^{17}O NMR SPECTROSCOPY OF LACTAMS

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Abstract - Natural abundance ^{17}O nmr spectroscopic data for 36 lactams acquired in acetonitrile at 75°C are reported: relationships between ^{17}O chemical shift and structure are discussed.

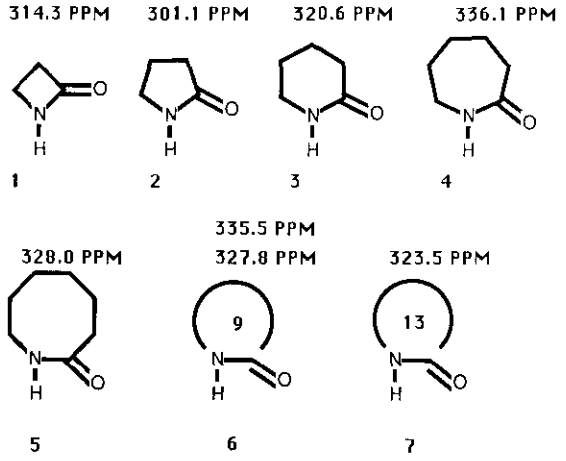
The chemistry and spectroscopy of the amide functional group has been and continues to be intensely studied, in large part due to its importance in determining the structure of proteins. Lactams serve as excellent models for peptides and proteins since the possible conformations of the amide functional group are limited by the cyclic structure. Lactams also provide the opportunity to study *cis*- and *trans*-amide configurations since small-ring lactams are geometrically forced into a *cis*-configuration and large-ring lactams assume the *trans* configuration of acyclic amides.[1,2] The number of applications of ^{17}O nmr spectroscopy to a wide variety of structural questions is growing rapidly.[3] Recent reports have shown that ^{17}O chemical shift data correlates well with torsion angles for a wide range of functional groups[4-6] including amides.[7,8] In rigid planar amides and imides steric interactions produce large downfield shifts which parallel bond angle deformations and which correlate with local repulsive van der Waals energies.[9,10] Consequently, it appears that ^{17}O nmr spectroscopy should be a sensitive method for study of structural variations of lactams and it provides a method to directly probe the oxygen atom of the amide functional group. A number of nmr investigations of lactams have appeared including ^{13}C nmr studies,[11-14] ^{15}N nmr investigations[11,12] and limited ^{17}O studies of 5-membered ring lactams.[9,12] The closely related thiohydantoins have also been studied by ^{17}O nmr spectroscopy.[15]

This communication reports ^{17}O chemical shift data for 36 lactams ranging in ring size from 4 to 13. Included in this report are data on 12 5-membered ring lactams and 19 6-membered ring lactams which provide some insight into the influence of structure variation on the ^{17}O chemical

shifts of these classes of lactams. The ^{17}O nmr data for the lactams determined, at natural abundance, from 0.5 M solutions in dry acetonitrile at 75°C are listed below. The ^{17}O nmr chemical shifts range from approximately 265 ppm for lactams in which the carbonyl group is delocalized by extensive conjugation to approximately 365 ppm for lactams in which the carbonyl group is partially electronically isolated from the amide nitrogen. Analysis of chemical shift differences with structure variations for lactams must take into account a hydrogen-bonding component; this is especially the case since at the concentrations required for ^{17}O nmr studies lactams are known to be associated.[1,2] Hydrogen bonding with the carbonyl oxygen should result in an upfield shift of its ^{17}O nmr signal.[16-18] The effect of the amide N-H donation to another system upon the shift of the donor amide carbonyl is not easily discerned.[19,20] Consequently, the net effect of differential hydrogen bonding is difficult to determine. Appropriate caution in interpretation of small chemical shift differences for lactams containing N-H groups thus should be observed.

