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Notes

Conformational Changes Induced by Europium Shift Reagent in Medium-Ring 3-Methoxycycloalkanones

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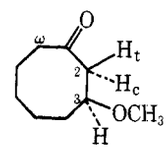
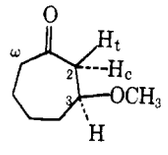
In connection with stereochemical studies on the photochemical[1] and base-catalyzed[2] addition of methanol to 2-cycloalkenones we investigated the LIS[3] spectra of the resulting 3-methoxycycloalkanones with $Eu(fod)_3$.[3,4] We observed a dramatic conformational change between the free and europium-coordinated forms of these compounds when the rings were sufficiently large so that the substrate could act as a bidentate ligand toward the europium.[5]

The four compounds whose spectra were studied in detail are **1**–**4**. Their complete spectra are described in the Experimental Section. Table I presents the data which supply conformational information, Figure 1 shows the most distinctive regions of the free and Eu-shifted spectra of **1**, and Figure 2 shows a plot of chemical shifts of selected protons in **1** as a function of added shift reagent.[6]



1



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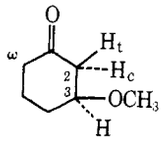

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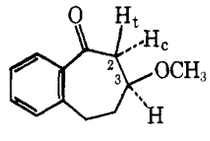
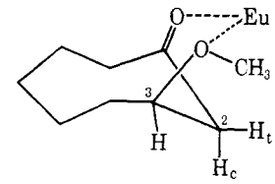


4

The H_2–H_3 coupling constants, which are approximately equal for the trans and cis protons in free **1** (7 Hz), change dramatically (to 8 and 3 Hz, respectively) when shift reagent is added. This difference can be attributed to changes in the dihedral angles as a consequence of bidentate coordination with the shift reagent.[7] The methoxyl group in coordinated **1** is pseudoaxial as shown,[8] whereas in free **1** the methoxyl is probably pseudoequatorial. This model for complexed **1** gives dihedral angles for H_3–H_{2t} and H_3–H_{2c} of 30 and 115°, respectively, consistent with the observed large and small coupling constants.[9] Eu-complexed **1** has a sufficiently rigid structure that the geminal coupling between the H_2 protons (12 Hz) was readily observed. Other data which support this structure are the appreciable difference between Δ's for H_{2t} and H_{2c} with $\Delta(H_{2t} > H_{2c})$ as expected from the model, and the approximately equal Δ's for the methoxyl and ω protons.



Also, the large difference in Δ's for the C-2 and ω protons would be inconsistent with having the europium coordinated symmetrically with the carbonyl oxygen.

As the ring size decreases (**1** → **2** → **3**) a series of changes in the spectral data occurs which indicates that bidentate coordination with the shift reagent decreases. The H_3–H_2 coupling constant differences in free and complexed **2** are still evident, though somewhat smaller than in **1**; in **3** (and in **4**, which has a more rigid seven-membered ring than **2** because of the benzene ring) this difference has vanished. The difference in Δ's for H_{2t} and H_{2c} decreases with decreasing ring size, as does the Δ for H_3 and for the methoxyl protons. Finally, the Δ for the ω protons increases and becomes comparable to that of the H_2 protons, suggesting that coordination becomes more symmetric at the carbonyl oxygen. It seems likely from these data that some bidentate coordination is still important in **2**, but that in **3** and **4** the shift reagent coordinates predominantly with the carbonyl oxygen.[10] All coordinated structures are fairly rigid, however, since in each case a large geminal coupling constant for the H_2 protons is readily observable in the europium-shifted spectra.

Experimental Section

Materials. 3-Methoxycycloalkanones were obtained by known procedures[1,11,12] and were purified by GLC and/or column chromatography.

