^{13}C Nuclear Magnetic Resonance of *N*-Heterocycles. Part 2.[1] Natural Abundance Carbon-13 and Nitrogen-15 Nuclear Magnetic Resonance Studies of Δ^3- and Δ^4-Pyrrolin-2-ones and Model Compounds

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Carbon-13 and nitrogen-15 Fourier transform n.m.r. spectra of Δ^3- and Δ^4-pyrrolin-2-ones and their *N*-methyl and -acetyl derivatives, and those of succinimide, maleimide, pyrrolidin-2-one, piperidin-2-one, and 2-piperidone, have been measured and analysed. Carbon and nitrogen shifts are discussed in relation to charge density distributions and chemical reactivities for Δ^3- and Δ^4-pyrrolin-2-ones. Coupling constant values of these latter compounds are also reported.

Δ^3- AND Δ^4-PYRROLIN-2-ONES (3) and (6) are potential intermediates in the oxidation processes of natural and synthetic pyrrolic systems, and have been studied previously by proton n.m.r.[2] They and their *N*-methyl derivatives have been isolated during oxidations of pyrrole [2,3] and of methylpyrrole,[3] respectively. The high reactivity [3] of the parent compounds and the interesting pharmacological properties recently reported for Δ^3-pyrrolin-2-one [4] have prompted a new study by ^{13}C and ^{15}N n.m.r. spectroscopy, and a search for correlations between the n.m.r. parameters and, variously, the charge density distribution, the reactivity, and the pharmacological properties.

Only a limited number of cyclic compounds [5-8] have been studied by a combination of ^{13}C and ^{15}N n.m.r., despite the power of the alliance, mainly because of the difficulties of observing the latter spectra at natural abundance.[9] For non-cyclic molecules, such as amides, much more work has been reported.[10,11]

EXPERIMENTAL

The ^{13}C spectra (at 25.18 MHz) and the ^{15}N spectra (at 9.12 MHz), each at natural abundance, were recorded on a Varian XL-100-15 and a Bruker HFX-90 spectrometer, respectively. The single frequency, selective heteronuclear decoupling experiments for the determination of $^2J_{CH}$ and $^3J_{CH}$ were performed with 90 dB of decoupling power on the Gyrocode unit of the XL-100-15 instrument. The chemical shifts are given in p.p.m. downfield from internal Me_4Si for ^{13}C, and from external 5M-$NH_4^+NO_3^-$ in 2M-HNO_3 (in which the shift difference between the nitrogen nuclei is 354.1 p.p.m.) for ^{15}N spectra, and are accurate within ± 0.1 p.p.m. The concentrations used, with $[^2H_6]$acetone as solvent, were *ca.* 30% for the ^{13}C and 50% for the ^{15}N measurements, respectively, unless otherwise specified in Table 1.

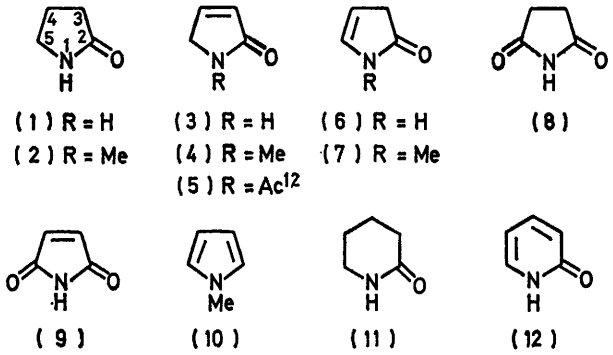
Δ^4-Pyrrolin-2-one (6) and the methyl derivative (7) were never isolated from solution,[2,3] since they are unstable. All the spectra were recorded using 9 : 1 mixtures of the Δ^3- and Δ^4-isomers in $[^2H_6]$acetone solution, under anhydrous conditions. The reactive Δ^4-isomer could then be preserved for a long time. The ^{15}N signal for (7) was, however,