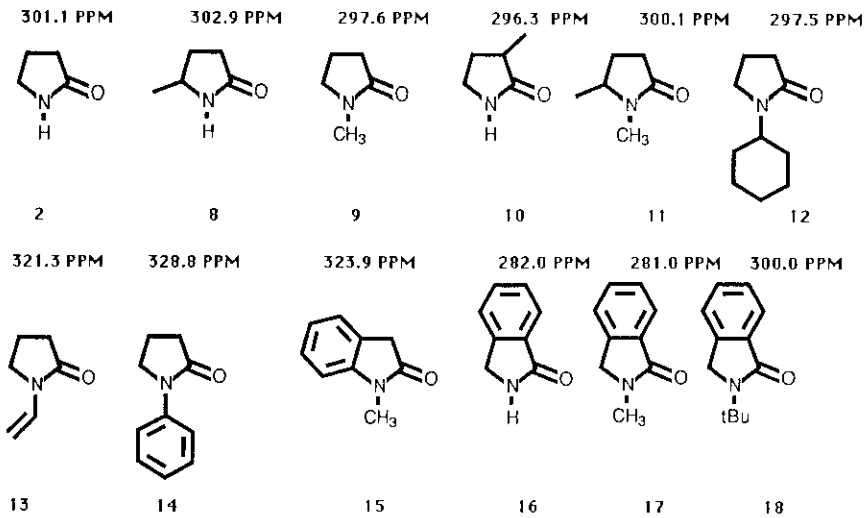
Scheme 1 contains seven lactams ranging in ring size from 4-13. The small ring lactams, ring size 4 to 8, give chemical shifts ranging from 301 to 336 ppm and showed no monotonic relationship with ring size which was also the case for their ^{15}N data.[11] Two signals for the 9-membered ring lactam **6** were observed for the *cis/trans* geometric pair.[1,2] Further study is required to assign the two signals to the corresponding isomers. These two signals were separated by approximately 8 ppm which is almost 3 times greater than the separation noted in their ^{15}N spectra.[11] The signal for the large ring lactam **7** occurred at 323 ppm and is in the region of simple (*trans*) amides.[19] It is apparent that ^{17}O nmr spectroscopy provides an alternative method for study of *cis/trans* relationships in lactam systems.

SCHEME 1



Scheme 2 contains a series of substituted 5-membered ring lactams. Substitution of an alkyl group at the 5-position of the lactam ring (**8**) has a small deshielding effect, whereas α-substitution (**10**) causes a 5 ppm shielding shift. As a result of comparison of the ^{17}O nmr chemical shifts of (**9-12**), it is clear that substitution of an alkyl group on the nitrogen atom which does not make large steric demands on the carbonyl group does not have a pronounced effect on the chemical shift. However, large groups such as the t-butyl group (compare **17** and **18**) cause significant downfield changes in the chemical shift. The signal for the *t*-butyl compound **18**, as noted, experiences a large downfield shift relative to **17** and doubtlessly reflects a role by repulsive van der Waals interactions.[9,10] In this study, the groups capable of conjugation with the amide group of the 5-membered ring lactams when attached to nitrogen (**13-15**) all result in downfield shifts of the carbonyl ^{17}O nmr signal by 25-30 ppm compared to the parent *N*-methyl compound **9**. This result is consistent with the electronic isolation of the carbonyl group from the nitrogen atom by reduction of availability of the nitrogen lone-pair for delocalization over the carbonyl group and reflects an increase in double bond character of the amide carbonyl group. The two compounds, **16** and **17**, have a benzene ring fused to the 5-membered lactam ring in such an arrangement that delocalization of the carbonyl group is expected. An upfield shift of approximately 16 ppm is noted for the signal of **17** compared to that of **9** which is consistent

