stirring, the aldehyde (1–3 equiv) was added to the reaction mixture, and the solution was stirred for another 1.5–2 h at −78 °C. The reaction mixture was quenched with NH_4Cl (saturated aqueous) at this temperature, and the product was extracted with ether or chloroform. After being dried over Na_2SO_4, the extract was concentrated in vacuo. The tin-containing byproduct was removed on a silica gel column (CCl_4), and the product was eluted with ethyl acetate. The eluate was concentrated in vacuo and purified by column chromatography or TLC.

Reaction of Ethyl Benzoate with Benzaldehyde (Run 26). The reaction was carried out by using reagent A (0.5-mmol scale of the ester (75 mg)) and the aldehyde (53 mg, 0.5 mmol). The analysis of the crude material by NMR using TCE indicated that the product was the aldol 8 ($R^1 = R^2 = C_6H_5$, 71%). Purification by column chromatography ($CHCl_3$) gave a pure sample: ^{1}H NMR δ 3.16 (d, J = 7.0 Hz, 2 H), 5.20 (t, J = 6.4 Hz, 1 H), 7.00–8.10 (m, 10 H).

Reaction of Ethyl Benzoate with Propanal (Run 27). The reaction was carried out by using reagent A (1.0-mmol scale of the ester (150 mg)) and the aldehyde (58 mg, 1.0 mmol). Purification by column chromatography ($CHCl_3$) gave the aldol 8 ($R^1 = C_6H_5$, $R^2 = C_2H_5$, 153 mg, 86%): ^{1}H NMR δ 1.00 (dist t, J = 6.4 Hz, 3 H), 1.21–1.72 (m, 2 H), 3.00 (d, J = 6.0 Hz, 2 H), 3.53 (br s, 1 H), 3.80–4.25 (m, 1 H), 7.40–7.90 (m, 5 H); IR, ν_{max} 3680–3130, 2970, 2930, 2880, 1670, 1595, 1450, 1210 cm^{-1}. The product was identical with the authentic sample prepared by the LDA-induced aldol reaction of acetophenone and propanal.

Reaction of Methyl Octanoate with Benzaldehyde (Run 28). The reaction was carried out by using reagent C (0.5-mmol scale of the ester (71 mg)) and the aldehyde (53 mg, 0.5 mmol). Purification by column chromatography ($CHCl_3$) gave the aldol 8 ($R^1 = C_7H_{15}$, $R^2 = C_6H_5$, 122 mg, 98%): MS, m/z 164 ($M^+ - C_6H_{12}$), 107 (base peak), 79, 77, 73; ^{1}H NMR δ 0.93–1.30 (m, 13 H), 2.20 (dist t, J = 7.0 Hz, 2 H), 2.60 (d, J = 5.0 Hz, 1 H), 2.64 (d, J = 8.0 Hz, 1 H), 3.59 (br s, 1 H), 5.00 (dd, J = 5.0 Hz and 8.0 Hz, 1 H), 7.20 (m, 5 H); IR ν_{max} 3630–3130, 3070, 2960, 2930, 2880, 2860, 1710, 1455, 1050 cm^{-1}. The product was identical with an authentic sample prepared from 2-nonanone and benzaldehyde using LDA.

Reaction of Methyl Octanoate with Propanal (Run 29). The reaction was carried out by using reagent C (0.5-mmol scale of the ester (74 mg)) and the aldehyde (78.3 mg, 1.35 mmol). Analysis of the crude material by NMR using TCE indicated that the product was the aldol 8 ($R^1 = C_7H_{15}$, $R^2 = C_2H_5$, 66%). Purification by column chromatography ($CHCl_3$) gave a pure sample: ^{1}H NMR δ 0.90–1.30 (m, 18 H), 2.40 (m, 4 H), 2.85 (br s, 1 H), 3.87 (m, 1 H).

Reaction of Ethyl *O*-Benzyl-L-lactate with Benzaldehyde (Run 30). The reaction was carried out by using reagent A (0.5-mmol scale of the ester (104 mg)) and the aldehyde (159 mg, 1.5 mmol). The crude material was first separated by TLC ($CHCl_3$) into two layers (R_f 0.5, 0.2), and the lower layer was further purified by TLC (Et_2O/hexane (1/1)) to give a pure sample of 8 ($R^1 = C_9H_{11}O$, $R^2 = C_6H_5$, 67 mg, 60%). For 8: ^{1}H NMR δ 1.22 (d, J = 7.0 Hz, 3 H), 2.71–2.98 (m, 2 H), 3.43 (br s, 1 H), 3.76 (q, J = 7.0 Hz, 1 H), 4.41 (br s, 2 H), 4.88–5.19 (m, 1 H), 7.14–7.32 (s, 10 H).

Dehydration of 8 (49 mg, 0.17 mmol) was carried out by using a catalytic amount of $TsOH-H_2O$ in benzene (2 mL) at room temperature for 73 h. The column chromatography ($CHCl_3$) gave 2-(benzyloxy)-5-phenyl-4-penten-3-one (34 mg, 74%): ^{1}H NMR δ 1.35 (d, J = 7.0 Hz, 3 H), 3.97 (q, J = 7.0 Hz, 1 H), 4.46 (s, 2 H), 6.88–7.82 (m, 12 H).

Reaction of Ethyl *O*-Benzyl-L-lactate with Ethanal (Run 31). The reaction was carried out by using reagent A (0.5-mmol scale of the ester (104 mg)) and the aldehyde (66 mg, 1.5 mmol). The crude material was first separated into two layers (R_f 0.6, 0.1) by TLC ($CHCl_3$), and the lower layer was further purified by TLC (Et_2O/hexane (1/1)) to give a pure sample of 8 ($R^1 = C_9H_{11}O$, $R^2 = CH_3$, 67 mg, 60%): ^{1}H NMR δ 1.18 (d, J = 7.0 Hz, 3 H), 1.33 (d, J = 7.0 Hz, 3 H), 2.53–2.75 (m, 2 H), 2.75 (br s, 1 H), 3.80 (q, J = 7.0 Hz, 1 H), 3.93–4.31 (m, 1 H), 4.48 (s, 2 H), 7.26 (s, 5 H).

