pared by nucleophilic aromatic substitution reactions, which we believe to be unprecedented in the synthesis of a complex macrocycle.

Crystallization of **1** from $CHCl_3$-heptane gave crystals suitable for X-ray analysis.[7] This material proved to be a stable chloroform clathrate, and its structure is illustrated in Figure 1. Compound **1** adopts conformation **1c** in the crystal, in which the cavity is approximately 4.5 Å deep and 6 Å in diameter. Given the propensity of cavitands to form solvates,[8,9] it is not surprising that the chloroform of crystallization is nestled in the molecular bowl; however, we have no evidence of a specific association of **1** and chloroform in solution.

**Acknowledgment.** This work was supported in part by National Science Foundation Grant CHE-88121390 and by an Alfred P. Sloan Research Fellowship (to R.A.P.).

**Supplementary Material Available:** Crystallographic data and processing descriptions and tables of final atomic coordinates, bond lengths and angles, and anisotropic thermal parameters for **1**·$CHCl_3$ (10 pages). Ordering information is given on any current masthead page.

(7) A crystal of compound **1** measuring 0.08 × 0.24 × 0.26 mm was used for the X-ray measurements. Crystal data: $C_{42}H_{24}S_9 \cdot CHCl_3$, formula weight 936.6; monoclinic, space group $P2_1/c$; $a$ = 19.603 (4) Å, $b$ = 11.188 (3) Å, $c$ = 19.689 (4) Å, $\beta$ = 100.30 (2)°, $V$ = 4249 (2) Å$^3$, $Z$ = 4, $d_{calcd}$ = 1.46 g/cm$^3$. Intensity measurements were made with $3° < 2\theta < 114°$ by using graphite-monochromated Cu K$\alpha$ radiation at room temperature on a Nicolet $R3m$ diffractometer. A total of 5741 unique reflections were measured, and after background, Lorentz, and polarization corrections were applied, 3728 were considered to be observed [$|F_o| > 3\sigma(F_o)$]. Empirical absorption corrections were also applied, and the structure was solved by direct methods using the SHELXTL software. The occupancy of the chloroform was initially allowed to vary, and it was later fixed at the indicated full occupancy. The large temperature factors of the chloroform atoms as well as residual peaks in the difference Fourier maps suggested that the chloroform is disordered, but attempts to describe the disorder were not successful. In the final stages of refinement, all non-hydrogen atoms were refined with anisotropic temperature factors, and a riding model with idealized geometry was used for the hydrogens. Refinement with 496 parameters converged at $R$ = 0.092 and $R_w$ = 0.095 with goodness of fit = 1.66. Full details are provided in the Supplementary Material.

(8) Moran, J. R.; Karbach, S.; Cram, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 5826-5828.

(9) Cram, D. J.; Karbach, S.; Kim, H.-E.; Knobler, C. B.; Maverick, E. F.; Ericson, J. L.; Helgeson, R. C. *J. Am. Chem. Soc.* **1988**, *110*, 2229-2237.

## Cis/Trans Isomers in Cyclic Peptides without N-Substituted Amides

Dale F. Mierke, Toshimasa Yamazaki, Odile E. Said-Nejad, Eduard R. Felder,[‡] and Murray Goodman*

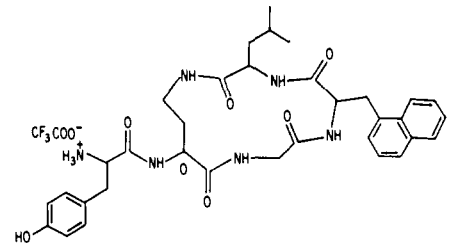
*Department of Chemistry*
*University of California, San Diego*
*La Jolla, California 92093*

*Received March 2, 1989*

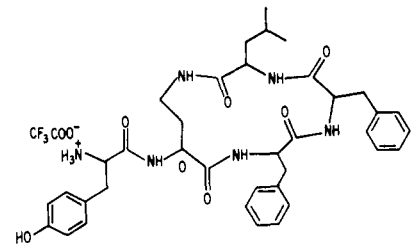
With the use of proton NMR, we observed configurational isomers containing cis amide bonds within a series of 14-membered cyclic peptides. These molecules are constrained but do not contain proline or any other N-substituted amino acid residues. To our knowledge this is the first report for such a cyclic peptide of this size that has an observable population of cis configurational isomers. Indeed the isomers of one of the compounds (Tyr-c[D-Glu-Phe-gPhe-D-retroLeu]) is composed of only 28% of the all trans structure, with two cis amide containing isomers accounting for 51% and 21%, respectively.