SCHEME 2

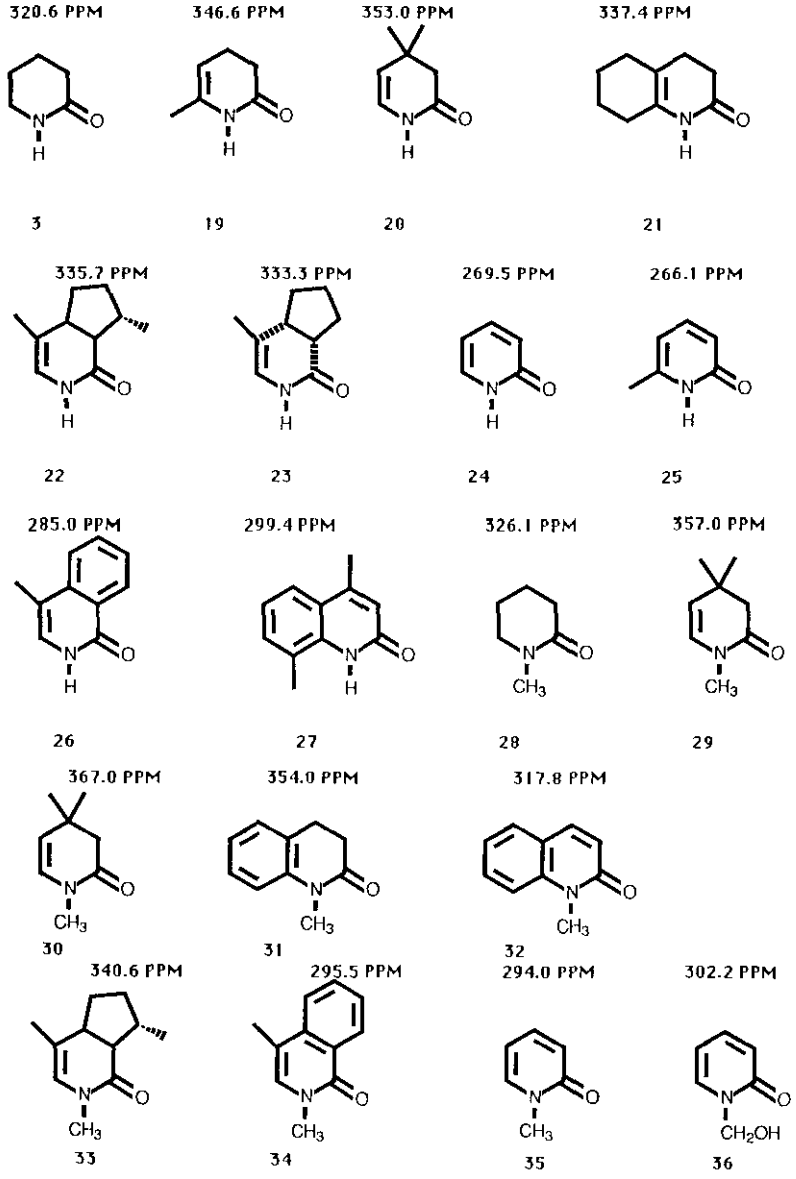


with a decrease in double bond character for the lactam carbonyl. A similar effect was noted for the ^{17}O nmr data for the pyrrolizin-3-one system.[21]

Scheme 3 contains the structures and the corresponding ^{17}O nmr data for 6-membered ring lactams. The structural variations in this series of lactams includes *N*-substitution, fused ring

systems, as well as incorporation of double bonds into the lactam ring. A large chemical shift range, from 266 to 367 ppm, is noted for this series. Introduction of groups which interact with the amide link by conjugation cause either shielding or deshielding of the carbonyl signal depending upon whether the group is in direct conjugation with the nitrogen (enelactams) or the carbonyl of the amide group. For example, enelactams **29-31** have double bond containing units which are attached to nitrogen and which are also isolated from the carbonyl group. These enelactams exhibit ^{17}O nmr signals downfield compared to the *N*-methyl piperidone (**28**), just as was noted

SCHEME 3



above for similar 5-membered ring lactams. However, compounds in which double bond systems are in conjugation with the amide carbonyl, **32, 34-36**, show substantial upfield shifts, reflecting the increased single bond character of their carbonyl groups as a consequence of delocalization. The results for these types of 6-membered ring lactams are also consistent with the data for the analogous 5-membered ring lactams. Substantial ^{17}O nmr chemical shift differences are noted between the enelactams **19-21**. In addition to conventional γ and δ effects, conformational changes may be making significant contributions to the shift differences. Further study involving systematic changes of structure are required to sort out the origin of these shift differences for these types of enelactams. It is clear from the results reported here that the carbonyl ^{17}O nmr chemical shift is quite sensitive to structural changes for lactams and the ^{17}O nmr method holds considerable promise for structural analysis of lactams and related compounds.

EXPERIMENTAL

The syntheses of the lactams (**19, 20, 22, 23, 26, 29, 30, 33, 34**) are described in the Ph.D. dissertation of D.W.S. at O.S.U; lactams **15** and **31** were synthesized by N.P. at O.S.U.; the remaining lactams used in this study were commercially available from Aldrich. The ^{17}O nmr spectra were recorded on a Varian VXR-400 spectrometer equipped with a 10 mm broad-band probe operated at 54.22 MHz. All spectra were acquired at natural abundance at 75°C in dry acetonitrile (Aldrich) containing 1% of 2-butanone. The concentration of the lactams employed in these experiments was 0.5 M. The signals were referenced to external deionized water at 75°C. The 2-butanone resonance (558$\pm$1 ppm) was used as an external check on the chemical shift measurements for these compounds. The instrumental settings were: spectral width 35 kHz, 2 K data points, 90°C pulse angle (40 ms pulse width), 300 ms acquisition delay, 29 ms acquisition time; typically 30,000 to 50,000 scans were required. The spectra were recorded with sample spinning and without lock. The signal-to-noise ratio was improved by applying a 25 Hz exponential broadening factor to the FID prior to Fourier transformation. The data point resolution was improved to $\pm$0.1 ppm by zero filling to 8 K data points. The reproducibility of the chemical shift data is estimated to be $\pm$1.0 ppm.

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