Reaction of Ethyl *O*-Benzyl-L-lactate with Propanal (Run 32). The reaction was carried out by using reagent A (0.5-mmol scale of the ester (104 mg)) and the aldehyde (87 mg, 1.5 mmol). The crude material was first separated into two layers (R_f 0.6, 0.1) by TLC ($CHCl_3$) and the lower layer was further purified by TLC (Et_2O/hexane (1/1)) to give 8 ($R^1 = C_9H_{11}O$, $R^2 = C_2H_5$, 78 mg, 66%): ^{1}H NMR δ 0.93–1.51 (m, 8 H), 2.60–2.66 (m, 2 H), 3.19 (br s, 1 H), 3.70–4.30 (m, 2 H), 4.56 (s, 2 H), 7.20 (s, 5 H).

Reaction of Ethyl *O*-Benzyl-L-lactate with Formaldehyde (Run 33). The reaction was carried out by using reagent A (0.5-mmol scale of the ester (104 mg)) and an excess of the aldehyde, which was prepared by heating paraformaldehyde. TLC purification (Et_2O/hexane (1/1)) gave 8 (53 mg, 51%), 7 (10 mg, 10%), and 11 (20 mg, 22%). For 8 ($R^1 = C_9H_{11}O$, R^2 = H): MS, m/z 135 ($M^+ - COC_2H_4OH$), 91 (base peak), 77, 73, 66, 55, 45, 43; ^{1}H NMR δ 1.26 (d, J = 7.0 Hz, 3 H), 2.50–2.71 (m, 2 H), 2.75 (br s, 1 H), 3.53–3.96 (m, 3 H), 4.40 (s, 2 H), 7.20 (br s, 5 H).

Ultrasound in Organic Synthesis. 13.[1] Some Fundamental Aspects of the Sonochemical Barbier Reaction

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The Barbier reaction of benzaldehyde, *n*-heptyl bromide, and lithium was effected under various sonochemical conditions. The rate of formation of 1-phenyloctanol depends strongly on the intensity of the ultrasonic waves and the temperature. For both parameters, an optimum is observed. An unusual variation of rate with temperature is evidenced, which reveals that the reaction is not mass-transport controlled. Electron microscopy examination of the metal shows the very important activation role of the acoustic waves, through the cavitation phenomenon.

Introduction

After a long period of scattered research, synthetic sonochemistry is presently the subject of more systematic works and applications especially in the case of heterogeneous reactions. The efficiency of ultrasonic waves in promoting various processes has been established,[2] but most of the works dealing with synthetically useful reactions are essentially descriptive. The physical and phys-

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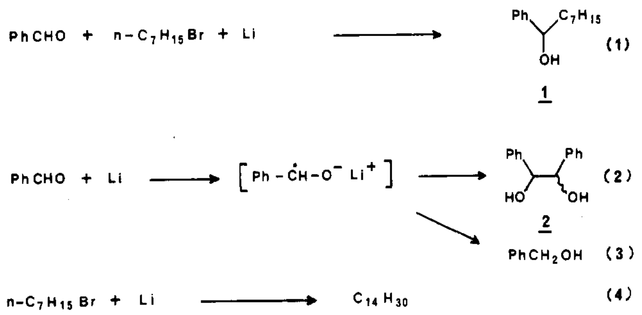
(1) Previous paper in this series, see: Einhorn, J.; Luche, J. L. *J. Org. Chem.* **1987**, *52*, 4124.

(2) For recent examples, see: (a) Boudjouk, P. *J. Chem. Educ.* **1986**, *63*, 427–429. (b) Suslick, K. S.; Casadonte, D. J. *J. Am. Chem. Soc.* **1987**, *109*, 3459–3461. (c) Henglein, A. *Z. Naturforsch. B: Anorg. Chem., Org. Chem.* **1985**, *40B*, 100–107. (d) Davidson, R. S.; Patel, A. M.; Safdar, A.; Thornthwaite, D. *Tetrahedron Lett.* **1983**, *24*, 5907–5910. (e) Yamashita, J.; Inoue, Y.; Kondo, T.; Hashimoto, H. *Chem. Lett.* **1986**, 407–408. (f) Brown, H. C.; Racherla, U. S. *Tetrahedron Lett.* **1985**, *26*, 2187–2190. (g) Luche, J. L.; Damiano, J. C. *J. Am. Chem. Soc.* **1980**, *102*, 7926–7928.

0022-3263/88/1953-1212$01.50/0

Scheme I

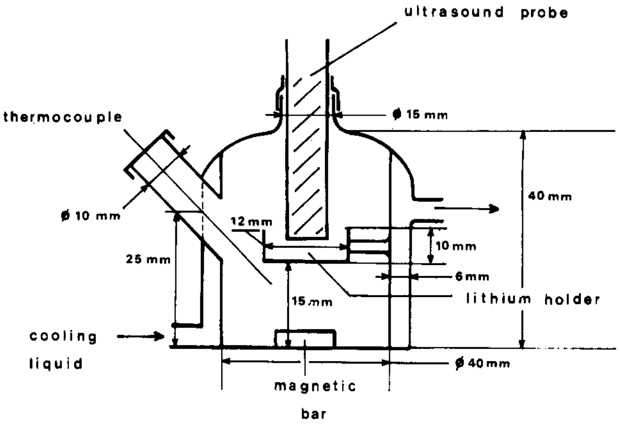


icochemical interactions of the waves with reactive systems are only schematically understood and remain to be explored, even if recent fundamental approaches appear quite promising.[3] Some authors have stated the importance of a few basically important factors.[4] For instance it has been shown that the solvent has a very marked influence through its physical properties.[5] Some other parameters, such as the geometry of the reactors[6] or the intensity of the acoustic waves, are known to be of importance. Particularly, the effects of the latter appear to be complex. Some authors have shown that chemical reactions are uniformly accelerated by an increase of the ultrasound intensity, while others observed that beyond an optimum, more intense waves result in lower rates or yields.[7] But in any case, it seems presently difficult to establish an exhaustive list of all the factors which intervene more or less directly during a sonication experiment. We chose to study the effects of two of them, among the more important ones, the temperature and the intensity, on a synthetically useful organometallic reaction, the Barbier synthesis.