The cyclic molecules, shown in Figure 1, were synthesized as part of our program to study structure-activity relationship in the field of peptide opiates and are related to the cyclic analogue of enkephalin designed by Schiller and coworkers, Tyr-c[D-$A_2$bu-Gly-Phe-Leu].[1] The first analogue replaces the phenylalanine at position four with a $\beta$-(1-naphthyl)alanine, a modification of the steric character of this biologically important aromatic side chain. The other analogues shown in Figure 1 contain phenylalanine at position three in place of glycine and incorporate the retro-inverso modification.[2] This family of analogues will allow us to examine the relationship between the enkephalins and the opiate active dermorphin and morphiceptin which contain phenylalanine at the third position.[3,4]

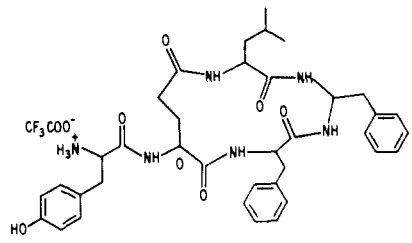
During the NMR analysis of three of the analogues (Tyr-c[D-$A_2$bu-Gly-D-Nal(1)-Leu], Tyr-c[D-$A_2$bu-Phe-gPhe-*R*-mLeu], and Tyr-c[D-Glu-Phe-gPhe-D-retroLeu])[5,6] the proton spectra



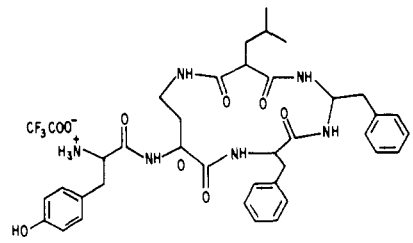

Tyr-c[D-$A_2$bu-Gly-(L and D)-Nal(1)-Leu]




Tyr-c[D-$A_2$bu-Phe-Phe-(L and D)-Leu]




Tyr-c[D-Glu-Phe-gPhe-(L and D)-retroLeu]




Tyr-c[D-$A_2$bu-Phe-gPhe-(S and R)-mLeu]

**Figure 1.** Structures of a series of cyclic molecules related to enkephalin and dermorphin. Within this series Tyr-c[D-$A_2$bu-Gly-D-Nal(1)-Leu], Tyr-c[D-$A_2$bu-Phe-gPhe-*R*-mLeu], and Tyr-c[D-Glu-Phe-gPhe-D-retro-Leu] are composed of a fraction of isomers containing cis amide structures.

(1) Schiller, P.; DiMaio, J. *Nature (London)* **1982**, *297*, 74-76.
(2) Goodman, M.; Chorev, M. *Acc. Chem. Res.* **1979**, *12*, 1-7.
(3) Erspamer, V.; Melchiorri, P. In *Growth Hormone and Other Biologically Active Peptides*; Pecile, A., Müller, E. E., Eds.; Excerpta Medica: Amsterdam, 1980, pp 185-200.
(4) Chang, K.-J.; Killian, A.; Hazum, E.; Cautrecasas, P.; Chang, J.-K. *Science* **1981**, *212*, 75-77.

[‡]Current address: Pharmaceuticals Division, Ciba-Geigy Ltd., CH-4002 Basel, Switzerland.

