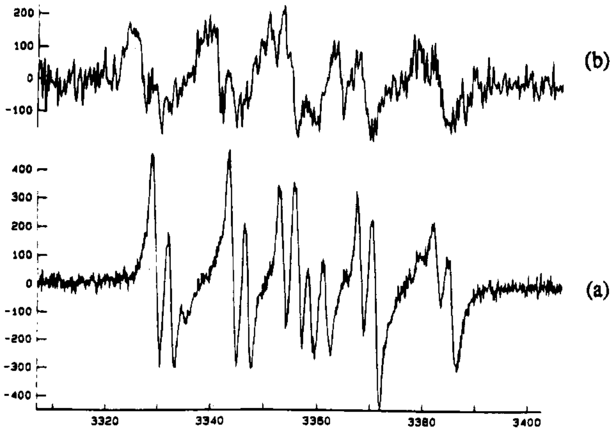


Figure 1. EPR spectrum of (a) **5a** and (b) **5b**.

The thermal addition in the presence of a 5% amount of azobis(isobutyronitrile) (AIBN)[9] is similar to the sonochemical addition (Table 1, entries 1−3). On the other hand, the latter is inhibited by addition of a 1 molar equiv of sodium azide (entries 4 and 5).[10] The sonochemically formed radical **4a** trapped by α-phenyl-*tert*-butyl nitrone (PBN) gave a 12 line EPR spectrum (Figure 1a), consistent with the formation of nitroxide **5a** (a_P = 24.5, a_N = 14.6, a_H = 3.0 G).[11] No signal was detected in the nonsonicated reaction.

The inhibitory effect of NaN_3 can be interpreted by the reaction of **4a** with the azide ion, giving anion **6** and the azidyl radical decomposed to nitrogen (Scheme 1).[12] Accordingly, the phosphonate anion **6** should be of reduced reactivity in the addition, a prediction verified experimentally (entries 6 and 7). The recently mentioned inertness of sodium and potassium diethyl phosphonate in this reaction confirms this interpretation.[2a] In contrast, in the presence of 10% trifluoroacetic acid, the yields are increased by ca. 25%, in agreement with previous results related to the additions of carbon centered radicals to protonated imines.[13]

The generality of these observations was investigated by reacting the bis(hexadecyl) ester **1b**[14] and dioxaphosphorinane-2-oxide **1c**[15] (Table 2).

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(1) For example: Walling, C. *J. Am. Chem. Soc.* **1988**, *110*, 6846−6850. Ashby, E. C.; Sun, X.; Duff, J. L. *J. Org. Chem.* **1994**, *59*, 1270−1278.

(2) For recent papers, see: (a) Yager, K. M.; Taylor, C. M.; Smith, A. B. *J. Am. Chem. Soc.* **1994**, *116*, 9377−9378. (b) Bongini, A.; Camerini, R.; Hofman, S.; Panunzio, M. *Tetrahedron Lett.* **1994**, *35*, 8045−8048. (c) Hubert, C.; Oussaid, B.; Etemad-Moghadam, G.; Koening, M.; Garrigues, B. *Synthesis* **1994**, 51−55.

(3) The 13 mm probe fitted to a Vibracell generator is dipped by 0.5 cm into the solution, keeping all the geometrical parameters constant in all the experiments. The optimal energy output determined with the Weissler reaction[4] corresponds to the formation of 2.1 × 10^{-2} mmol of I_3^- in 30 min at 20 °C from a 1 M aqueous KI solution saturated with CCl_4.

(4) For a discussion of this reaction, see: Henglein, A. In *Advances in Sonochemistry*; Mason T. J., Ed.; JAI Press: London, U.K., 1993; Vol. 3, pp 17−83.

(5) Yields in the tables were determined by ^{31}P NMR spectroscopy. The spectra consist only in the signals of esters 1 and 3, unless otherwise mentioned. It was checked that a 100% NMR yield corresponds to a 85% isolated yield. New compounds provided satisfactory analytical and spectral data.