The Sonochemical Barbier Synthesis. We described qualitatively in the first paper in this series[2g] that sonication improves substantially the rates and yields of the Barbier reaction with respect to standard procedures.[8] One further advantage of the ultrasonic method is an extended domain of application. Thus we studied from a more fundamental point of view, the sonochemical formation of the addition alcohol as a function of time at different temperatures, under usual synthetic conditions. Although side reactions such as enolization and Wurtz coupling appeared to be of reduced importance, it was necessary to choose a chemical model with limited possibilities of evolution. Benzaldehyde, *n*-heptyl bromide, and lithium proved to be satisfactory. Among the various possibilities shown in Scheme I, only reactions 1 and 2 were found to occur significantly.

Experiments were run in a glass vessel shown in Scheme II, thermostated by circulation of a cooling liquid. The temperature homogeneity is ensured by magnetic stirring. Lithium is placed in the holder in loose contact with the emitting face of the ultrasonic horn. The reagents, carbonyl compound and organic halide in dry tetrahydrofuran (THF) solution are introduced in the cell with an inert standard hydrocarbon (hexadecane).

Scheme II



After starting the irradiation, the temperature is measured with a thermocouple placed outside the ultrasonic beam, to avoid sound absorption leading to erroneous readings. Samples are periodically withdrawn and analyzed by VPC. For the determination of polar compounds (pinacols) the aliquot is silylated immediately after withdrawal.

The ultrasound generator used in this work (Sonimasse) consists of a piezoelectric ceramic, emitting a constant 30-kHz frequency, coupled to a titanium horn (i.d. 8 mm). The intensity is adjusted by variation of the voltage applied to the ceramic between 0 and 1500 V. The accurate evaluation of the intensity I actually received on the reactive surface is difficult, due to absorption, diffusion, and reflection phenomena. Using the same relative positioning of the lithium sample and the horn within 1 mm (i.e., a small variation with respect to the ca. 35-mm wavelength) we considered as the variable parameter, the intensity I_0 at the tip of the horn, or more simply the voltage applied to the ceramic.

Using the same equipment for all the experiments described here resulted in a satisfactory self-consistency of the results, with an error margin of ca. 8% (±4%).

However, an accurate treatment of the data by the kinetic methods was not possible for the following reasons. A sufficient temperature stabilization in the cell proved to be extremely difficult and temperature jumps, 3–5 °C, were always observed during the first 5 min of the experiments. This thermal effect is due to sound absorption by the reaction medium. Blank experiments revealed that sonication of THF alone increases an initial temperature of 20 °C by 2–4 °C. This effect is even more pronounced for the highest intensities and, at low initial temperature (−50 °C), jumps as high as 15 °C were observed. They were attributed to more efficient sound absorption by a more viscous medium.

Another argument comes from the relationship between the rate of such an heterogeneous reaction and the area of the reactive surface of the metal.[9] It will be illustrated below that very important area variations occur during sonication, which make the analytical expression of the kinetic law extremely difficult to formulate. Despite these limitations, the general tendency and sequence of the results remain descriptive of the system and provide useful mechanistic information.

Preliminary experiments were effected to check the behavior of the reaction in the absence of sonic waves. In

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(3) Suslick, K. S.; Hammerton, D. A.; Cline, R. E. *J. Am. Chem. Soc.* **1986**, *108*, 5641–5642.

(4) (a) Pugin, B. *Ultrasonics* **1987**, *25*, 49–55. (b) Sehgal, C.; Yu, T. J.; Sutherland, R. G.; Verrall, R. E. *J. Phys. Chem.* **1982**, *86*, 2982–2986. (c) Saracco, G.; Arzano, F. *Chim. Ind. (Milan)* **1963**, *45*, 1394–1397.

(5) (a) Mason, T. J.; Lorimer, J. P.; Mistry, B. P. *Tetrahedron* **1985**, *41*, 5201–5204. (b) Suslick, K. S.; Gawienowsky, J. J.; Schubert, P. F.; Wang, H. H. *Ultrasonics* **1984**, 33–36.

(6) (a) Kessler, T.; Sharkey, A. G.; Friedel, R. A. *Rep. Invest. U.S., Bur. Mines* **1967**, *No. 7072*; *Chem. Abstr.* **1968**, *68*, 14671. See also: (b) Saracco, G.; Arzano, F. *Chim. Ind. (Milan)* **1968**, *50*, 314–318.

(7) (a) Weissler, A. *J. Acoust. Soc. Am.* **1953**, *25*, 651–657. (b) Margulis, M. A. *Ultrasonics* **1985**, *24*, 157–169.

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(9) Root, K. S.; Deutch, J.; Whitesides, G. M. *J. Am. Chem. Soc.* **1981**, *103*, 5475–5479.

