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(35) 250-W General Electric sun lamp.
(36) The absence of sulfone bands in the infrared spectrum and a molecular ion of *m/e* 322 in the mass spectrum suggested this compound to be $(CH_3)_2CHC(I){=}CH(I)$. 1,2-Diiodostyrene was an isolated product in the reaction of alkylsulfonyl iodides with phenylacetylene.[33]
(37) Truce and Wolf[33] have shown that the addition of *p*-tolylsulfonyl iodide to 3,3-dimethyl-1-butyne also gave both isomers; however, the trans-addition isomer predominated over the cis 55:45.
(38) This compound was identified as $(CH_3)_3C{-}C(I){=}CH(I)$ from its mass spectrum molecular ion *m/e* 336, and its NMR ($CDCl_3$): δ 1.40 [s, 9 H, $(CH_3)_3C-$], 7.24 (s, 1 H, vinyl proton).
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(40) This carbonyl compound has been identified as the β-keto sulfone, $CH_3CH_2SO_2CH_2COCH(CH_3)_2$, by both its mass (molecular ion, *m/e* 178) and NMR spectra ($CDCl_3$): δ 1.15 [d, 6 H, J = 6.5 Hz, $-CH(CH_3)_2$], 1.38 (t, 3 H, J = 7.5 Hz, $CH_3CH_2SO_2-$), 2.87 [septet, 1 H, J = 6.5 Hz, $-CH(CH_3)_2$], 3.21 (q, 2 H, J = 7.5 Hz, $CH_3CH_2SO_2-$), 4.13 (s, 2 H, $-SO_2CH_2C{=}O$).
(41) Thermal isomerization of the conjugated adducts to the nonconjugated adduct appears to have occurred during distillation.
(42) Elution chromatography of this crude oil on a column of silica gel caused isomerization to the more stable trans isomer and the nonconjugated isomer $PhCH_2CH_2CH_2SO_2CH_2C(Az){=}CH_2$, as well as hydrolysis of some of the material to the ketone ($PhCH_2CH_2CH_2SO_2CH_2COCH_3$).

Stereochemistry of β-Lactams Derived from α-Keto-γ-lactams by Ring Contraction. X-Ray Analysis and Differential Behavior with Shift Reagents of Difunctional β-Lactams

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The configurations of the α,α-disubstituted β-lactams **2**, **3**, and **4** were determined by X-ray analysis, and the results are used to explain the stereochemistry of β-lactams derived from α-keto-γ-lactams by oxidative ring contraction with periodate. The X-ray data provide indirect support for the proposed correlation of biological activity with the pyramidal nature of bonding to the β-lactam nitrogen. The behavior of the esters **7** and **8** toward the lanthanide shift reagents $Eu(dpm)_3$ and $Eu(fod)_3$ in both CCl_4 and $CDCl_3$ was also examined. Different results arose depending upon both ligand (dpm or fod) and solvent, and the differences are explained by invoking for $Eu(fod)_3$ a 2:2 bridged complex in CCl_4 and a mixture of bridged complex and 1:1 chelated complex in $CDCl_3$. In addition, $Eu(fod)_3$ was shown to be unstable to the carboxylic acids **1–4**, indicating a limitation on its utility for the characterization of carboxylic acids. Perturbation of conformational equilibria by coordination to shift reagents is illustrated.

The formation of β-lactams from α-keto-γ-lactams by oxidative ring contraction with periodate[1] can lead to two orientations for the new carboxyl group at the α carbon of the β-lactam. The mechanism of this rearrangement reaction has been investigated using 1-methyl-2,3-piperidinedione as the prototype,[2] and the proposed mechanism is illustrated in Scheme I for β-substituted α-keto-γ-lactams. It was anticipated that stereochemistry would be governed by the relative size of substituents in an orientation-determining stage approximated by structures **11** or **12**. Consistent with this view, only the trans isomer **1** was obtained when X = H.[1] When X = methyl, again only one isomer, **2**, was produced; however both isomers, **3** and **4**, occurred when X = bromine,[1] and this provided the possibility of defining the requirements for generating the isomer with the carboxyl group oriented cis (β) to the fused ring. Accordingly, we undertook the determination of the stereochemistry of β-lactams **2**, **3**, and **4** by X-ray crystallographic analysis, and we now report the results of these studies along with their mechanistic implications.