NMR Measurements. All NMR spectra were measured in $CDCl_3$ with Me_4Si as an internal reference, using a Varian T60 or HA-100 spectrometer. LIS spectra were recorded by adding increasing weighed amounts of $Eu(fod)_3$ (Aldrich Chemical Co.) to a known weight of the substrate in $CDCl_3$. The LIS chemical shifts were plotted against the weight of $Eu(fod)_3$, and Δ (Table I) is the extrapolated value of the chemical shift difference in parts per million for a mole ratio of 1:1 of shift reagent/substrate. All coupling constants in the LIS shifted spectra were verified by appropriate decoupling experiments.

NMR Data. For **1** (unshifted spectrum): δ 1.05–2.10 (m, 8 H, C-4–C-7 methylenes), 2.25–2.45 (m, 2 H, C-8 methylene), 2.55–2.75 (m, 2 H, C-2 methylene), 3.30 (s, 3 H, methoxyl), 3.45 (m, 1 H, C-3 methine); irradiation at δ 1.85 (C-4 methylene) caused the multiplet at δ 3.45 to become a triplet, J = 7 Hz. For **1** (LIS shifted spectrum; mole ratio of $Eu(fod)_3/1$ = 0.39): δ 2.50–5.70 (m, 10 H, C-4–C-8), 6.22 (s, 3 H, methoxyl), 8.20 (m, 1 H, C-3 methine), 7.20 (d × d, 1 H, J = 12, 3 Hz, H_{2c}), 9.15 (d × d, 1 H, J = 12, 8 Hz, H_{2t}).

For **2** (unshifted spectrum): δ 1.50–1.96 (m, 6 H, C-4–C-6 methylenes), 2.27–2.43 (m, 2 H, C-7 methylene), 2.63–2.73 (m, 2 H, C-2 methylene), 3.20 (s, 3 H, methoxyl), 3.45 (m, 1 H, C-3 methine); irradiation at δ 1.73 (C-4 methylene) converted the C-3 methine signal to a doublet of doublets, J = 6.5, 4 Hz. For **2** (LIS shifted spectrum; mole ratio of $Eu(fod)_3/2$ = 0.53): δ 3.20–4.50 (m, 6 H, C-4–C-6 methylenes), 5.20 (s, 3 H, methoxyl), 6.90 (m, 1 H, C-3 methine), 7.90–8.30

Table I. Selected Features of the NMR Spectra of 1–4

Registry no.	Compd	$J_{H_{2t}H_3}$,[a] Hz		$J_{H_{2c}H_3}$, Hz		Δ[b]				
		Free[c]	$Eu(fod)_3$[e]	Free[c]	$Eu(fod)_3$	H_{2t}	H_{2c}	H_3	OCH_3	ω
6925-18-4	1	7.0	8.0	7.0	3.0	15.6	12.2	11.8	7	(7)[d]
17159-70-5	2	6.5	7.8	4.0	2.0	13.1	11.1	6.1	3.4	10.3
17429-00-4	3	6.5	6.7	4.2	4.0	11.2	10.4	4.9	2.5	10.8
62251-77-8	4	7.5	7.0	5.0	4.0	10.1	9.8	5	2	

[a] J's are accurate to ±0.2 Hz. [b] Δ values are the chemical-shift differences (extrapolated; see Experimental Section for details) between the unshifted protons and the chemical shift for a 1:1 mol ratio of $Eu(fod)_3$ to substrate. [c] These values could not be observed directly, but were obtained by irradiating the C-4 methylene protons (at δ 1.85, 1.73, 1.95, and 2.00 in **1**, **2**, **3**, and **4** respectively). [d] The peak due to the ω protons in **1** is broad and appears with other protons; the value is approximate. [e] Registry no.: **1** $Eu(fod)_3$, 63548-86-7; **2** $Eu(fod)_3$, 63548-87-8; **3** $Eu(fod)_3$, 63588-61-4; **4** $Eu(fod)_3$, 63548-88-9.