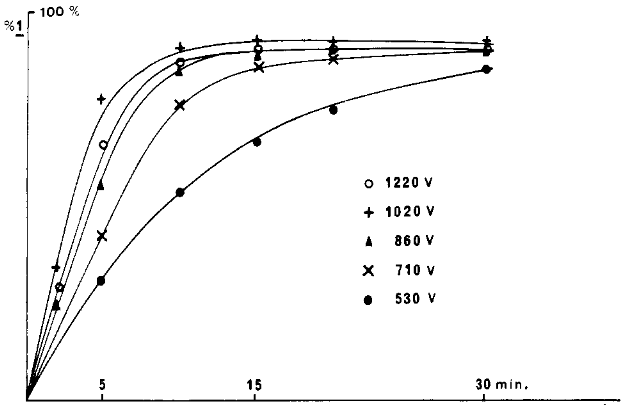

Figure 1. % of alcohol 1 vs time, for various values of the intensity, at 20 °C.

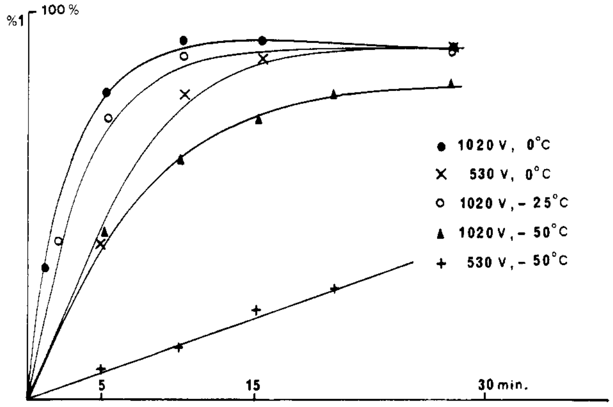

Figure 2. % of alcohol 1, for various intensities and temperatures.

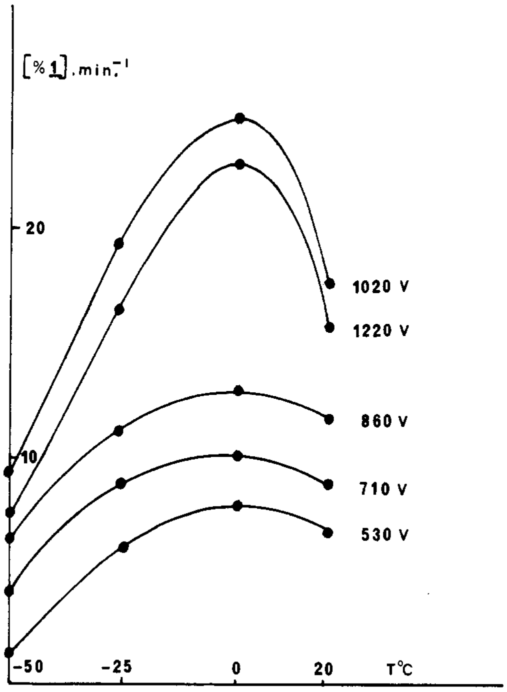

Figure 3. Initial rate vs temperature.

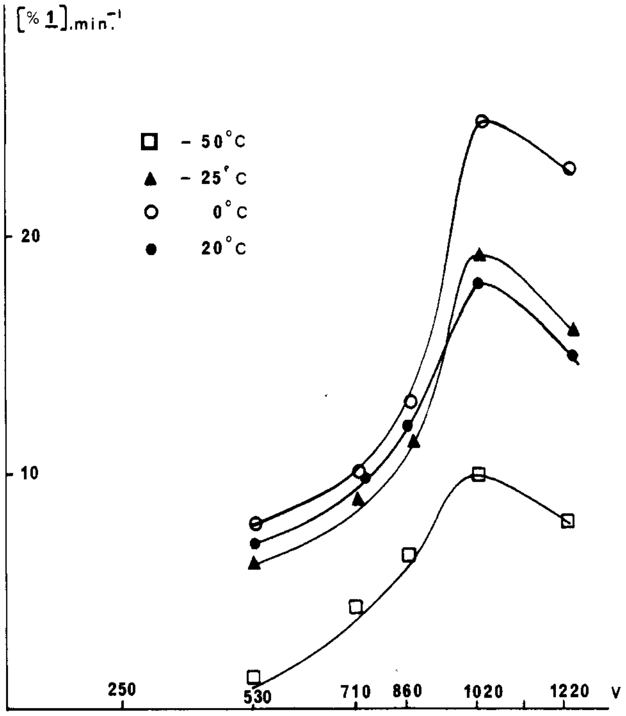

Figure 4. Initial rate vs intensity.

the cell used for the sonochemical runs, almost no reaction occurs at room temperature under vigorous magnetic stirring (1000 rpm) as the addition alcohol 1 is formed in only 8% yield in 7 h.

At an initial temperature of 20 °C under sonication, no reaction takes place for a voltage below 500 V, and the characteristic hissing of cavitation is not heard. For a voltage of 530 V, hissing is perceived, and the reaction does occur but rapidly stops if the generator is switched off. This observation seems to correlate the chemical reaction to cavitation. A more intense cavitation should give rise to a faster reaction. This expectation is verified experimentally when the voltage is increased up to 1020 V, but beyond this optimum, the reaction slows down (Figure 1).

As cavitation is strongly dependent on temperature,[10] experiments were effected at 0, -25, and -50 °C (initial temperatures) and are depicted in a simplified form in Figure 2.

In order to explicit these results, the initial rates of the reactions,[11] V_0, were plotted against temperature (Figure 3). The diagram reveals that the usual behavior consisting in a monotonous decrease of the rate by lowering the temperature is not verified under our conditions. In contrast, a rate maximum occurs for an initial temperature of 0 °C, at any intensity level. The complex variation of V_0 as a function of intensity is visualized in Figure 4, in which an optimal value of ca. 1020 V appears clearly.

Table I. Final Percentages of 2 under Various Conditions

T °C	% of 2 at intensity, V				
	530	710	860	1020	1220
20	4	6	3	5	7
0	3	4	4	7	6
-50	13	11	5	10	8

The influence of both factors, temperature and intensity, on side product formation was also examined. In every case, Wurtz coupling hydrocarbon and benzyl alcohol were detected in very small amounts, less than 5% each and for most experiments ca. 1-3%. The only quantitatively important undesired product is 1,2-diphenyl-1,2-ethanediol (2) which can amount up to 13% in low-temperature and intensity sonications (Table I).