0002-7863/89/1511-6847$01.50/0 

**Table I.** Rates of Exchange between Cis and Trans Configurational Isomers in DMSO at 30 °C

| analogue | % cis | rate ($s^{-1}$) | | $\Delta G^{\ddagger}$ (kJ $mol^{-1}$) | |
|---|---|---|---|---|---|
| | | c → t | t → c | c → t | t → c |
| Tyr-c[D-$A_2$bu-Gly-D-Nal(1)-Leu] | 22 | 1.2 ± 0.2 | 0.72 ± 0.09 | 74 | 76 |
| Tyr-c[D-$A_2$bu-Phe-gPhe-*R*-mLeu] | 21 | 2.0 ± 0.1 | 1.6 ± 0.1 | 72 | 74 |
| | 13[a] | | | | |
| Tyr-c[D-Glu-Phe-gPhe-D-retroLeu] | 51 | 1.6 ± 0.2 | 1.4 ± 0.2 | 74 | 72 |
| | 21[a] | | | | |

[a] The rates for the smaller of the cis configurational isomers could not be accurately measured.

indicated more than one set of distinct resonances for each compound (both the Tyr-c[D-$A_2$bu-Phe-gPhe-R-mLeu] and Tyr-c-[D-Glu-Phe-gPhe-D-retroLeu] have two additional sets of resonances). The assignment of the resonances was carried out with HOHAHA and ROESY experiments.[7-9] From the Roesy spectra chemical exchange between the different sets of resonances was oberved.[10] Strong NOE's between $\alpha$ protons of adjacent residues allowed for the assignment of the additional sets of resonances of populations containing cis amide linkages. The minor isomer, accounting for 22%, of Tyr-c[D-$A_2$Bu-Gly-D-Nal(1)-Leu] has a cis arrangement about the D-$A_2$bu-Gly amide bond. The two cis isomers of Tyr-c[D-$A_2$bu-Phe-gPhe-*R*-mLeu] contain cis amide bonds between Phe-gPhe and mLeu-D-$A_2$bu side chain, accounting for 21% and 13% of the population, respectively. The major isomer of Tyr-c[D-Glu-Phe-gPhe-D-retro-Leu], 51% of the population, has a cis amide linkage about the D-Glu-Phe amide bond. The other cis isomer accounting for 21% has a cis arrangement between Phe-gPhe.

An example illustrating the chemical exchange between configurational isomers is shown in Figure 2 for Tyr-c[D-Glu-Phe-gPhe-D-retroLeu]. Exchange was only observed between the trans and cis configurational isomers (i.e., no exchange was seen between cis isomers). The rates and kinetics of the chemical exchange has been measured by using one-dimensional saturation transfer experiments at various temperatures.[11-13] The results are shown in Table I. The rates of interconversion are similar to the values reported by Grathwohl and Wüthrich for proline containing linear peptide sequences which may be indicative of similar energy barriers for cis/trans transitions.[12,14]

The observation of cis and trans isomers within this series is unexpected. The results from the NMR analysis of the series of enkephalin analogues (with glycine at the third position) containing the same retro-inverso modifications have been reported.[15,16] There was no evidence of multiple resonances or configurational isomers. It therefore must be concluded that the additional constraint from the replacement of phenylalanine with $\beta$-(1-naphthyl)alanine is the source of the observed configurational isomers. It is interesting to note that this effect occurs in only one of the two diastereomeric pair of analogues.

Two of the analogues which show multiple configurational isomers are partially modified retro-inverso analogues of the parent peptides (Tyr-c[D-$A_2$bu-Phe-Phe-(L and D)-Leu]). One has only a *gem*-diaminoaralkyl residue (Tyr-c[D-Glu-Phe-gPhe-D-retro-Leu]), while the other contains both a *gem*-diaminoaralkyl and a malonyl residue (Tyr-c[D-$A_2$Bu-Phe-gPhe-*R*-mLeu]). It has been shown that the retro-inverso modification increases the flexibility about the $\phi$ and $\psi$ bonds.[17,18] The origin of these cis amide containing structures must stem from the replacement of Gly with Phe at position 3 plus a combination of effects arising

