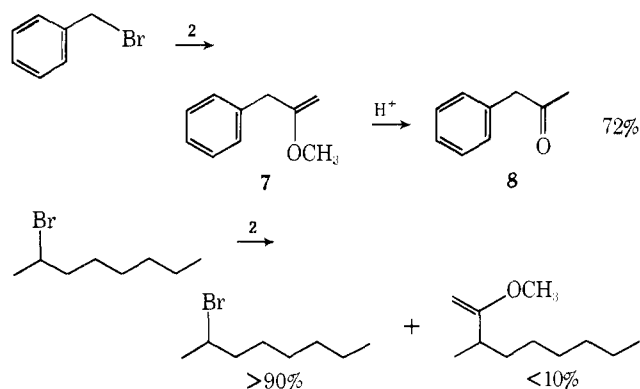**Scheme II**

lute acid (0.025 N HCl) in methanol–water (4:1) afforded the 1,4-diketone, 5,5-dimethyl-3-acetylcyclohexanone (**5c**) (see Scheme I) in 80% distilled yield.[8,9] Ozonolysis of **4c** in dichloromethane–methanol (9:1) at −60°,[10] followed by addition of dimethyl sulfide,[11] resulted in a 73% distilled yield of the γ-ketoester,[12] 5,5-dimethyl-3-carbomethoxycyclohexanone (**6c**)[8] (see Scheme I).

Concerning alkylations of the cuprate (**2**) with halides, we noted that Baldwin[1] was unsuccessful in alkylating MVL (**1**) with benzyl bromide (presumably due to trans metalation) nor was any mention made of alkylations with secondary halides. Addition of benzyl bromide to the cuprate (**2**) at −40° followed by stirring at 0° for 5 hr yielded the desired crude α-(α-methoxyvinyl)toluene (**7**). The enol ether was then hydrolyzed in the same manner as **4c** to product 1-phenyl-2-propanone (**8**)[8] in 72% distilled yield (based on benzyl bromide). Attempted distillation of the crude enol ether (**7**) afforded a 2:3 mixture of **7** and its double bond isomer. Treatment of 2-bromooctane in the same fashion, with the cuprate, followed by stirring at 0° for 4 hr and room temperature for 15 hr, however, resulted in a greater than 90% recovery of the starting alkyl bromide. These results are summarized in Scheme II.

A typical procedure for the generation and reaction of lithium di(α-methoxyvinyl)cuprate with electrophiles is demonstrated with 5,5-dimethyl-2-cyclohexen-1-one (**3c**). A solution of MVL prepared according to Baldwin[1] from 5.24 ml (69.6 mol) of methyl vinyl ether and 54.4 ml (43.5 mmol) of 0.8 M t-BuLi in 30 ml of THF was cooled to below −40° and added over 15 min via a glass-jacketed dropping funnel containing Dry Ice–isopropyl alcohol to a solution of 4.17 g (21.9 mmol) of purified cuprous iodide[3] and 6.30 ml (85.8 mmol) of dimethyl sulfide[5] in 30 ml THF at −40° (mole ratio CH2=CHOCH3-t-BuLi–CuI–CH3SCH3 ≈ 3:2:1:4). After stirring for 30 min, 1.80 g of 5,5-dimethyl-2-cyclohexen-1-one (**3c**) (14.5 mmol) in 15 ml of THF was added over 10 min to the yellow mixture and stirred at −40° for 10 min and then at −10° for 45 min. The red mixture was then quenched with 20% NH4Cl and extracted with ether and the crude product isolated and distilled, affording 1.76 g (67%) of 5,5-dimethyl-3-(α-methoxyvinyl)-2-cyclohexen-1-one (**4c**); bp 73–76° (0.25 mm): ^{1}H NMR (CCl4) δ 3.87 (d, 1, J = 2.5 Hz), 3.80 (d, 1, J = 2.5 Hz), 3.57 (s, 3), 1.4–2.8 (m, 7), 1.1 (s, 3), 0.92 (s, 3); ir (film) 1724, 1661, 1631 cm⁻¹. High resolution mass spectrum gave an M⁺ 182.1327 (C11H18O2).