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[10] Suslick, K. S.; Gawienowsky, J. J.; Schubert, P. F.; Wang, H. H. *J. Phys. Chem.* **1983**, *87*, 2299-2301. Ibisi, M.; Brown, B. *J. Acoust. Soc. Am.* **1967**, *41*, 568-572.

[11] For simplicity, the initial slopes of the curves % 1 as a function of time are denoted as "initial rates" although this denotation is incorrect, strictly speaking.

Table II. Molar Percentages of Alcohol 1 vs Time (±4%)

T, °C	intensity, V	molar % of 1 at time, min 1	2	5	10	15	20	30
20	1220		30	67	88	92		92
	1020		35	78	91	93		93
	860		29	55	87	89		95
	710			42	77	88	90	90
	530			31	54	66	74	86
0	1220	28	46	75	91			
	1020	32	50	78	91			
	860			63	92	95		
	710			53	84	90		90
	530			38	78	87	92	92
-25	1220		32	62	85	89		90
	1020		39	73	87	89		90
	860			53	80	91	95	95
	710			42	72	83	88	92
	530			33	57	73	75	82
-50	1220			36	59	73	79	83
	1020			43	61	72	80	82
	860			35	75	87	90	90
	710			20	39	47	52	52
	530			6	12	22	28	43

Table III. Preactivation Experiments. Molar Percentage of Alcohol 1 vs Time (±4%) at 20 °C

intensity, V	molar % of 1 at time, min 1	2	5	10	15	20	30
1020	18	37	77	94		94	
530		21	46	77	87	88	

Table IV. Initial Slopes of the Curves % 1 vs Time

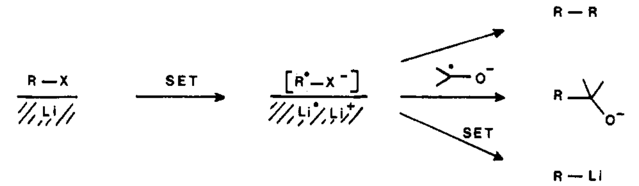
T, °C	slope at intensity, V 1220	1020	860	750	530
20	15 ± 2	18 ± 2	12 ± 2	9 ± 2	7 ± 1
0	23 ± 2	25 ± 2	13 ± 2	10 ± 2	8 ± 2
-25	16 ± 2	19 ± 2	12 ± 2	10 ± 2	6 ± 1
-50	8 ± 1	10 ± 1	7 ± 1	4 ± 0.5	1.5 ± 0.5

Discussion

From a fundamental point of view, the mechanism by which ultrasonic waves are effective, appears from the intensity and temperature effects, to be more complex than a simple cleaning of the surface. As stated above, the influence of the intensity deserves some comments.

Intensity is defined by the equation $I = 2\rho c\pi^2 A^2 f^2$, where ρ, c, A, and f represent respectively the density of the medium, the velocity of the wave, the maximum elongation along the propagation axis, and the frequency.[12] The complex effect of I on the course of a sonochemical reaction is illustrated by the theoretical approach of Margulis.[7b] According to this author, the rate of a reaction is proportional to I^2 for the lower values of I near the cavitation threshold. This dependence comes from the proportionality of both the spatial density of the cavitation bubbles and their individual collapse energy, to the intensity of the ultrasonic wave. For medium values of I, the rate become proportional to I, and a rate decrease is predicted for the highest values. It is important to note that these calculations were made from data on water sonolysis, i.e., a homogeneous sonochemical reaction. The experimental diagram representing the initial rate V_0 of the Barbier reaction as a function of the intensity (Figure 4) exhibits a marked resemblence to the theoretical diagram. A similar dependence was also evidenced for the three-phase sonochemical hydrogenation of olefins with gaseous hydrogen on a Raney Nickel catalyst.[6b] Even if the domain of the curves shown in Figure 4 between the cavitation threshold (530 V) and the optimum at 1020 V could not be expressed by a satisfactory analytical equation of the form $V_0 = f(I^n)$, elements exist which would lead to the conclusion that cavitation dependent sonochemical reactions should exhibit the same influence of ultrasonic intensity.

Scheme III



From a physical point of view, the rate decrease observed between 1020 and 1220 V cannot be interpreted in a simple manner. Among various hypotheses, a possible explanation is that a too much intense wave produces a large amount of cavitation bubbles which will diffuse and disperse the acoustic energy before it reaches the reactive surface.

The state of this surface is another problem, raised by the fact that the key step of the Barbier reaction has been shown to be a single electron transfer[13] (SET), as in the case of other organometallic reactions[14] (Scheme III) occuring on the metal surface.

Two different hypotheses can be formulated. It can be supposed that the ultrasonic wave is able to remove small, highly activated particles from the metal[15] which would react as a dispersion with the organic components. The large area of the metallic suspension thus produced would explain the high overall rate of the reaction. Sodium and potassium, but not lithium, can be dispersed as very fine suspensions in aromatic solvents, but not in THF.[16] The

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(12) Boucher, R. M. G. *Br. Chem. Eng.* **1970**, *15*, 363-367.

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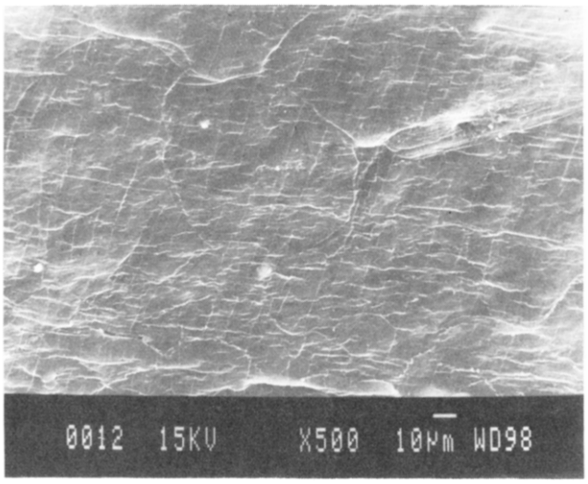

Figure 5. Original state of lithium (magnification 500).