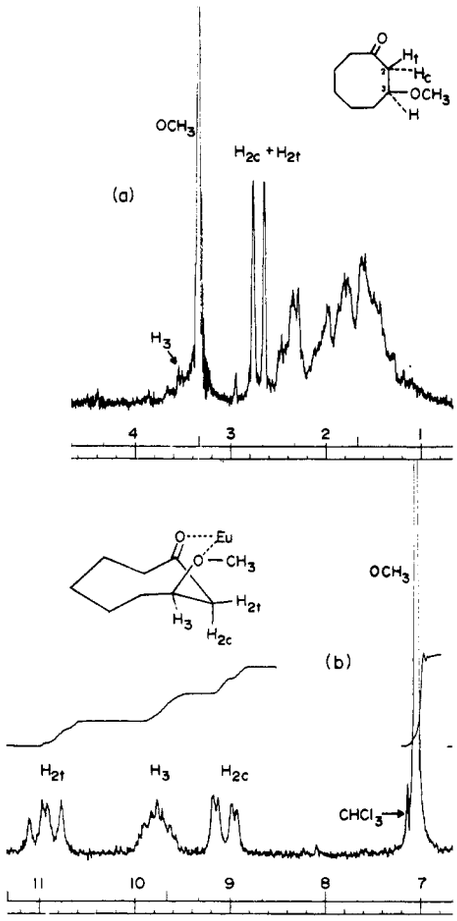


Figure 1. (a) The NMR spectrum of **1** (60 MHz); the peaks for H_{2c} and H_{2t}, which appear to be a doublet, are in fact complex multiplets at 100 or 180 MHz. (b) A portion of the LIS spectrum of **1**, mole ratio of $Eu(fod)_3$/**1** = 0.53.

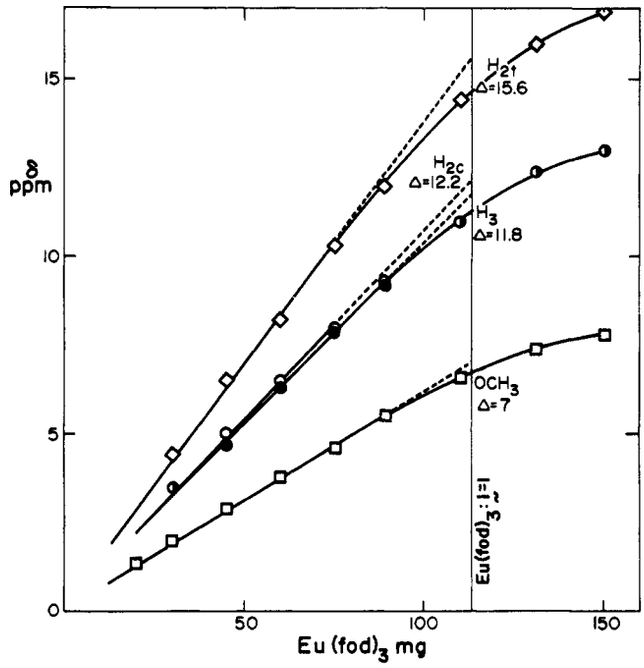


Figure 2. The chemical shifts of selected protons in **1** as a function of added shift reagent. The C-8 methylene protons fall on a curve nearly coincidental with that for the methoxyl protons.

(m, 2 H, C-7 methine), 8.70 (d × d, 1 H, J = 14.5, 2 Hz, H_{2c}), 9.60 (d × d, 1 H, J = 14.5, 7.8 Hz, H_{2t}).

For **3** (unshifted spectrum): δ 1.50–2.15 (m, 4 H, C-4, C-5 methylenes), 2.20–2.40 (m, 2 H, C-6 methylene), 2.40–2.60 (m, 2 H, C-2 methylene), 3.25 (s, 3 H, methoxyl), 3.60 (m, 1 H, C-3 methine); irradiation at δ 1.95 (C-4 methylene) converted the methine signal to a doublet of doublets, J = 6.5, 4.2 Hz. For **3** (LIS shifted spectrum; mole ratio of $Eu(fod)_3$/**3** = 1.11): δ 5.00–6.20 (m, 4 H, C-4, C-5 methylenes), 5.50 (s, 3 H, methoxyl), 7.8 (m, 1 H, C-3 methine), 10.80 (m, 2 H, C-6 methylene), 11.60 (d × d, 1 H, J = 15, 4 Hz, H_{2c}), 12.10 (d × d, 1 H, J = 15, 6.7 Hz, H_{2t}).