(6) Luche, J. L.; Einhorn, C.; Einhorn, J.; Sinisterra-Gago, J. V. *Tetrahedron Lett.* **1990**, *31*, 4125−4129

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Scheme 1

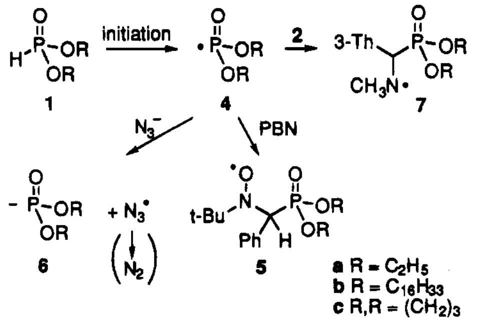
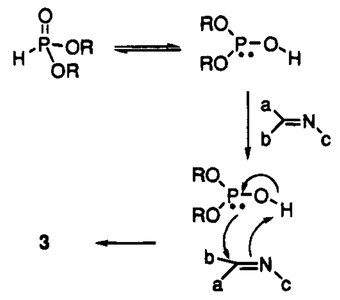


Table 2. Reactions of Phosphonates 1b and 1c

ester	ultrasonic condns	yield (%)	thermal condns	yield (%)
1b	1 h	50	1 h	48
1b	1 h, 1 equiv of NaN_3	45	1 h, 1 equiv of NEt_3	10
1c	1.5 h	88	1.5 h	71
1c	1.5 h, 1 equiv of NaN_3	66	1.5 h, 1 equiv of NaN_3	35
1c			1.5 h, 1 equiv of NEt_3	36

Scheme 2



From compound **1b**, the reaction occurs with no sonochemical effect, no significant quenching by sodium azide, and a low 10% yield in the presence of bases. Very low amounts of nitroxide **5b** are detected in the reaction run in the presence of PBN (Figure 1b). The mechanism postulated for the reaction of **1a** should be of minor importance in this case, and a polar mechanism, e.g., as in Scheme 2, may occur.[2,7]

Results from **1c** are more complex. The thermal and sonochemical additions of **1c** to **2** are only partially quenched by sodium azide and bases. In the presence of PBN, a six line EPR pattern is observed for the thermal process (Figure 2a, $a_N = 14.5$, $a_H = 3.6$G), compatible with trapping of **7** by PBN.[16] The sonicated reaction gives a much more intense, composite, EPR signal (Figure 2b).[17]

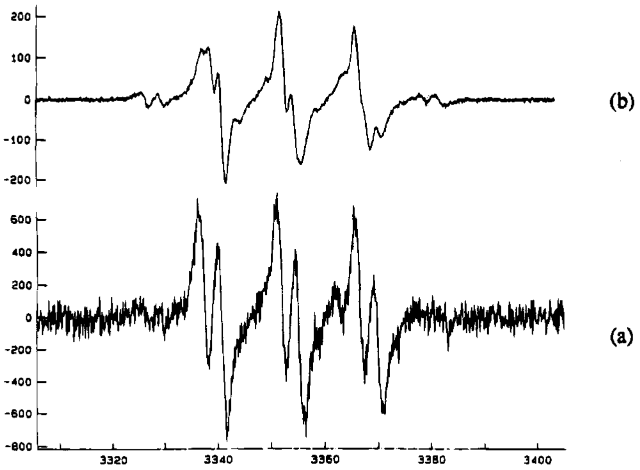


Figure 2. EPR spectrum of reaction **1c** + **2** + PBN after (a) stirring and (b) sonication.

A mixed mechanism can be deduced for this addition, with a polar contribution, and a free radical one enhanced under sonication.

The mechanism of the sonocleavage, supposed to occur inside the cavitation "hot spot",[19] is not yet known. However the sonochemistry rules, although being still to be interpreted in a general manner, receive here an illustration. If a mechanistic continuum, from polar to radical, exists in the reactions described here, the question may be raised for a number of other ones. The sensitivity of radical reactions to sonochemical activation should provide new methods for the elucidation of such complex processes.

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Supplementary Material Available: Description of the sonochemical experiments and set-up. Spectroscopic and analytical data for **3b** and **3c** (2 pages).

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[17] a_N (13.8 G) and a_H (2.1 G) values of the three more intense lines in the spectrum of Figure 2b are compatible with the addition to PBN of an oxygen-centered radical.[18]

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