In summary, lithium di(α-methoxyvinyl)cuprate provides an efficient route to γ-diketones and γ-ketoesters from α,β-unsaturated ketones and complements MVL with regard to alkylations of halides.[13]

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(1) J. E. Baldwin, G. A. Höfle, and O. W. Lever, *J. Am. Chem. Soc.*, **96**, 7125 (1974), and references therein.
(2) For a review of conjugate additions and reagents, see *Org. React.*, **19**, 1 (1972).
(3) Recrystallized from aqueous potassium iodide, followed by treatment with refluxing THF in a Soxhlet extractor.
(4) We have observed the black color of lithium divinyl cuprate in our laboratory; vinylcuprates: (a) E. J. Corey and R. L. Carney, *J. Am. Chem. Soc.*, **93**, 7318 (1971); (b) J. Hooz and R. B. Layton, *Can. J. Chem.*, **48**, 1626 (1970); (c) H. O. House, R. A. Latham, and C. D. Slater, *J. Org. Chem.*, **31**, 2667 (1966).
(5) We have found dimethyl sulfide to be superior to other complexing agents such as di-n-butyl and diisopropyl sulfide and tri-n-butylphosphine, due to its ease of removal on work-up; for another example of its use, see R. D. Clark and C. H. Heathcock, *Tetrahedron Lett.*, 1713 (1974).
(6) Analogous color changes are involved in the formation and use of lithium diallyl cuprate; see H. O. House and W. F. Fischer, Jr., *J. Org. Chem.*, **34**, 3615 (1969).
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(8) Satisfactory ^{1}H NMR, ir, and elemental analyses.
(9) The conjugate addition of lithium di(phenylthio)methylcopper reagents to α,β-unsaturated ketones, followed by CuCl2–CuO/aqueous acetone hydrolysis, also provides 1,4-diketones; see T. Mukaiyama, K. Narasaka, and M. Furusato, *J. Am. Chem. Soc.*, **94**, 8641 (1972).
(10) Use of methanol as solvent resulted in hydrolysis of the enol ether prior to ozonolysis. The methanol is added to a solution of the enol ether (e.g., **4c**) in dichloromethane at −60° just before ozonolysis; for another example utilizing these conditions, see R. D. Clark and C. H. Heathcock, *Tetrahedron Lett.*, 2027 (1974).
(11) J. J. Pappas, W. P. Keaveney, E. Gancher, and M. Berger, *Tetrahedron Lett.*, 4273 (1966).
(12) For another recent approach to the synthesis of γ-ketoesters, see P. A. Wehrli and V. Chu, *J. Org. Chem.*, **38**, 3436 (1973).
(13) NOTE ADDED IN PROOF. Professor R. K. Boeckman has informed us that he and Professor J. E. Baldwin have independently synthesized lithium di(α-ethoxyvinyl)cuprate and shown that it enters into conjugate additions with ketones. We thank Professors Boeckman and Baldwin for informing us of their results prior to publication.

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Lanthanum-139 as a Nuclear Magnetic Resonance Probe of Macromolecular Dynamics

Sir:

Nuclear relaxation rates reflect in principle the molecular dynamics in solution. Particularly sensitive in this regard are nuclei possessing a quadrupole moment (spin $I > \frac{1}{2}$), for which the molecular motion modulates the interaction between the nuclear quadrupole moment and intramolecular electric field gradients. The longitudinal relaxation rates of such nuclei are related (to a good approximation[1]) to the correlation time, τ_c, characteristic of the molecular motion by[2]

$$1/T_1 = C\left(\frac{\tau_c}{1 + \omega^2\tau_c^2} + \frac{4\tau_c}{1 + \omega^2\tau_c^2}\right) \quad (1)$$

where ω is the nuclear resonance frequency and C is a constant for a given nucleus and chemical environment. Thus measurements of longitudinal relaxation rates at several frequencies should permit an unequivocal determination of the correlation time. Attempts to study macromolecular dynamics via the above relationship using quadrupole nuclei such as ^{2}H, ^{23}Na, and ^{35}Cl have met with difficulties in the interpretation, the main reason being the little specificity and the weakness of the chemical interactions leading to rapid local motions.[3-5]

Recent spectroscopic and magnetic resonance studies (for a review cf. ref 6) have shown that the lanthanide ions form strong and specific complexes with a number of proteins and nucleic acids. Among the trivalent rare-earth ions, only lanthanum and lutetium are diamagnetic, and it appears
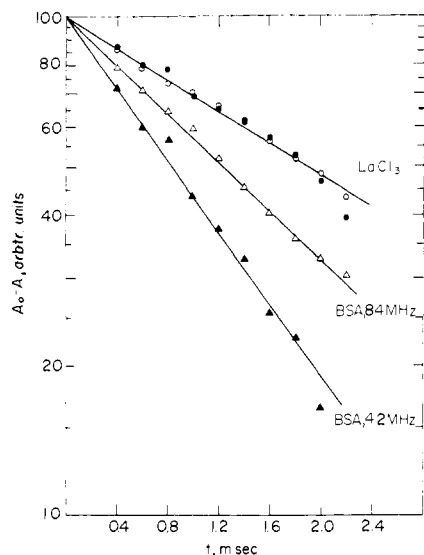
Figure 1. The exponential decay of the magnetization difference (in normalized arbitrary units) of ^{139}La as a function of the time interval, t, between the 180 and 90° pulses in the presence (triangles) and the absence (circles) of BSA at 8.4 (open symbols) and 4.2 MHz (filled symbols).