For **4** (unshifted spectrum): δ 2.00 (q, 2 H, J = 5 Hz, C-4 methylene), 2.80–3.15 (m, 4 H, C-2 and C-5 methylenes), 3.27 (s, 3 H, methoxyl), 3.68 (d × q, 1 H, J = 7.5, 5 Hz, C-3 methine), 7.05–7.66 (m, 4 H, arom); irradiation at δ 2.0 (C-4 methylene) converted the methine signal to a doublet of doublets, J = 7.5, 5 Hz, whereas irradiation at δ 3.68 (C-3 methine) converted the C-4 signal to a triplet, J = 5 Hz. For **4** (LIS shifted spectrum; mole ratio of $Eu(fod)_3$/**4** = 1.30): δ 5.50 (s, 3 H, methoxyl), 8.80 (m, 1 H, C-3 methine), 12.60 (d × d, 1 H, J = 13.5, 4 Hz, H_{2c}), 13.08 (d × d, 1 H, J = 13.5, 7 Hz, H_{2t}).

Acknowledgment. We are indebted to the National Science Foundation (GP 43659X) for financial support of this research.

Registry No.—$Eu(fod)_3$, 17631-68-4.

References and Notes

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(6) With all four compounds, the curves are initially linear, but begin to flatten before a 1:1 mole ratio of shift reagent/substrate.
(7) For other examples of bidentate complexes, see G. E. Wright and T. Y. Tang Wei, *Tetrahedron*, **29**, 3775 (1973); R. Schüttler and R. W. Hoffman, *Tetrahedron Lett.*, 5109 (1973); M. R. Willcott III and R. E. Davis in ref 3, p 159; B. L. Shapiro, M. D. Johnson, Jr., and M. J. Shapiro, *J. Org. Chem.*, **39**, 796 (1974); N. Dennis, B. Ibrahim, and A. R. Katritzky, *J. Chem. Soc., Perkin Trans. 1*, 2307 (1976); N. Dennis, A. R. Katritzky, and R. Rittner, *ibid.*, 2329 (1976).
(8) Cyclooctanone conformations have been reviewed by F. A. L. Anet, *Top. Curr. Chem.*, **45**, 169 (1974).

(9) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed, Pergamon Press, 1969, Chapter 4-2.
(10) One feature of the shifted spectrum suggests that even in 3 the europium may not be coordinated symmetrically with the carbonyl oxygen. At a 1:1 mole ratio of shift reagent/substrate the C-2 methylene protons are nicely separated to two doublet of doublets spread out over 1 ppm, whereas the ω (C-6) methylenes form a much narrower band (0.4 ppm) and appear as a triplet (in the unshifted spectra the peaks due to these two methylenes have nearly equal widths, 0.15 and 0.20 ppm, respectively).
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Preparation of *tert*-Butyl Thioesters

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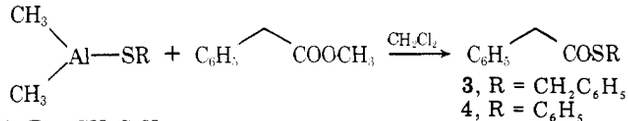
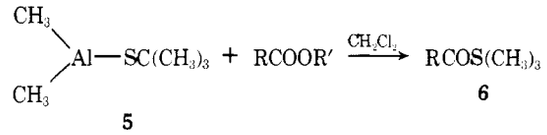
There has been considerable interest recently in activating carboxyl groups for the purpose of synthesizing macrocyclic lactones.[2] Masamune et al.[3a] have described a method of carboxyl activation using *tert*-butyl thioesters. These workers have developed preparations of *tert*-butyl thioesters from the corresponding acid chlorides or mixed anhydrides and thallous 2-methylpropane-2-thioate.[3] It has been reported that diethylaluminum ethanethiolate will open propiolactone and butyrolactone to the ω-hydroxy ethyl thioesters.[4] Corey briefly reported in 1973[5,6] that the aluminum reagents **1** and **2**, pre-