It was also anticipated that use of a lanthanide shift reagent (LSR) could lead to definition of relative stereochemistry. The shift reagent $Eu(dpm)_3$ (dpm = dipivaloylmethanato) differentiated between the bromo isomers, and the limitations on its use for determining stereochemistry are discussed. On the other hand, use of $Eu(fod)_3$ (fod = 1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionato) led to essentially no differentiation. The results of the use of both reagents in CCl_4 and $CDCl_3$ are discussed in terms of composition of LSR–substrate complexes.

In addition, perturbation of conformational equilibria by coordination to shift reagents is illustrated, and limitations on the use of chelate shift reagents with carboxylic acids are discussed.

Results and Discussion

Previously the syntheses of compounds **9** (X = H) and **10** (X = CH_3 and Br) were described along with their reaction with periodate to form the β-lactams **13**.[1] For X = H and CH_3 only one isomer was formed, but for X = Br both iso-

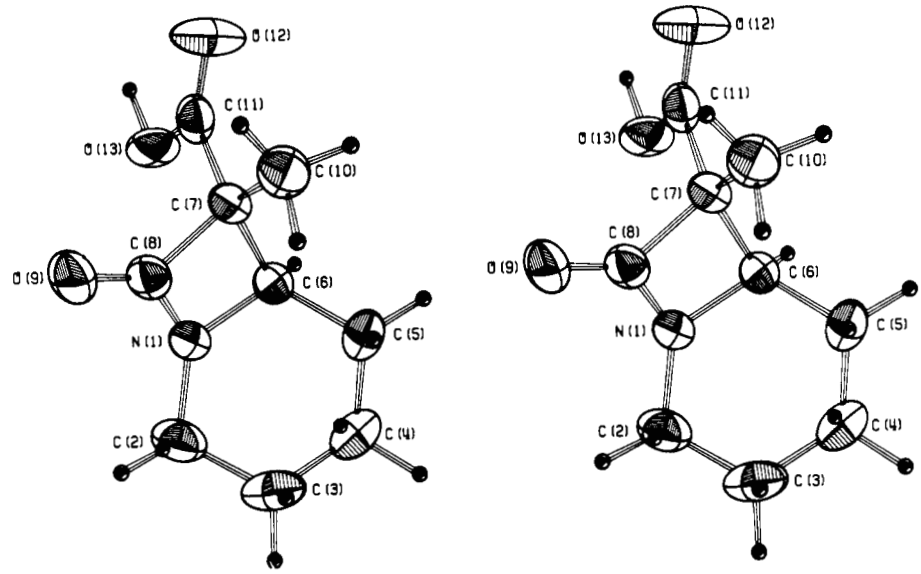
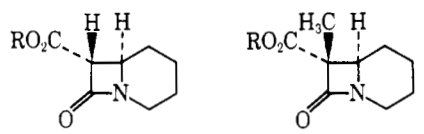
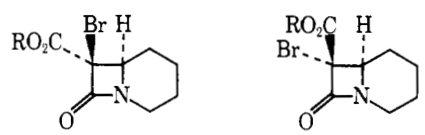


Figure 1. Stereoplot of 7α-carboxy-7β-methyl-8-oxo-6α*H*-1-azabicyclo[4.2.0.]octane (**2**).

mers were produced in a ratio of 9:1. The configurations of the methyl (**2**, Figure 1) and bromo (**3, 4**) compounds were determined by X-ray analysis and are given below, with



R = H	**1**	**2**
R = CH_3	**5**	**6**

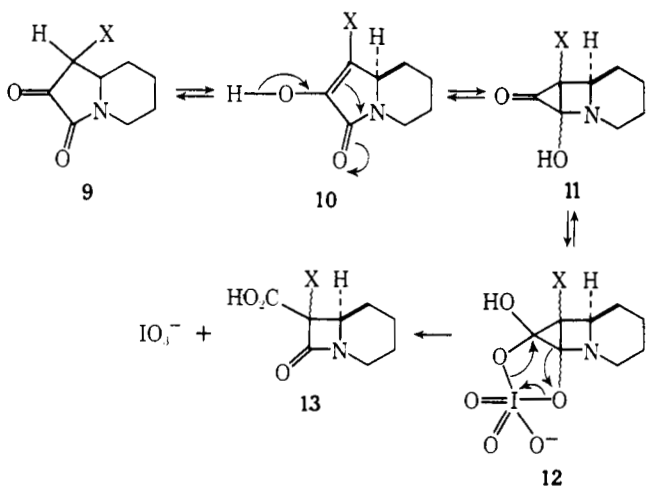


R = H	**3**	**4**
R = CH_3	**7**	**8**

structure **3**, the 7β-bromo compound, corresponding to the major bromo isomer. Two modes of reaction for an intermediate such as **11** have been proposed;[2] since the minor mode is not available for β-substituted α-ketoacyl derivatives, only the major mode of reaction is illustrated in Scheme I.