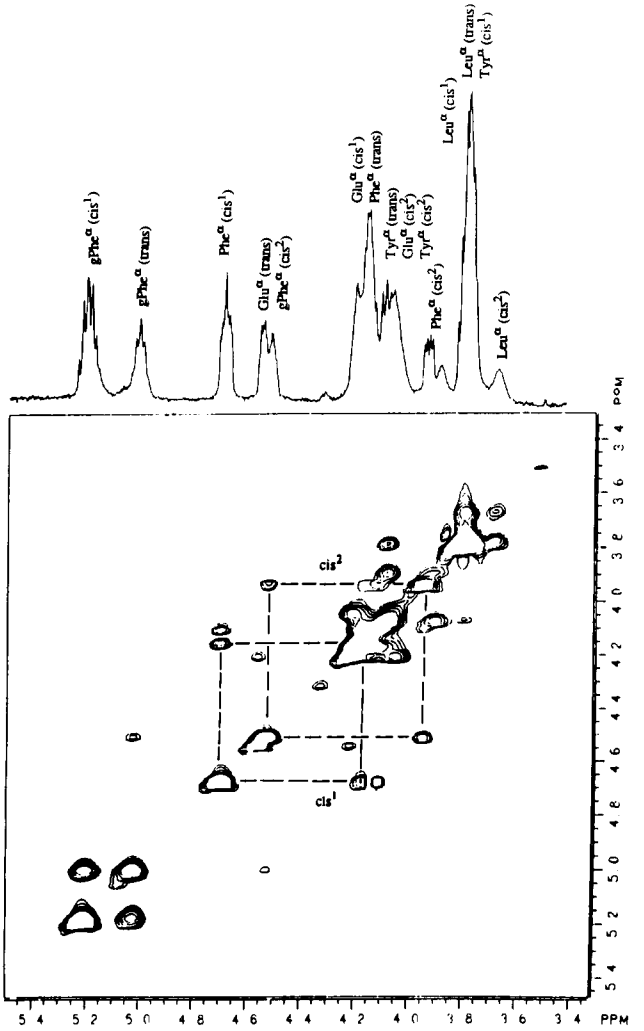



**Figure 2.** Expansion of two-dimensional ROESY spectrum illustrating the exchange between cis and trans configurational isomers of Tyr-c[D-Glu-Phe-gPhe-D-retroLeu] observed in DMSO-$d_6$ at 40 °C with a mixing time of 300 ms. The diagonal and all of the cross peaks except for those highlighted are positive intensity indicating chemical exchange. The cross peaks highlighted are NOE's between the $\alpha$ protons of D-Glu and Phe (labeled cis1) and Phe and gPhe (labeled cis2) indicating cis configurations about the D-Glu-Phe and Phe-gPhe amide bonds, respectively.

(5) $A_2$bu represents $\alpha,\gamma$-diaminobutyric acid, Nal(1) represents $\beta$-(1-naphthyl)alanine. The retroLeu nomenclature indicates that the leucine amino acid has been inserted into the molecule in the reverse direction.

(6) The chirality of the leucine in Tyr-c[D-$A_2$bu-Phe-gPhe-(*S* and *R*)-mLeu] was determined by NOE's and chemical shifts (see: Deber, C.; Joshua, H. *Biopolymers* **1972**, *11*, 2493-2503).

(7) Davis, D.; Bax, A. *J. Am. Chem. Soc.* **1985**, *107*, 2820-2821.
(8) Bothner-By, A. A.; Stephens, R. L.; Lee, J.; Warren, C. D.; Jeanloz, R. W. *J. Am. Chem. Soc.* **1984**, *106*, 811-813.
(9) Bax, A.; Davis, D. G. *J. Magn. Reson.* **1985**, *63*, 207-213.

(10) The phase-sensitive ROESY spectra were acquired with 2 K data points in the $f_2$ domain and 256 points in the $f_1$ domain by using a GN-500 spectrometer operating at 500 MHz. The mixing time was varied from 75 to 750 ms with a spin locking field of 2.5 KHz. The temperature was varied from 30 to 60 °C. Tetramethylsilane was used as an internal reference for the determination of chemical shifts.