that lanthanum-139, a nucleus of spin $I = \frac{7}{2}$ with natural abundance of 99.91% and NMR sensitivity (relative to that of protons) of 5.92% should be a good NMR probe. Presented in this communication are our preliminary results of the relaxation rates of lanthanum-139 in solutions containing bovine serum albumin (BSA). The binding of lanthanides to BSA has previously been established from studies of water proton relaxation rates using Gd^{3+} as a paramagnetic probe and from difference spectra of Nd^{3+}.[7]

The lanthanum-139 magnetic resonance was observed at 8.4 and 4.2 MHz with a Bruker Model 322S Pulsed NMR spectrometer equipped with a Hewlett-Packard Model 5480A signal analyser. Longitudinal relaxation rates, $1/T_1$, were determined by the 180-90° pulse method, by which the magnetization amplitude A is measured as a function of the time interval, t, between the two pulses and the relaxation time obtained from the relation

$$A = A_0[1 - 2\exp(-t/T_1)] \qquad (2)$$

where A_0 is the amplitude in the absence of the 180° pulse.[8] The uncertainty in the $1/T_1$ values obtained in the present work is estimated to be less than $\pm 5\%$.

All solutions were made in 50 mM MES (2[N-morpholino]ethane sulfonic acid) buffer at pH 6.2 with tetramethylammonium as the cation. The protein solutions contained 0.9 mg/ml BSA (1.3×10^{-5} M) and the $LaCl_3$ concentration was 0.18 M. Measurements were done at the ambient probe temperature of $23 \pm 2°$.

The differences of the magnetization amplitudes, $A_0 - A$, obtained in solutions of $LaCl_3$ in the presence and in the absence of BSA are shown in Figure 1. The decays are exponential with the time interval, t, between the pulses, as predicted by eq 2. It is seen that the relaxation is faster in the presence of BSA and that the relaxation rate is further enhanced at the lower frequency, whereas the relaxation rate in the absence of protein is frequency independent within the limits of experimental error. The relaxation rates calculated using eq 2 are summarized in Table I.

The observed relaxation rate in the protein solution is the weighted average of the relaxation rates of the free and complexed species, which for a dilute protein solution (in which the concentration of free La^{3+} is very little changed) and rapid chemical exchange is given by[9]

Table I. Longitudinal Relaxation Rates (in sec^{-1}) of Lanthanum-139 in the Absence and in the Presence of BSA

	8.4 MHz	4.2 MHz
$LaCl_3$	365 ± 8	361 ± 10
$LaCl_3$ + BSA	568 ± 12	835 ± 10
$1/T_{1p}$	203 ± 20	474 ± 20

$$1/T_{1,\text{obsd}} = 1/T_{1f} + P_b/T_{1b}$$

and by defining the "excess relaxation",

$$1/T_{1p} \equiv 1/T_{1,\text{obsd}} - 1/T_{1f}$$

one obtains, $1/T_{1p} = P_b/T_{1b}$, where P_b is the fraction of complexed species and $1/T_{1b}$ is their relaxation rate. It is $1/T_{1b}$ that is related to the correlation time and the resonance frequency by eq 1. Thus the ratio of the $1/T_{1p}$ values at the two frequencies contains only the correlation time, τ_c, as an unknown, and it can readily be calculated. From the results in Table I we obtain $\tau_c = 2.25 \times 10^{-8}$ sec with an estimated uncertainty of $\pm 10\%$. At present a small contribution of chemical exchange to the relaxation rates cannot be ruled out and therefore our value of τ_c should be regarded as a lower limit. We note, however, that this value is in excellent agreement with the value of 2.0×10^{-8} sec calculated[3] from the Stokes-Einstein formulas.

The results presented here indicate that lanthanum-139 should be a useful NMR probe for studying macromolecular dynamics in solution.

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Salt–Molecule Matrix Reactions. Infrared Spectra of the $M^+HCl_2^-$ and $M^+Cl_3^-$ Ion Pairs in Solid Argon

Sir:

In 1968 Noble and Pimentel[1] condensed the microwave discharge products of Ar-HCl-Cl$_2$ samples and assigned new infrared bands to the HCl$_2$ radical. Subsequently, Milligan and Jacox[2] observed the same species by vacuum ultraviolet photolysis of HCl and mercury-arc photolysis of alkali atom-HCl samples and suggested the HCl$_2^-$ identification. Similar controversies have arisen over HBr$_2$ radical[3] or anion.[4] The matrix reaction of an alkali chloride salt and HCl should produce the ion-pair $M^+HCl_2^-$ for investigation of the HCl$_2^-$ spectrum. Nelson and Pimentel[5] observed