The 7β-methyl group of **2** and the bromine of the major isomer **3** both have the same orientation as the 7 proton in **1**, i.e., cis to the fused ring. The β-lactams of this series (**1, 2, 3**) have the carboxyl on the less hindered face of the β-lactam ring, consistent with the proposal that the size of the substituent X determines the stereochemistry in the β-lactams **13**. Measurements which appear to reflect the effective size of substituents suggest that bromo is somewhat larger than, or at least comparable to, the methyl group.[3] For this simple carbocyclic system, formation of the minor bromo isomer **4** then suggests that an effective size approximating bromo defines a lower limit for substituents which will force a change in stereochemical preference.

Scheme I
Mechanism of Oxidative Ring Contraction of β-Substituted α-Keto-γ-lactams



X-Ray Analyses. The refined crystallographic structures were stereographically plotted (e.g., Figure 1) using the ORTEP computer program.[4] An estimate of errors in positional parameters, bond lengths, and bond angles is summarized in Table I. Bond distances and angles are given in Table II. The degree of planarity of the β-lactam ring is reflected in the measurements shown in Table IIIA, and dihedral angles involving the ring fusion are given in Table IIIB. Atomic parameters and structure factor tables appear in Tables V, VI, and VII.[5]

Among those fused ring β-lactams which have been studied in detail by X-ray diffraction,[6] the biologically active compounds (e.g., penicillin G,[6a] cephaloridine,[6b] and cephaloglycine[6b]) contain the β-lactam nitrogen at the apex of a pyramid with the nitrogen atom raised about 0.24 Å (cephalosporins) to 0.40 Å (penicillin G) above the plane of the attached atoms. On the other hand, biologically inactive 7β-phenoxyacetamido-Δ^2-deacetoxycephalosporanic acid[6b] and the fused β-lactam **14**[6c] contain the β-lactam nitrogen raised only about 0.07 Å above the plane of the attached atoms. Based on the data from penicillin G and the cephalosporins, it has been suggested that, as one among a number of factors, biological activity may be correlated

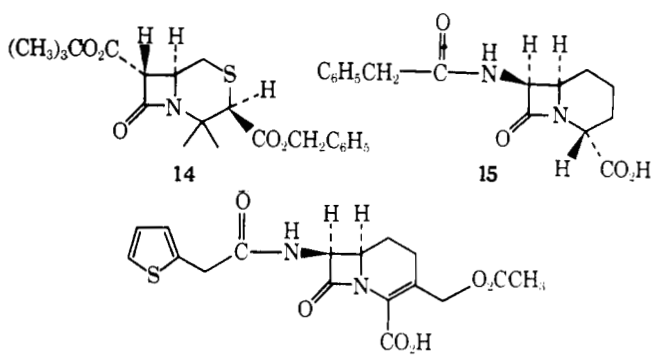


Table I

Compd	2	3	4
A. Refinement Parameters			
R index ($R = \Sigma \|\|F_0\| - \|F_c\|\| / \Sigma \|F_0\|$)	0.079	0.055	0.045
Weighted *R* ($R' = w(F_0^2 - F_c^2)^2 / \Sigma w F_0^4$)	0.028	0.017	0.009
Final calculated shifts, fraction of standard deviation	0.00	0.25	0.00
Positional uncertainty, Å			
C	0.009	0.008	0.007
N	0.007	0.007	0.006
O	0.007	0.005	0.006
Br		0.0008	0.0007
Bond distance uncertainty, Å			
C–C	0.016	0.010	0.010
C–N	0.014	0.009	0.009
C–O	0.012	0.009	0.009
C–Br		0.006	0.007
Bond angle uncertainty, deg	0.9	0.7	0.6
B. Crystal Parameters			
Formula	$C_9H_{13}NO_3$	$C_8H_{10}BrNO_3 \cdot H_2O$	$C_8H_{10}BrNO_3$
Crystallization media	Acetone–hexanes	Chloroform–hexanes	Chloroform–hexanes
Crystal habit	Acicular	Prismatic	Acicular
Crystal size, mm	0.10 × 0.10 × 0.15	0.30 × 0.50 × 0.80	0.05 × 0.15 × 0.25
Cell dimensions, Å	a = 8.164 (3)	a = 7.709 (1)	a = 8.049 (3)
	b = 10.825 (2)	b = 12.577 (2)	b = 10.306 (6)
	c = 15.356 (6)	c = 11.588 (2)	c = 12.524 (6)
	β = 135.70 (2)°	β = 109.23 (1)°	β = 113.55 (3)°
Space group	$P2_1/c$	$P2_1/c$	$P2_1/c$
Molecules/unit cell	4	4	4
Density observed, g/cm^3	1.29	1.62	1.69
Density calculated, g/cm^3	1.28	1.67	1.73
Number of reflections	973	1093	970
Nonzero reflections	848	1061	898
Linear absorption coefficient μ, cm^{-1}	8.1	57.8	63.1