TABLE 1

Values of ^{15}N and ^{13}C chemical shifts (p.p.m.) [a]

Compd.	N	C-2	C-3	C-4	C-5	CH_3	Others
(1)	95.0	179.4	30.6	21.3	42.7		
(2)	87.9	174.3	30.8	18.2	49.4	29.3	
(3)	94.5	175.5	127.6	147.6	49.5		
(4)	87.5	174.5	127.7	144.6	55.3	28.4	
(5)	146.7	170.5	127.4	149.0	51.5	24.2	169.7 [c]
(6)	120.4	180.8	37.1	105.1	130.9		
(7)	*b*	178	37.0	104.2	135.6		
(8)	155.4 [d]	179.0 [c]	30.2 [c]	30.2 [c]	179.0 [c]		
(9)	123.4	172.2 [c]	135.8 [c]	135.8 [c]	172.2 [c]		
(10)	121 [f,g]	121.7	108.4	108.4	121.7	35.4	
(11)	92.8	171.9	32.1	(23.1)	(21.8)		42.4 [i]
(12)	145 [g]	165.0 [h]	120.8 [h]	142.0 [h]	106.6 [h]		136.1 [i]

[a] Downfield from NH_4^+ (external 5M-NH_4NO_3) for ^{15}N, and from internal Me_4Si for ^{13}C; solvent is $[^2H_6]$acetone; concentrations 50% for ^{15}N measurements and 30% for ^{13}C. [b] Not detected. [c] Acetyl CO frequency. [d] In $(CD_3)_2SO$; in H_2O, the value is 155 p.p.m.[9] [e] Concn. *ca.* 10%. [f] In MeOH (50%). [g] These values are derived from those quoted by Witanowski [9] by using the observed difference in our NH_4NO_3 sample between its two nitrogen shifts, *viz.* 354.1 p.p.m. [h] Assigned in $(CD_3)_2SO$ by Takeuchi *et al.*[12] [i] C-6 frequency.



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[9] E. W. Randall in 'Nitrogen N.M.R.,' eds. M. Witanowski and G. A. Webb, Plenum Press, London, 1973.
[10] M. Witanowski, L. Stephaniak, and H. Januszwski in 'Nitrogen NMR,' eds. M. Witanowski and G. A. Webb, Plenum Press, London, 1973.
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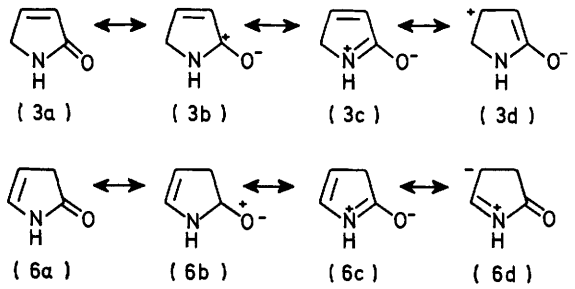
[12] Y. Takeuchi and N. Dennis, *Org. Magnetic Resonance*, 1975, **7**, 244.

not detected, presumably because of an n.m.r. saturation effect, even after addition of tris(acetylacetonato)chromium as a relaxation reagent to the solution.

RESULTS AND DISCUSSION

^{13}C *Results*.—Table 1 shows that the differences between the olefinic C-4 and C-3 shifts are +20.0 and +16.9 p.p.m. for the unsubstituted compound (3) and for *N*-methyl-Δ^3-pyrrolin-2-one (4), respectively. These values are similar in sign and magnitude to the values for cyclopent-2-enone (+31.3) and cyclohex-2-enone (+21.4).[13] These differences (and the overall low field values for C-4 in comparison with normal shifts for olefinic carbon atoms) are characteristic of the conjugation of the double bond with the C=O group [structure (3d)]. This effect is also indicated by the magnitude of the shifts for C-2 (see below). These differences, however, are smaller than those for cyclopentenone, which shows that the additional possibility of such structures as (3c) in the amides affects the electron density distribution in the double bond. (This type of effect is sometimes referred to as competitive conjugation and is mentioned again below.)