1, R = $CH_2C_6H_5$
2, R = C_6H_5

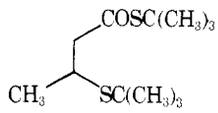
pared from trimethyl aluminum and the corresponding mercaptan, react with methyl phenylacetate to produce the thioesters **3** and **4**, respectively, in good yield. We have found that the corresponding *tert*-butyl reagent **5**, prepared in situ from trimethyl aluminum and *tert*-butyl mercaptan in methylene chloride, reacts with a variety of functionalized methyl and ethyl esters at room temperature to produce *tert*-butyl thioesters **6**. We believe that this method of prep-



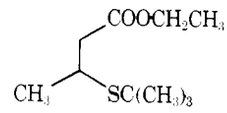
5 **6**

aration may have some advantages over Masamune's procedures.[3] The method avoids using toxic thallium reagents and often the methyl and ethyl esters are more readily available than the acids or acid chlorides. In addition, reagent **5** is a very mild Lewis acid whereas Masamune's reagent systems are basic. Thus, for base-sensitive compounds, the aluminum thioate method might be preferable in the synthesis of *tert*-butyl thioesters.

In Table I are shown isolated yields for a number of representative esters which have been converted to the corresponding *tert*-butyl thioesters. In general, the rate of reaction for ethyl and methyl esters is nearly identical. Ethyl crotonate, on treatment with **5**, gave a mixture of products, **6** and **7**, re-



6



7

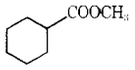
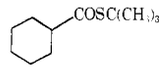
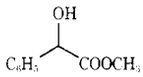
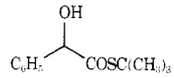
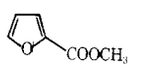
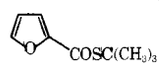
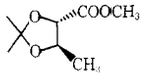
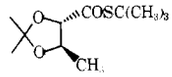
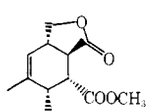
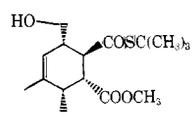
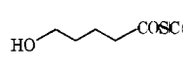
sulting from 1,4-addition of *tert*-butyl mercaptan to the double bond. Similar results were obtained with both dimethyl fumarate and ethyl cinnamate. Thus, it appears that α,β-unsaturated esters will generally give conjugate addition products with reagent **5**.

Lactones also react with reagent **5** to produce ω-hydroxy *tert*-butyl thioesters. The rate of reaction of **5** with γ-lactones is considerably faster than the rate of reaction with methyl esters, as can be seen from the example in Table I. δ-Valerolactone is readily converted to the hydroxy *tert*-butyl thioester on treatment with **5**.

Experimental Section

General Procedure for Preparation of *tert*-Butyl Thioesters. To a solution of 0.4 mL (1.0 mmol) of 2.5 M trimethyl aluminum in

Table I. Synthesis of *tert*-Butyl Thioesters from Methyl and Ethyl Esters and Lactones[a]

Starting ester	Registry no.	*tert*-Butyl thioester	Compd no.	Registry no.	Isolated yield, %
$C_6H_5COOCH_3$	93-58-3	$C_6H_5COSC(CH_3)_3$	8[7]	13291-44-6	90
$C_6H_5COOCH_2CH_3$	93-89-0	$C_6H_5COSC(CH_3)_3$	8[7]		95
$CH_3(CH_2)_{16}COOCH_2CH_3$	111-61-5	$CH_3(CH_2)_{16}COSC(CH_3)_3$	9	33563-87-0	100
$C_6H_5CH_2COOCH_2CH_3$	101-97-3	$C_6H_5CH_2COSC(CH_3)_3$	10	61049-77-2	80
	4630-82-4		11[3]	54829-37-7	80
	771-90-4		12	63599-51-9	90
	611-13-2		13	63599-52-0	75
	63640-49-3		14	63599-53-1	85
	63599-50-8		15	63599-54-2	90
	542-28-9		16	63599-55-3	60