Table II
Bond Distances and Angles for Compounds 2–4

		Distance, Å						Angle, deg						Angle, deg		
Atom	Atom[a]	2	3	4	Atom	Atom	Atom	2	3	4	Atom	Atom	Atom	2	3	4
N(1)	C(2)	1.46	1.44	1.43	C(6)	N(1)	C(2)	126	125	125	R(10)	C(7)	C(6)	119	118	114
N(1)	C(6)	1.48	1.48	1.48	C(8)	N(1)	C(2)	136	135	137	C(11)	C(7)	C(6)	114	114	116
N(1)	C(8)	1.33	1.33	1.33	C(8)	N(1)	C(6)	96	96	97	R(10)	C(7)	C(8)	114	113	111
C(2)	C(3)	1.54	1.52	1.53	C(3)	C(2)	N(1)	107	108	109	C(11)	C(7)	C(8)	112	118	116
C(3)	C(4)	1.52	1.53	1.52	C(4)	C(3)	C(2)	113	111	112	C(11)	C(7)	R(10)	112	107	112
C(4)	C(5)	1.54	1.54	1.54	C(5)	C(4)	C(3)	112	112	112	C(7)	C(8)	N(1)	94	92	92
C(5)	C(6)	1.51	1.52	1.53	C(6)	C(5)	C(4)	108	108	107	O(9)	C(8)	N(1)	134	133	133
C(6)	C(7)	1.57	1.56	1.57	C(5)	C(6)	N(1)	111	109	109	O(9)	C(8)	C(7)	133	135	135
C(7)	C(8)	1.54	1.53	1.54	C(7)	C(6)	N(1)	87	85	86	O(12)	C(11)	C(7)	125	123	122
C(7)	R(10)	1.52	1.93	1.94	C(7)	C(6)	C(5)	122	122	121	O(13)	C(11)	C(7)	111	112	113
C(7)	C(11)	1.52	1.51	1.52	C(8)	C(7)	C(6)	84	86	85	O(13)	C(11)	O(12)	124	125	125
C(8)	O(9)	1.24	1.23	1.23												
C(11)	O(12)	1.19	1.19	1.19												
C(11)	O(13)	1.33	1.30	1.31												

[a] R = Br for compounds 3, 4; R = CH_3 for compound 2.

with the degree of nonplanarity of the β-lactam nitrogen atom.[6b]

The pyramidal character of the β-lactam nitrogen of compounds **2–4** is reflected in the measurements given in Table IIIC. Not surprisingly, the deviations for all three β-lactams lie well below the range observed for active compounds. If the variation among the three β-lactams can be taken as a rough indication of the magnitude of the effect of peripheral groups on skeletal structure, then the deviation from planarity for the cephalosporin analog **15**[7] would be expected to lie approximately in the range found for β-lactams **2–4**, that is, below the range apparently required for activity. The observed inactivity of **15** accordingly can be viewed as consistent with the proposed correlation of biological activity with the pyramidal character of the β-lactam nitrogen.

Table III

Compd	2	3	4
A. Planarity of β-Lactam Ring[a]			
Atom, deviation, Å			
N(1)	−0.009	−0.045	0.000
C(6)	0.008	0.038	0.000
C(7)	−0.007	−0.037	0.000
C(8)	0.009	0.044	0.000
O(9)	0.071	0.151	0.002
C(11)	−1.317	−1.311	1.224
B. Dihedral Angles Involving the Ring Fusion			
Dihedral angle, deg			
7–8–1–2	163.7	166.1	166.7
7–6–1–2	166.2	169.0	169.0
8–1–6–5	121.3	115.3	121.7
8–7–6–5	111.6	104.0	110.1
C. Pyramidal Nature of N(1)[b]			
Derivation, Å			
N(1)	−0.121	−0.143	0.089
C(11)	−1.103	−1.231	1.411

[a] Atoms 1, 6, 7, and 8 were used to define the least-squares plane. Atoms 9 and 11 were given zero weight. Atom 11 serves to define the positive and negative directions. [b] Atoms 2, 6, and 8 were used to define the plane. Atoms 1 and 11 were given zero weight. Atom 11 serves to define the positive and negative directions.

