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Unexpected Effect of Shift Reagents on Diastereotopic Protons in Some β-Lactams.[1]

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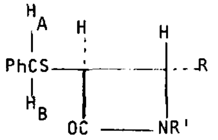
The chemical shift of diastereotopic protons should be non-equivalent in general, but in some molecules of low asymmetry and in certain solvents this non-equivalence may be too small to be observable on a 60 MHz NMR spectrometer. For example. the methylene group of the phenylacetyl side chain of penicillin G (7) is resolved into an AB quartet at 250 MHz but not at 100 or 60 MHz[2] Since lanthanide induced shifts (LIS) are believed to be dependent on the distance of a proton from the metal as well as a certain internuclear angle[3-8], the addition of a shift reagent could alter the chemical shift of diastereotopic protons to different extents and modify the degree of this non-equivalence.

The spectrum of (1a)[9] in $CDCl_3$ solution shows a single peak at τ6.05 for the diastereo topic protons H_A and H_B. The addition of Eu $(DPM)_3$,$Yb(DPM)_3$,$Eu(FOD)_3$ or $Pr(FOD)_3$ leads to the appearance of an AB pattern (J=13 Hz), the non-equivalence of the chemical shift of H_A and H_B increases with the progressive addition of the lanthanide reagent. The geminal coupling constant remains unaltered at different concentrations of the shift reagent. Similar results were obtained with 1b and 1c[10]

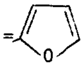
In the PMR spectrum of (2),[10] the diastereotopic protons are isochronous and they continue to be so even on the addition of large amounts of $Eu(FOD)_3$ and $Pr(FOD)_3$ reagents. An unexpected situation arises in the case of (3),[10] (5)[11] and (6)[12] in which H_A and H_B are slightly non-equivalent and produce an AB pattern. Upon the addition of $Eu(FOD)_3$ in small increments the non-equivalence gets smaller and eventually a singlet is observed for two protons. Additional reagent causes the singlet to shift to lower field but it does not resolve itself into an AB pattern. Similar behavior is observed with $Eu(DPM)_3$ and $Yb(DPM)_3$. On the contrary, when $Pr(FOD)_3$ is the shift reagent, an AB pattern is displayed by the diastereotopic protons. Their non-equivalence in chemical shift is augmented by higher concentrations of the reagent.

In (4a) the slightly non-equivalent H_A and H_B protons appear as a complex multiplet centered around τ6.82. With the addition of 0.334 mole of Eu(FOD)$_3$/mole of (4a), the signals for the two protons are separated and appear as distinct multiplets centered around τ5.18 and 6.00; comparable to the resolution obtained on a 90 MHz spectrometer. Similar results were obtained with (4b). In the PMR spectrum of penicillin G methyl ester (7), the chemical shift of the proton at C-6 is more sensitive to Eu(FOD)$_3$ than the proton at C-5 indicating that the lanthanide is mostly in the vicinity of the amide group of the side chain and/or the β-lactam ring and away from the ring sulfur. It was surprising therefore to observe that addition of 0.376 mole of Eu(FOD)$_3$/mole of (7) or 0.348 mole of Pr(FOD)$_3$/mole of (7) failed to convert to an AB quartet, the signal for the methylene group of the side chain of penicillin G methyl ester.

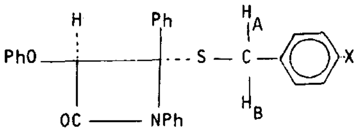
We are unable at present to account for the unexpected LIS observed nor can we offer any explanation for the difference in the behavior of Eu and Pr shift reagents. It is obvious, however, that the currently accepted theories about LIS are not entirely satisfactory and that caution must be exercised in drawing conclusions from LIS data.[13]



(1) a, R = R' = Ph

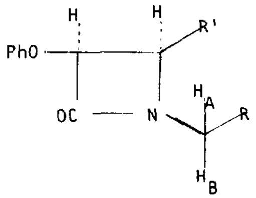
b, R =  ; R' = $C_6H_4OCH_3$(p)

c, R = $C_6H_4OCH_3$(p); R' = $C_6H_4CH_3$(p)

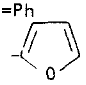


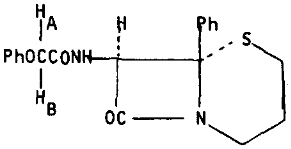
(2) X = H

(3) X = NO_2

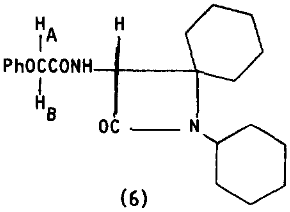


(4) a, R = C_2H_5, R' = Ph

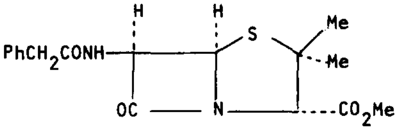
b, R = CH_3, R' = 



(5)



(6)



(7)

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13. All the new compounds reported in this communication were characterized by satisfactory elemental and spectroscopic analyses. The NMR spectra were recorded on a Varian A-60A spectrometer operating at 60 MHz using TMS as an internal standard.