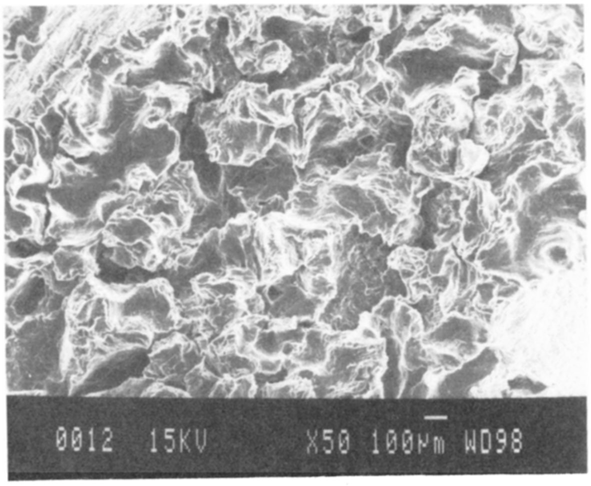

Figure 6. Lithium surface after 15 min sonication at 860 V and room temperature (magnification 50).

dispersing effect hypothesis should then be rejected. A second possibility consists in considering that even in a solvent like THF, with low viscosity, low surface tension, and high vapor pressure, cavitation is able to modify the state of the surface. This hypothesis was examined by scanning electron microscopy.

In Figure 5, the original state of lithium appears as a smooth surface with a limited number of defects. Sonication in THF, in the absence of chemical reagents for 15 min at 860 V and room temperature produces a very important and general disorganization on all the exposed surface (Figure 6).

The hammering effect of the cavitating liquid generates a large number of lattice defects. If we assume that the initiation process for the formation of organolithium reagents offers similarities to that of their Grignard analogues, all these defects behave as initiation sites and the initial rate of the reaction is a direct function of the density of these sites.[17] In opposition to chemical agents, which are not able to create activated pits,[17] ultrasonic irradiation produces them in large amounts, and a high initial rate is the consequence.

The chemical attack, as shown in Figures 7 and 8, is visualized by the presence of deep craters, which indicate that the corrosion propagates into the mass of the metal, with an important area increase. The corrosion pits are continuously renewed and develop in depth and size, as it is known that cavitation is produced with a greater efficiency at the neighborhood of irregularities (crevice effect).[18]

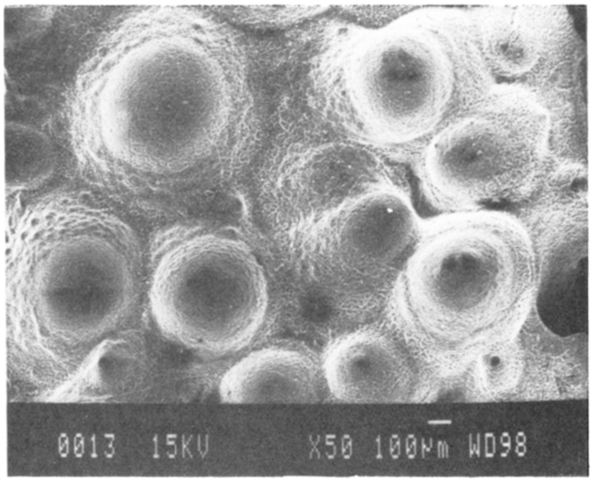

Figure 7. Lithium surface after 5-min chemical attack, 20 °C, 860 V (magnification 50).

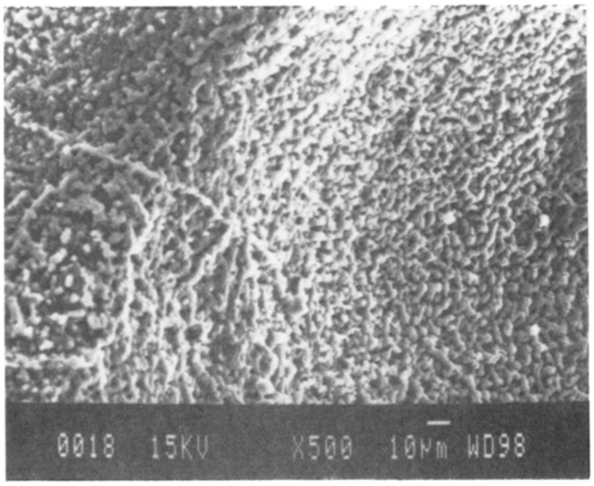

Figure 8. Same sample as in Figure 7 (magnification 500).

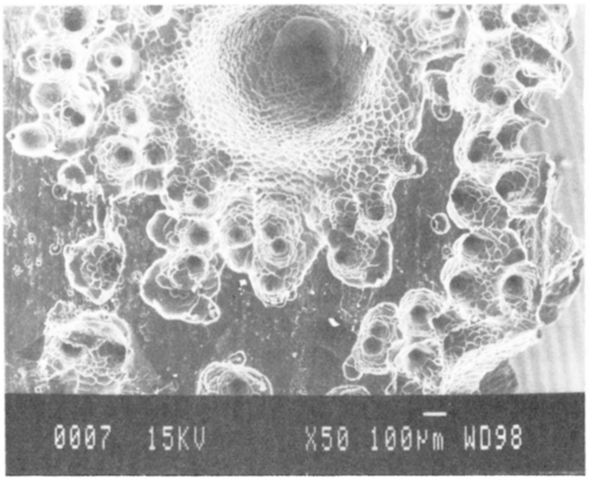

Figure 9. Lithium surface after 5-min chemical attack, −50 °C, 530 V (magnification 50).