The recently synthesized cephalosporin analog **16** has been shown to have antimicrobial activity comparable with the activity of cephalothin.[8] From the above point of view, a deviation from planarity about the β-lactam nitrogen of 0.24–0.40 Å, probably close to 0.30 Å, would be predicted. This increased nonplanarity undoubtedly would result from introduction of the C(2)–C(3) double bond into the six-membered ring.

Shift Reagent Analyses. The β-lactam esters **7** and **8** contain two functional groups which might coordinate with a shift reagent: the lactam and ester carbonyls. If there is any preference for coordination at the ester carbonyl, then the distance from the lanthanide atom to the bridgehead proton would be greater in 7β-methoxycarbonyl isomer **8** than in 7α-methoxycarbonyl isomer **7**. If the angle dependence of the lanthanide induced shifts (LIS) is negligible, then the simplified McConnell–Robertson relationship suggests that the difference in distance will be reflected linearly in a difference in the induced shift for the bridgehead proton.[9-11] Accordingly, we examined the behavior of $Eu(dpm)_3$ and $Eu(fod)_3$ in order to ascertain their utility in stereochemical studies of α,α-disubstituted β-lactams.

Initial studies with $Eu(fod)_3$ indicated that this reagent differentiates only insignificantly between the isomers **7** and **8**; however, use of $Eu(dpm)_3$ led to significant differences in the induced shift for the bridgehead proton which will be considered later. Our interpretation of the behavior of the β-lactams **7** and **8** in the presence of shift reagents rests on a suggestion of apparent changes in preferred coordination site depending upon both shift reagent and solvent. A position of preferred coordination is in turn inferred from relative induced shifts for various substrate protons. The actual coordination site is of no concern, since we are interested only in changes in apparent coordination site relative to other potential sites.

In the general structure **17** the protons of particular interest are those attached to C-2 (H-2α and H-2β) and to the bridgehead carbon (H-6). Signals for all three protons have been assigned[7] on the basis of line shape, the anisotropic effect of the lactam carbonyl on the chemical shifts for the C-2 protons, and comparison with spectra of similar compounds.[13] In addition, we have confirmed the H-6 assignment by spin decoupling experiments with ester **5** in the presence of $Eu(fod)_3$.[5]

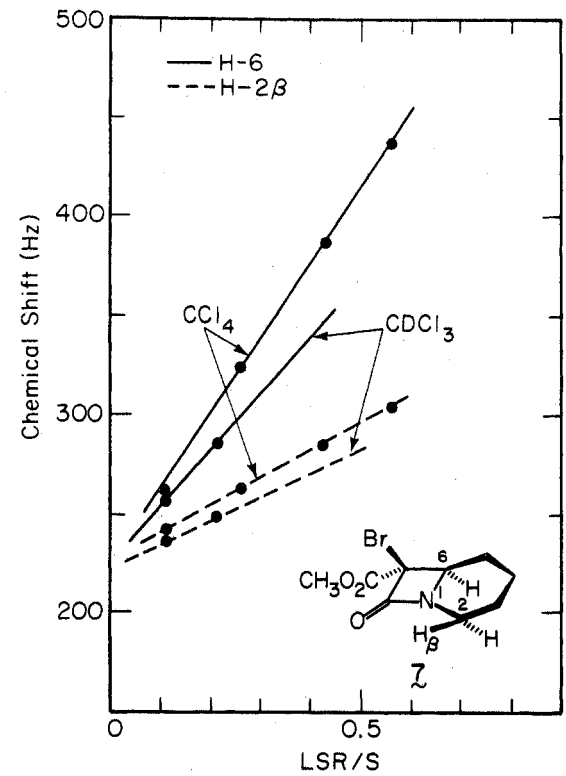
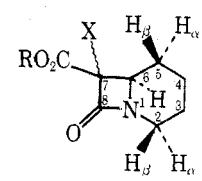


Figure 4. Lanthanide induced chemical shifts for H-6 and H-2β of **7** in $CDCl_3$ and CCl_4 as a function of increasing $Eu(dmp)_3$ concentration: $[7]_{CDCl_3} = 0.30\ M$, $[7]_{CCl_4} = 0.16\ M$.