The shifts of C-3 and C-4 are, unexpectedly, more sensitive to *N*-methylation [see (4)] than to *N*-acetylation [see results for (5)], despite the conjugative possibilities for the latter. This methylation effect is surprising, since a γ-effect is absent in model compounds: compare the C-3 shifts for 1-methylpyrrolidine (24.6) [14] and pyrrolidine (25.7),[15] and also those for 1-methylpyrrole (108.4) and pyrrole (108.2).[13]

An interesting observation is that the shift of the equivalent olefinic carbon atoms in maleimide (9) is the mean of the values of C-3 and C-4 in (3).

The behaviour of the C-4 shift in the Δ^4-pyrrolin-2-ones is in sharp contrast to its behaviour in the Δ^3-isomers. First, the movement of the double bond to the 4,5-position breaks its conjugation with the carbonyl, and restores the C-4 shift to its high-field value. Additionally a new conjugation with the nitrogen lone pair becomes possible, as in enamines. These two conjugations have different consequences for the charge density at C-4, and the result is a further shift to higher field in the Δ^4-compounds, which give values at even higher field than for pyrrole (108.2 p.p.m.).[13] The importance, in valence bond terms, of structure (6d), or alternatively the evidence for a high electron density at C-4 and a low density at C-5, enables one to rationalize the high reactivity [3] of (6) and (7).

The β-methyl effect at C-5 in the Δ^4-compounds is a 5.8 p.p.m. shift downfield, the normal direction for saturated centres, but the magnitude is smaller, *e.g.* +9.8 p.p.m. for pyrrolidine and its 1-methyl derivative. On the other hand the β-methyl effect at C-2 in the Δ^3-cases, (3) and (4), is an upfield shift and of about the same value (−1.0 p.p.m., *cf.* −1.0 and −0.7) as for formamide, *N*-methylformamide (s-*cis*-isomer), and *NN*-dimethylformamide. A shift in this direction is expected as a consequence of the blocking of hydrogen bonding by methylation. Since the β-methyl effect on the carbonyl carbon atom of cyclopentanone is +6 p.p.m.,[13] the effect of the hydrogen bonding in Δ^3-pyrrolin-2-one (3) must be *ca.* +7 p.p.m. A similar value for hydrogen bonding effects was deduced by Stothers for carboxylic acids.[13]

The C=O shift values are in the normal amide range (160—180 p.p.m.). The value for (3) shows a small (−3.9 p.p.m.) upfield shift with respect to that for (1), smaller but in the same direction as the conjugation effects found with αβ-unsaturated carbonyl compounds.[1] The same effect is absent in the pair of *N*-methyl derivatives (2) and (4), but is even more pronounced (−6.8 p.p.m.) for maleimide (9) *versus* succinimide (8). By contrast the presence of unsaturation αβ to the amide nitrogen such as in (6) or (7) does not affect the shift of the carbonyl carbon atom. This invariance may be quite a general effect, at least in the absence of complications such as hydrogen bonding, as shown for example by the same values found for dimethyl- *versus* phenylformamide.[14]

This interesting finding appears to contradict the conclusion drawn from i.r. results, which show that the introduction of a double bond or a second oxo-group α to the amide nitrogen produces a larger CO stretching frequency and (by inference) a higher CO bond order.[16,*] However it is consistent with the ^{15}N results discussed below. It implies that the involvement of the nitrogen lone pair in a second conjugation, additional to that involving the carbonyl, does not affect the situation at the carbonyl. Or in other words the idea so frequently used [17] that an increase in the possibility of enamine resonance structure, as for instance (6d), implies necessarily a decrease of the amide resonance in the amide bond [*viz.* structure (6)] does not apply in this case.