(11) Forsen, S.; Hoffman, R. *J. Chem. Phys.* **1964**, *40*, 1189-1196.
(12) Grathwohl, C.; Wüthrich, K. *Biopolymers* **1981**, *20*, 2623-2633.
(13) Sanders, J. K. M.; Mersh, J. D. *Prog. NMR Spectrosc.* **1982**, *15*, 353-400.

(14) As an example a rate of 2.2 $s^{-1}$ was measured for $CF_3CO$-Gly-Gly-Pro-Ala-$OCH_3$ in DMSO at 50 °C by using saturation transfer experiments.

(15) Mammi, N.; Hassan, M.; Goodman, M. *J. Am. Chem. Soc.* **1985**, *107*, 4008-4013.
(16) Mammi, N. J.; Goodman, M. *Biochemistry* **1986**, *25*, 7607-7614.
(17) Stern, P.; Chorev, M.; Goodman, M.; Hagler, A. T. *Biopolymers* **1983**, *22*, 1885-1900.
(18) Stern, P.; Chorev, M.; Goodman, M.; Hagler, A. T. *Biopolymers* **1983**, *22*, 1901-1917.

from the diaminoaralkyl residue at position 4 and chirality of residue 5.

We have prepared many 14-membered cyclic analogues of the parent Tyr-c[D-$A_2$bu-Gly-Phe-(L and D)-Leu].[19-21] While most of these molecules exhibit only trans amide structures, we have shown in this communication that three of the eight peptides shown in Figure 1 exhibit cis amide containing isomers. In addition, we demonstrate, with the use of proton NMR, that it is possible to assign the specific bonds involved in the cis structures. The full understanding of the origin of these structural effects will require much more research into the energies and steric constraints of such molecules.[22,23]

**Acknowledgment.** We would like to thank Dr. Peter Schiller of the Clinical Research Institute of Montreal for many helpful discussions in the design of the molecules examined here. We acknowledge the support of the National Institutes of Health (DK 15410). One of us (E.R.F.) acknowledges a research fellowship from Ciba-Geigy Ltd.

(19) Berman, J.; Goodman, M. *Int. J. Peptide Protein Res.* **1984**, *2o*, 610–620.
(20) Richman, S.; Goodman, M.; Nguyen, T.; Schiller, P. W. *Int. J. Peptide Protein Res.* **1985**, *25*, 648–662.
(21) Mierke, D. F.; Lucietto, P.; Schiller, P. W.; Goodman, M. *Biopolymers* **1987**, *26*, 1573–1586.
(22) Mierke, D. F.; Said-Nejad, O. E.; Schiller, P. W.; Goodman, M. *Biopolymers* **1989**, submitted for publication.
(23) Mierke, D. F.; Yamazaki, T.; Felder, E. R.; Said-Nejad, O. E.; Schiller, P. W.; Goodman, M., manuscript in preparation.

## Homogeneous Sonochemistry in Radical Chain Reactions. Sonochemical Hydrostannation and Tin Hydride Reduction

Eiichi Nakamura,* Daisuke Machii, and Tsuyoshi Inubushi

*Department of Chemistry*
*Tokyo Institute of Technology*
*Meguro, Tokyo 152, Japan*
*Received April 3, 1989*

Irradiation of homogeneous liquids with high-intensity ultrasound[1] produces characteristic thermal nonequilibrium[2] conditions by creating localized superheated sonochemical cavities, wherein a maximum temperature over 2000 K can be readily realized. In contrast to its heterogeneous counterpart,[3] homogeneous sonochemistry[4] has remained virtually unexplored as a means for effecting chemical reactions[5]—a consequence of its poor efficiency due to the very small size and the exceedingly short lifetime (<2 μs) of the cavities. We have investigated the possibilities of utilizing homogeneous sonochemistry for the controlled initiation of radical chain reactions: radicals generated in the short-lived "hot spots"[3] undergo chain reactions in the bulk medium in such a way that the low concentration of the initial radical species may be compensated by the length of the chain. We report here the first synthetic application of this concept by describing hydrostannation (Scheme I) and tin hydride reduction initiated by sonochemical thermolysis of $R_3SnH$.[6]