17

In Figures 2 and 4, the induced shift for H-6 is much greater than the roughly comparable shifts seen for H-2α and H-2β, suggesting that with $Eu(dpm)_3$ a site of significant coordination is the ester carbonyl. As expected for europium coordination at the ester, the induced shift for H-6 was found to be greater for 7α-methoxycarbonyl isomer **7** than for 7β-methoxycarbonyl isomer **8**.[5] However, the magnitude of this difference was not large and was found to be comparable to the variance in the ratio of H-2β/H-6 shifts seen for **5** and **7** with $Eu(fod)_3$, indicating significant sensitivity to the size of the substituent, X. The method thus appears to be useful only when both isomers are available for comparison and when the substituent, X, can be expected not to coordinate with the shift reagent.

Since the completion of these investigations, $Eu(fod)_3$ has been reported to be stable to carboxylic acids.[14] It was conceivable that use of the acids **3** and **4** with $Eu(fod)_3$ could at least attenuate the severe limitations on use of the ester, but it was found that $Eu(fod)_3$ was unstable to all of the acids **1–4**.[5]

Perturbation of the conformation of the fused six-membered ring of esters **5**, **7**, and **8** was detected in the presence of both $Eu(fod)_3$ and $Eu(dpm)_3$ by monitoring the line shape for H-6.[5] The example represented by these fused bi-

cyclic molecules is somewhat unique in that the conformationally mobile portion, the six-membered ring, is fused to an immobile portion, the four-membered lactam, with the shift reagent binding to the immobile portion and the bridgehead proton (H-6) available as monitor.

Although our intent was to determine the utility of shift reagents for defining the stereochemistry of α,α-disubstituted β-lactams, other features of the behavior of these fused ring β-lactams with shift reagents were evident. These features are the subject of the following comments.

Factors Affecting Complex Composition. In Figures 3[5] and 5 (for CCl_4), the induced shift for H-2β is seen to be greater than the comparable shifts seen for H-6 and H-2α, suggesting that with Eu(fod)$_3$ in CCl_4 the site of preferred coordination is the β-lactam carbonyl. In contrast, we found that with Eu(dpm)$_3$ in CCl_4 coordination at the ester carbonyl is significant. As illustrated in Figures 4 and 5, results in $CDCl_3$ are qualitatively unchanged with Eu(dpm)$_3$ but significantly different with Eu(fod)$_3$. For Eu(dpm)$_3$ the reduction in the absolute value of induced chemical shifts on change of solvent from CCl_4 to $CDCl_3$ can be attributed to greater solvent association with the shift reagent in $CDCl_3$,[9] but it is evident from comparison of relative slopes that a change in solvent has not affected significantly the site of preferred coordination. On the other hand, a similar comparison of relative slopes in Figure 5 indicates that for Eu(fod)$_3$ a change in solvent from CCl_4 to $CDCl_3$ has altered significantly the apparent average position of the europium atom. This new position can be viewed as an average between the two previously inferred positions.

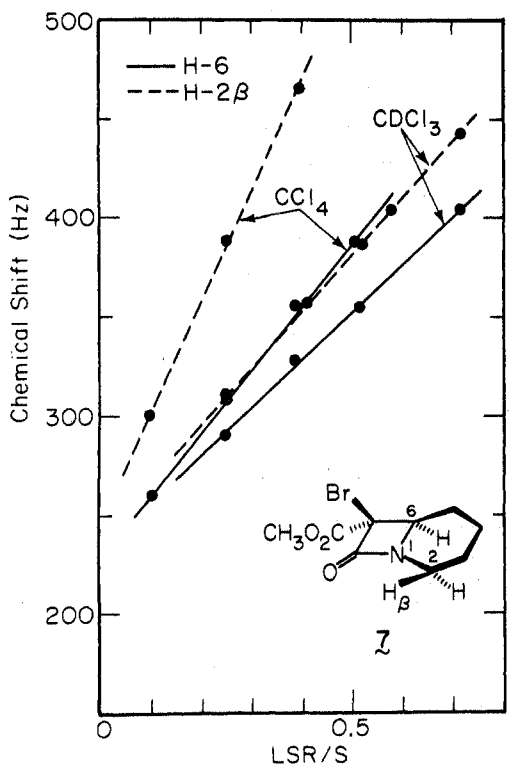


Figure 5. Lanthanide induced chemical shifts for H-6 and H-2β of **7** in $CDCl_3$ and CCl_4 as a function of increasing Eu(fod)$_3$ concentration: $[7]_{CDCl_3} = 0.38\ M$, $[7]_{CCl_4} = 0.30\ M$.