Decreasing the intensity and the temperature (530 V, −50 °C) has the effect of reducing the spatial density of

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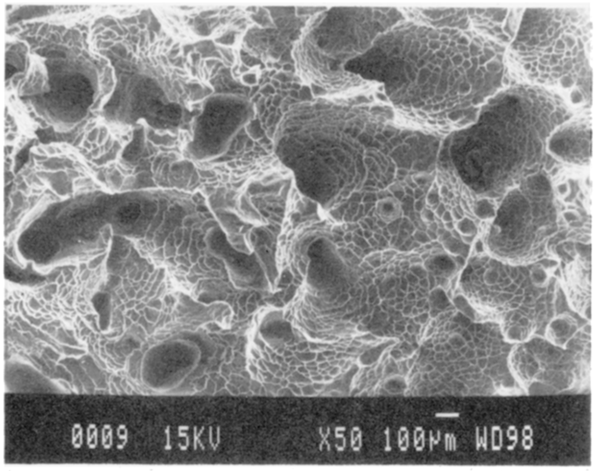

Figure 10. Lithium surface after 5-min chemical attack, −50 °C, 860 V (magnification 50).

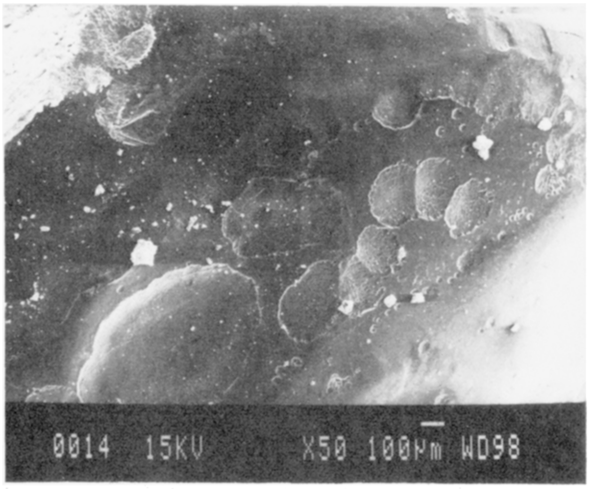

Figure 11. Lithium surface after 5-min chemical attack under stirring, −20 °C (magnification 50).

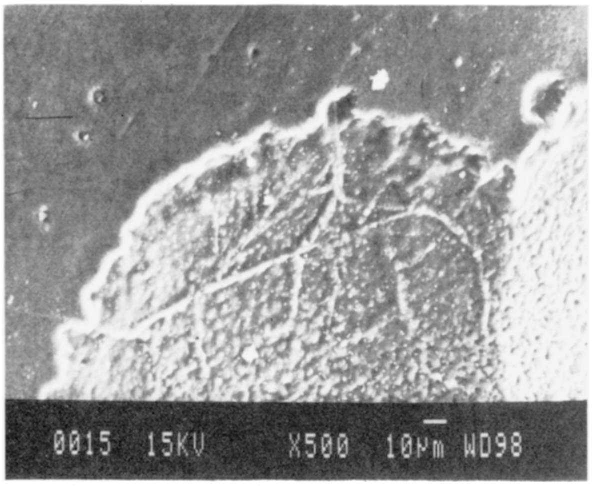

Figure 12. Same sample as in Figure 11 (magnification 500).

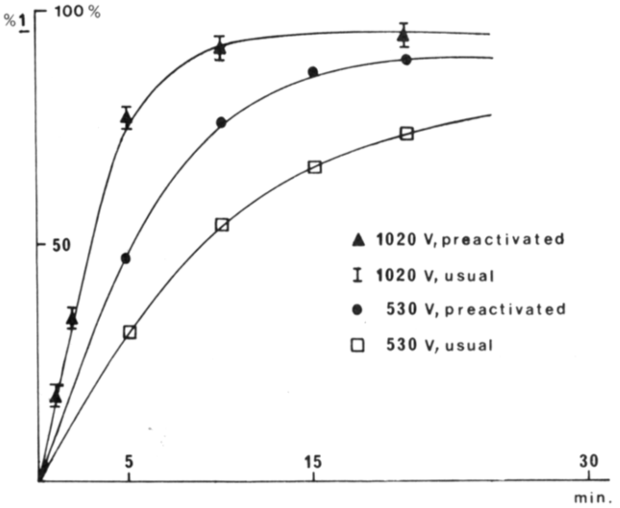

Figure 13. Effect of preactivation.

the bubbles[7b] and then of the number of activated pits (Figure 9). As expected, a rather low V_0 is observed. However at the same temperature, sonication at 1020 V restores the highly activated pattern and enhances the initial rate (Figure 10).

For the sake of comparison, similar experiments were conducted under stirring without sonication. From Figures 11 and 12, it can be seen that the chemical attack propagates on the surface of the sample with the formation of shallow corrosion zones. A slow reaction results, accompanied by a very limited area variation (compare Figures 8 and 12).

The difference between the corrosion patterns obtained under stirring and sonication indicates that the role of the latter is of importance not only during the initiation but also in the propagation of the attack.

At temperatures above 0 °C, the variation of the initial rate V_0 is inverse to that of temperature, which means an increase of V_0 with viscosity. These reactions should then not be mass transport limited.[10,19] Microstreaming effects in the vicinity of the surface, produced by the sonic waves and known to accelerate considerably mass transport phenomena,[18] are most probably responsible for this unusual behavior, even for low intensity values. Under these conditions, the limiting factors can be the creation of activated sites (initiation) and/or the SET (corrosion) which both occur on the metal surface. In an attempt to dissociate these two factors, reactions were effected at 20 °C and two intensities, 530 and 1020 V, after an initial 5-min preactivation of the metal at 1020 V in the absence of the reagents.