**Scheme I**

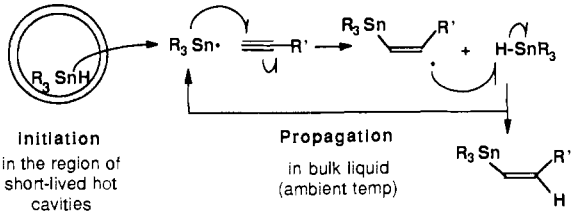
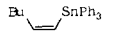
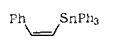
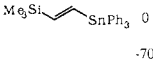
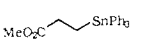
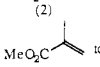
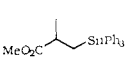
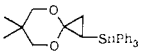



**Table I.** Sonochemical Hydrostannylation with $Ph_3SnH$[a]

| entry | substrate (equiv) | solv | sonochemical time (h) | sonochemical temp (°C) | sonochemical %yield[c] (%cis)[d] | major product | control temp (°C) | control %yield[e] | acceln[b] |
|---|---|---|---|---|---|---|---|---|---|
| 1 | n-BuC≡CH (5) | neat | 3 | 7 | 95 (92) |  | 0 | 1 | >1 x $10^2$ |
| 2 | | toluene[f] | 2 | 7 | 86 (91) | | 7 | 3 | 1 x $10^2$ |
| 3 | | THF | 0.25 | 7 | 72(93) | | | | |
| 4 | PhC≡CH (3) | toluene | 4 | -8 | 50 (≥92) |  | 7 | 13[g] | ~10 |
| 5 | | THF[f] | 1.5 | -55 | 61 (87) | | | | |
| 6 | $Me_3SiC$≡CH (3) | toluene | 5 | -8 | 78 (8) |  | 0 | 0 | >6 x $10^2$ |
| 7 | $Me_3SiC$≡CH | THF[f] | 8 | -55 | 39[g] (17) | | -70 | <1 | 1 x $10^2$ |
| 8 |  (2) | toluene[f] | 2.5 | 6 | 94 |  | 8 | <2 | 1 x $10^2$ |
| 9 |  (2) | toluene | 5 | 7 | 63 |  | 0 | <1 | 1 x $10^2$ |
| 10 |  (0.5) | toluene | 5 | 7 | 83 |  | 0 | 6 | >1 x 10 |

[a] The reaction was carried out in a 0.5 M solution except in entry 2 where a 0.25 M solution was used. Temperatures refer to those measured with a thermocouple immersed in the reaction mixture. In low-yield runs, high levels of material balance were observed. [b] Approximation rate acceleration assuming first-order kinetics. [c] Isolated yield except in entries 2 and 3 where GLC yields are reported. [d] Determined by GLC except in entries 4 and 5 where the ratio was determined by $^{13}C$ NMR. [e] Determined by NMR or GLC. [f] With AIBN (10 mol %). [g] Ca. 10% of $Ph_3SnH$ was recovered.

The thermally initiated radical hydrostannation of alkynes represents an important synthetic entry to vinylstannanes.[7] The reaction is normally carried out by heating a mixture of an organotin hydride and an alkyne at 50–100 °C in the presence of an initiator.[8] High-intensity ultrasound now has been found to smoothly initiate the reaction even below 0 °C through the selective thermolysis of the tin hydride reagent in the region of the short-lived hot spots. Thus, sonochemical irradiation of a mixture of $Ph_3SnH$ (0.44 g, 1.25 mmol) and 1-hexyne (0.72 mL, 6.25 mmol) under argon for 3 h (0 °C bath; 7 °C internal temperature) gave the desired vinylstannane in 95% yield (0.51 g) with 92% cis selectivity (Table I, entry 1).[9] Without irradiation, <1%