^{15}N *Results*.—The ^{15}N shift value for the five-membered

* The i.r. comparisons between pyrrolidin-2-one (1) (ν_{CO} 1 695 cm^{-1}), Δ^3-pyrrolin-2-one (3) (1 675 cm^{-1}) and, respectively, succinimide (8) (1 700 and 1 760 cm^{-1}) and maleimide (9) (1 700 and 1 760 cm^{-1}) are in line with that statement.

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[15] G. C. Levy and G. L. Nelson, ' Carbon-13 Nuclear Magnetic Resonance for Organic Chemists,' Wiley–Interscience, New York, 1972.
[16] L. J. Bellamy, ' Advances in Infrared Group Frequencies,' Methuen, London, 1969, p. 123.
[17] For example see R. Sweet in ' Cephalosporins and Penicillins,' Academic Press, New York, 1972.

ring lactam (1) varies slightly (*ca.* 4 p.p.m.) with the solvent and the concentration.* Variations with ring size and with geometry at the CN bond (*cis* or *trans*) are also of similar magnitude (*ca.* 9 and 2 p.p.m., respectively). The shift found for (1) is within 4 p.p.m. of the value for *N*-ethylacetamide (101 p.p.m.);[9] thus the ring closure (each has *cis*-geometry) has little effect.

The nitrogen shift is the same for (1) and (3), and for (2) and (4). We may conclude that in Δ^3-cases the conjugation between the αβ-double bond and the carbonyl group has no effect at the nitrogen atom. The simplest explanation is that neither the electron density at nitrogen nor the bond order at nitrogen is much affected. Again, therefore, the conjugations are not competitive, this time in the Δ^3-series.

By contrast the signal for the nitrogen in Δ^4-pyrrolin-2-one (6) occurs 20 p.p.m. to low field with respect to that in (1), the shift being close to the value for pyrrole.[7] This effect is even larger if an additional carbonyl group is introduced α to the amide nitrogen, for example in succinimide (8) as compared with (1), or in maleimide (9) or acetylpyrrolinone (5) as compared with (3). Even if we allowed for the possibility of some σ-effects, it is clear that the π-effects are important and that delocalization of the nitrogen lone pair is enhanced by the presence of αβ-unsaturation. We expect then a low electron density at the nitrogen in (5) and (6), in agreement with the calculations described later, and in the imides (8) and (9).

This supports the mechanism of alkaline hydrolysis of imides suggested[18] from kinetic results, which showed that the rate-determining step is the ionisation reaction, involving nucleophilic attack at the nitrogen. The enhanced localization of positive charge on the imide nitrogen, deduced from the ^{15}N shift values, should make nucleophilic attack easier at the nitrogen than at the carbon atom.

Charge Density Distribution.—The electron densities (Table 2) have been calculated by the CNDO method for Δ^3- and Δ^4-pyrrolin-2-ones (3) and (6) and for pyrrolidin-2-one (1), using values for bond lengths and bond angles available from the literature for similar compounds. Two structures have been considered for the derivative (1), which is conformationally mobile in solution, one of planar geometry (1a), and one of bent form (1b) obtained by moving C-4 out of the plane, with an angle of twist of 20°.

The trend of the charge density distribution is qualitatively in agreement with the n.m.r. results; *viz.* the electron density is less at C-4 than at C-3 in (3), whereas it is much greater at C-4 in the isomer (6). The nitrogen atom also has a very low electron density in (6) with respect to (1) and (3), whereas C-2 can be considered invariant (if we bear in mind the approximations of the method). The significant increase of negative charge on the oxygen for (3) with respect to (1) and (6) is consistent with the conjugation of the carbonyl group with the αβ-double bond.

Coupling Constants.—The one-bond and long-range C,H-coupling constants have been obtained, by first-order analysis, for compounds (3)—(7) (Table 3). For the less abundant Δ^4-isomers only the one-bond couplings have been measured owing to the low concentration of these products in the mixtures. The magnitudes of the reported interactions lie in the expected ranges.[13,19] Possibly ^2J[C(2),H(3)] and ^2J[C(4),H(5)] are negative in sign.