At 1020 V the reactions with and without preactivation proceed at the same rate. In this case, it is likely that the SET is rate limiting, as active sites are either preexisting or produced very rapidly in a large amount. For the lower intensity value, the preactivated reaction occurs faster than the usual one, for which the activation step should then be most probably rate limiting. As there is a direct relationship between the intensities and rates of the preactivated reactions, a confirmation is obtained that the ultrasonic waves have a direct effect on the corrosion step, the SET.

From a more practical point of view, as the more appropriate conditions for high rates and yields correspond to high intensities, synthetic applications of the sonochemical method can be effected without preactivation of the metal without loss of efficiency.[20]

Decreasing the temperature below 0 °C probably has two effects: an increase of the solution viscosity can slow down the diffusion phenomena, and the SET becomes thermo-

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(20) As an application of these findings the in situ generation of chloromethyllithium will be described in a future paper: Einhorn, C.; Allavena, C.; Luche, J. L. *J. Chem. Soc., Chem. Commun.*, in press.

dynamically less favored. These two effects can combine to make the Barbier reaction significantly slower, even if the cavitational pitting keeps its efficiency (Figure 10). As a result, the usual rate dependence on temperature is observed.

Conclusion

The remarkable accelerating effect of the ultrasonic waves has been evidenced by semiquantitative experiments, which served to determine optimal intensity and temperature conditions. These two factors have the important influence that was suspected at the origin of our study. However from the present work it cannot be stated that cavitation is the only important phenomenon. No information has been obtained on the effects of noncavitational shock waves, or the frequency.[21] This work then has to be considered as an approach for a better knowledge of the interaction of ultrasound with a heterogeneous system, but the problem in its generality cannot be considered as fully understood.

Experimental Section

Freshly distilled benzaldehyde (530 mg, 5 mmol), 895 mg (5 mmol) of 1-bromoheptane, and 1130 mg of hexadecane in 30 mL of dry THF (from benzophenone–Na) were placed in the reaction vessel with 139 mg of lithium (20 mmol, 3-mm wire, <0.01% Na, from Alfa). The cell was thermostated at the desired initial temperature under magnetic stirring (1000 rpm). Sonication was started with the desired intensity, and analytical samples were periodically withdrawn (0.3 mL), quenched (1 N aqueous HCl), and extracted with ether. After drying, the sample was analyzed by VPC on a Erba Science chromatograph, equipped with a 10% Carbowax 20 M, 2 m × 2 mm i.d. column, with temperature programmed from 70 to 200 °C (5 °C/min). Identification of the peaks was effected by comparison and coinjection with authentic specimens. For the determination of the polar pinacols, the analytical sample was silylated with bis(trimethylsilyl)trifluoroacetamide in dry pyridine at 80 °C for 15–30 min.[22]

VPC response factors (K), determined by standard procedures,[23] were as follows: benzaldehyde, 1.9; hexadecane, 1; 1-phenyloctanol, 1.4; n-heptyl bromide, 1.7; tetradecane, 1; benzyl alcohol, 2.2; 1-phenyloctanol trimethylsilyl ether, 0.9; 1,2-diphenyl-1,2-ethanediol bis(trimethylsilyl) ether, 0.8. Molar concentrations of the addition alcohol, C^i, were determined by the same procedure. From the stoichiometry of the reaction, the final maximum molar concentration of alcohol 1 was equal to the initial molar concentration of aldehyde C_0, thus the yields correspond to 100 C^i/C_0. These values were determined 4 times. For each measurement the difference between extreme values was taken as the initial error. The mean value of all the initial errors was taken as the final error (±4%). The error on the initial rates V_0 was determined graphically.

Micrographs were obtained with a scanning electron apparatus, JEOL JSM-840.

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Registry No. 1, 19396-73-7; PhCHO, 100-52-7; n-$C_7H_{15}Br$, 629-04-9; Li, 7439-93-2.

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[21] For an unexpected effect of frequency on an organolithium reaction, see: Einhorn, J.; Luche, J. L. *Tetrahedron Lett.* **1986**, *27*, 1791–1792.

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Synthesis of Tetrahydrolipstatin and Tetrahydroesterastin, Compounds with a β-Lactone Moiety. Stereoselective Hydrogenation of a β-Keto δ-Lactone and Conversion of the δ-Lactone into a β-Lactone

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Stereoselective syntheses of tetrahydrolipstatin (1) and tetrahydroesterastin (2) are described. The key intermediate β-keto δ-lactone 7 is hydrogenated stereoselectively to yield hydroxy δ-lactone 9, which is transformed into hydroxy β-lactone 10. Esterification of 10 with (*S*)-*N*-formylleucine under Mitsunobu's conditions yields tetrahydrolipstatin (1). Esterification of 10 with (*S*)-*N*-acetylasparagine under the same conditions yields 17 (mixture of two diastereomers), which gives by saponification hydroxy β-lactone 18. Reaction of the latter with the mixed anhydride of (*S*)-*N*-Z-asparagine, hydrogenation, and acetylation give tetrahydroesterastin (2).

Our interest in tetrahydrolipstatin (1) (Figure 1), an inhibitor of pancreatic lipase,[1] has led us to undertake the synthesis of this class of compounds. We have recently published several synthetic approaches,[2,4] and we want to report herein a highly stereospecific synthesis based on the preparation of a suitably substituted β-keto-δ-lactone 7, its stereoselective conversion into β-hydroxy δ-lactone 9 by hydrogenation, and transformation of the latter into hydroxy β-lactone 10, which serves as an intermediate for the preparation of tetrahydrolipstatin (1) as well as of tetrahydroesterastin (2), a closely related compound.[3]

Starting aldehyde 3[4] is condensed with the anion of lithium octanoate to yield hydroxy acid 4 as a mixture of diastereomers, which by deprotection yields hydroxy acid 5. Cyclization gives β-hydroxy δ-lactone 6 as a mixture of

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