(1) Cf.: Suslick, K. S.; Hammerton, D. A.; Cline, R. E., Jr. *J. Am. Chem. Soc.* **1986**, *108*, 5641.
(2) On the growing interests in nonequilibrium processes, see: Freeman, G. R., Ed *Kinetics of Nonhomogeneous Processes*; Wiley: New York, 1987.
(3) (a) Renaud, P. *Bull. Chim. Soc. Fr., Ser. S* **1950**, *17*, 1044. Fry, A. J.; Herr, D. *Tetrahedron Lett.* **1978**, 1721. Luche, J. L.; Damiano, J. C. *J. Am. Chem. Soc.* **1980**, *102*, 7926. de Souza-Barboza, J. C.; Petrier, C.; Luche, J. L. *J. Org. Chem.* **1988**, *53*, 1212. (b) Reviews: Kimura, T.; Ando, T. *Yuki Gosei Kagaku Kyokaishi* (*J. Synth. Org. Chem. Soc. Jpn*) **1988**, *46*, 1124. Lindley, J.; Mason, T. J. *Chem. Soc. Rev.* **1987**, *16*, 275. Abdulla, R. F. *Aldrichim. Acta* **1988**, *21*, 31. Moon, S. *CHEMTECH* **1987**, 434. Boudjouk, P. *J. Chem. Educ.* **1986**, *63*, 427. Mason, T. J. *Ultrasonics* **1986**, *24*, 245. (c) For a recent report on an ultrasound-accelerated Diels–Alder reaction, see: Lee, J.; Snyder, J. K. *J. Am. Chem. Soc.* **1989**, *111*, 1522.
(4) (a) Suslick, K. S. *Adv. Organomet. Chem.* **1986**, *25*, 73. Suslick, K. S. *Mod. Synth. Methods* **1986**, *4*, 1. (b) Lorimer, J. P.; Mason, T. J. *Chem. Soc. Rev.* **1987**, *16*, 239.
(5) For a very important exception to this statement, however, see: Suslick, K. S.; Schubert, P. F.; Goodale, J. W. *J. Am. Chem. Soc.* **1981**, *103*, 7342. Suslick, K. S.; Goodale, J. W.; Schubert, P. F.; Wang, H. H. *Ibid.* **1983**, *105*, 5781. See also: Brown, H. C.; Racherla, U. S. *Tetrahedron Lett.* **1985**, *27*, 2187. Menéndez, J. C.; Trigo, G. G.; Söllhuber, M. M. *Tetrahedron Lett.* **1986**, *27*, 3285. Kruus, P.; Patraboy, T. J. *J. Phys. Chem.* **1985**, *89*, 3379.
(6) Cf. ESR detection of radical species upon thermolysis of $R_4Sn$ and ditins: Rehorek, D.; Janzen, E. G. *J. Organomet. Chem.* **1984**, *268*, 135.
(7) Kuivila, H. G. *Adv. Organomet. Chem.* **1964**, *1*, 47. van der Kerk, G. J. M.; Noltes, J. G. *Ibid.* **1959**, *9*, 106. Leusink, A. J.; Budding, H. A.; Marsman, J. W. *J. Organomet. Chem.* **1967**, *9*, 285. Leusink, A. J.; Budding, H. A.; Drenth, W.; *Ibid.* **1967**, *9*, 295.
(8) A recent method for chemical initiation: Nozaki, K.; Oshima, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 2547.
(9) (a) The reactions were carried out under argon with an immersion-type ultrasound generator (20 kHz, 200 W used at $^1/_{10}$ to $^4/_{10}$ of the full power without grossly affecting the efficiency, with a tapered titanium horn) using a glass reactor installed with a thermocouple similar to the one described by Suslick.[4a] A cup horn apparatus (fitted to the above generator[3b,4b]) and a common "ultrasound cleaner" (27 kHz, 150 W) gave qualitatively the same results.

0002-7863/89/1511-6849$01.50/0 