These data suggest the importance of a fundamental difference between the two shift reagents, and we propose that the apparent change in coordination site can be attributed primarily to a difference in type of shift reagent–substrate complex.[15] The results with Eu(dpm)$_3$ are readily accommodated by the 1:1 monomeric complex usually proposed for this reagent. The lactam carbonyl would be expected to be more basic than the ester carbonyl, and the available data indeed suggest that amides are stronger donors than esters.[9] Preferred coordination at the lactam is thus expected and chelation with the ester carbonyl would introduce the observed differentiation between isomers.[17] However, it is evident in comparison that coordination at the ester is negligible with Eu(fod)$_3$. To account for this result and for the difference in solvent effects, we suggest that Eu(fod)$_3$ in CCl_4 forms with these fused ring β-lactams a 2:2 bridged complex in which each substrate molecule functions as a bridging ligand between the two europium atoms.[18] In such a bridged, eight-coordinate complex, chelation by substrate is not possible, and a preference for coordination at the more basic lactam carbonyl is viewed as the dominant force.[19]

Support for the proposal of this rather exclusive difference in complex structure can be drawn from a number of considerations.[20] The preponderance of evidence suggests that Eu(dpm)$_3$ is monomeric in solution, regardless of solvent and concentration. On the other hand, Eu(fod)$_3$ forms aggregates whose concentrations increase in the order chloroform, carbon tetrachloride, *n*-hexane, self-association being negligible in $CHCl_3$ but quite significant in CCl_4.[21] It also appears, as previously mentioned, that for Eu(dpm)$_3$ the principal complex formed between reagent and substrate is a monomeric 1:1 adduct; but for the fod reagents, a variety of complexes has been suggested, including the bridged complex proposed above.[9,18,20]

One property in particular appears to provide a unifying explanation. That is the varying tendency of europium to undergo coordinative expansion depending upon its acidic character. The basics of the argument have been presented[20] with the implication that the dominating difference between Eu(fod)$_3$ and Eu(dpm)$_3$ with regard to self-association is the increase in the tendency of the europium atom toward coordinative expansion caused by a change in ligand from dpm to the much more electron-withdrawing fod. A preference toward eight-coordination instead of seven-coordination has also been noted.[20] In this context Eu(dpm)$_3$, with its reduced tendency toward coordinative expansion and its large effective size, is viewed as having an aversion toward oligomer formation and a preference for only 1:1 substrate adducts; whereas Eu(fod)$_3$, with its increased tendency toward coordinative expansion and its reduced effective size, prefers oligomer formation and other than monomeric 1:1 substrate adducts, all of these latter complexes being eight-coordinate if possible. It is then reasonable to propose that Eu(fod)$_3$–nonpolar substrate adducts of apparent 1:1 composition in CCl_4 are best represented by an eight-coordinate 2:2 bridged complex.[22]

The solvent effect on Eu(fod)$_3$ behavior can be explained using the same argument. The change in medium polarity on going from CCl_4 to $CDCl_3$ can stabilize the polarity introduced by the fod ligands, in this way reducing the tendency toward coordinative expansion. The result is reduced self-association[21] and a proposed increase in the presence of monomeric 1:1 substrate adducts as chelates. The data for **7** and Eu(fod)$_3$ in $CDCl_3$ can accordingly be viewed as reflecting an equilibrium between a bridged complex and a monomeric 1:1 chelated complex.

No change in LIS was seen with *n*-hexanoic acid and Eu(fod)$_3$ on change of solvent from CCl_4 to $CDCl_3$.[5] This result is expected if *n*-hexanoic acid is considered to provide polarity sufficient for eradication of the tendency of Eu(fod)$_3$ toward self-association, thus allowing the acid to form with Eu(fod)$_3$ a monomeric complex in either solvent. Consequently, even in CCl_4, it appears likely that for Eu(fod)$_3$ there is an undefined range with regard to sub-

strate polarity within which there will exist both a bridged and a monomeric complex. To extract quantitative information about substrate structure by use of the McConnell–Robertson relationship it is necessary that there be only one complex in solution. It therefore appears that the utility of $Eu(fod)_3$ for structural studies of this type is quite limited.

Experimental Section

X-Ray Analysis of 2–4. The crystal structures of compounds 2–4 were concluded in a routine manner. Since all three analyses were similar, they will be reported together. Suitable crystals were grown from appropriate solvents (see Table VII) by the slow evaporation technique. The crystals were surveyed and 1 Å intensity data sets (maximum $\sin\theta/\lambda = 0.5$) were obtained on a Syntex P1 diffractometer using copper radiation (λ = 1.5418 Å) at 22°C. Crystal density was measured by the flotation technique in aqueous zinc chloride. Final unit cell dimensions were obtained using a least-squares fit of ten high angle reflections ($2\theta > 40°$). The diffractometer was equipped with a graphite incident beam monochromator mounted in the perpendicular mode. During data collection a θ–2θ scan technique was employed, the scan rate was 2°/min in 2θ, the scan range was 1.0° above $K\alpha_2$ and 1.0° below $K\alpha_1$, and the background was counted for half the scan time on each side of the peak. A single check reflection was monitored every 30 reflections and indicated no crystal damage since it was reproducible within counting statistics.

The diffractometer output was processed using subprograms of the CRYM crystallographic computer system.[23] The processing included corrections for background and for Lorentz and polarization effects. The polarization effect due to the graphite monochromator was included in these corrections.[24] No corrections were made for absorption. The data processing also included calculation of the F^2 value and its standard deviation for each reflection. The standard deviations were assigned on the basis of the equation

$$\sigma^2(I) = S + \alpha^2(B_1 + B_2) + (dS)^2$$

where S is the scan count, B_1 and B_2 are the background counts, d is an empirical constant equal to 0.02, and α is the scan time to total background time ratio. All intensities with a value less than two times the standard deviation were set equal to zero with zero weight. Finally, the data sets were placed on an approximately absolute scale by means of Wilson statistics.

Determination of Structure and Refinement. Trial structures for compounds 3 and 4 were obtained by conventional Patterson and Fourier techniques. In both cases the first electron density map revealed every nonhydrogen atom. A trial set of phases for compound 2 was obtained through the reiterative application of Sayre's equation.[25,26] A trial structure was obtained with the first E map. The trial structure for compounds 2 and 4 refined routinely to an acceptable R index. A difference Fourier was required in compound 3 to locate a water of crystallization. Upon the inclusion of the water molecule, refinement proceeded smoothly to an acceptable R index (see Table I). The latter stages of the refinement procedure included a full matrix least-squares treatment of coordinates, anisotropic temperature factors, and scale factor in one matrix. Methylene and methine hydrogen positions were calculated; all other hydrogen positions were located by difference Fourier techniques. While hydrogen positions were added to the structure factor calculations in the latter stage of refinement, their positions were not refined. The quantity minimized by the least-squares procedure was $\Sigma w(F_0^2 - F_c^2)^2$, where $w = 1/\sigma^2(F_0^2)$. Parameters pertinent to the refinement procedure are summarized in Table I. In each case a final difference Fourier revealed no missing or misplaced atoms.

Shift Reagent Studies. Materials. The acids 1–4 and the esters 5, 7, and 8 were prepared as described previously.[1] $Eu(dpm)_3$, obtained from Bio-Rad Laboratories, and $Eu(fod)_3$, obtained from Norell Chemical Co., were stored over $CaCl_2$ prior to use. Reagent grade CCl_4 (Mallinckrodt) and economy grade $CDCl_3$ (Bio-Rad) were used as solvents with Me_4Si as internal reference.

Sample Preparation. The substrates were dissolved in appropriate solvents, and weighed amounts of shift reagent were added in increments directly to the NMR tube.

NMR Measurements. Spectra were recorded on a Varian T-60 spectrometer and all shifts are given in hertz relative to Me_4Si. Decoupling experiments were carried out on a Varian HA-100 spectrometer, employing the frequency sweep mode.

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Registry No.—1, 42599-31-5; 2, 54409-84-6; 3, 54409-86-8; 4, 54409-87-9; 5, 53618-26-1; 6, 54409-85-7; 7, 42599-40-6; 8, 42599-41-7; $Eu(dpm)_3$, 15522-71-4; $Eu(fod)_3$, 17631-68-4.

Supplementary Material Available. Detailed discussion of proton signal assignments; the use of $Eu(dpm)_3$ for the determination of stereochemistry (including Figures 2 and 3, from which the data in Figures 4 and 5 with regard to studies in CCl_4 were taken); limitations on the use of $Eu(fod)_3$ with carboxylic acids and the conformational equilibrium perturbation; Table IV of coupling constants for H-6 as a function of increasing [LSR]; and Tables V, VI, and VII listing atomic parameters will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Business Office, Books and Journals Division, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.50 for photocopy or $2.50 for microfiche, referring to code number JOC-75-3208.

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