TABLE 2

CNDO calculated charge densities

Compd.:	(1)			(3)		(6)	
		(1a) *	(1b) *				
	q_π	q_{tot}	q_{tot}	q_π	q_{tot}	q_π	q_{tot}
N-1	1.799 6	5.220 7	5.222 9	1.784 6	5.209 7	1.734 6	5.166 6
C-2	0.794 4	3.638 3	3.634 5	0.795 3	3.643 2	0.801 8	3.642 3
C-3	0.976 9	4.058 4	4.065 9	1.027 4	4.068 8	0.969 2	4.052 3
C-4	0.964 5	3.994 3	3.989 9	0.944 5	3.979 8	1.134 2	4.089 5
C-5	0.960 8	3.896 1	3.900 9	0.967 3	3.904 9	0.978 2	3.897 7
O-2	1.414 2	6.365 4	6.366 5	1.453 0	6.393 1	1.404 3	6.352 9

* (1a) planar structure; (1b) bent structure.

TABLE 3

C,H-Coupling constants (Hz) for some pyrrolin-2-ones [a]

	(3)	(4)	(5)	(6)	(7)
^1J[C(3),H(3)]	175.4	176.0	178.5	133.0	128
^1J[C(4),H(4)]	174.2	175.0	176.0	179.5	180.0
^1J[C(5),H(5)]	142.2	142.0	146.0	185.0	180

	(3)	(5)		(3)	(5)
^2J[C(2),H(3)]	8.0 [b]	8.0	^3J[C(2),H(4)]	11.0 [b]	12.0
^2J[C(3),H(4)]	3.0	3.5	^3J[C(3),H(5)]	3.0	3.5
^2J[C(4),H(3)]	4.0	2.5	^3J[C(3),NH]	6.0	
^2J[C(4),H(5)]	5.0	6.0	^3J[C(4),NH]	5.0	
^2J[C(5),H(4)]	9.0	8.5	^3J[C(5),H(3)]	9.0	8.5
^2J[C(5),NH]	5.6				

[a] Values within ±0.5 Hz except for C-2. [b] The values are within ±1.0 Hz, because the C-2 signal is broad owing to the presence of other couplings ($J \leqslant 2$ Hz), which were not measured.

Conclusions.—Values of ^{13}C and ^{15}N chemical shifts give a reasonable qualitiative correlation with the calculated charge density distributions. In particular for Δ^3-pyrrolinones (3)—(5) there is evidence for conjugation of the carbonyl with both the αβ-double bond and the nitrogen atom.

In the Δ^4-pyrrolinones there is considerable delocalization of the nitrogen lone pair over both the olefinic and the carbonyl centres. This gives both a low electron density at the nitrogen and a high density at C-4, which explains the high observed reactivity of the enamine type[3] for these compounds. The introduction of a double bond or a second carbonyl group α to the amide nitrogen of (1) apparently does not affect the charge density at C-2. The reactivity in the Δ^3-series, and perhaps also the pharmacological properties recently

* This range is for the solvents [$^2H_6$]dimethyl sulphoxide, [^2H]chloroform, [$^2H_6$]acetone, and trifluoroethanol. Strong acids give values which are shifted by as much as 15—20 p.p.m. (E. H. Curzon and E. W. Randall, unpublished results).

[18] O. H. Wheeler and O. Rosado, in ' The Chemistry of Amides,' ed. J. Zabicky, Wiley, New York, 1970.

[19] G. Fronza, A. Gamba, R. Mondelli, and G. Pagani, *J. Magnetic Resonance*, 1973, **12**, 231.

demonstrated for (3),[4] may well involve the proposed[2] tautomeric equilibrium with the Δ^4-compounds, under catalytic conditions, which in the pharmacological case may involve the substrate.

The deduced low-electron density at the nitrogen of succinimide provides supporting evidence for the suggested mechanism of alkaline hydrolysis of imides,[18] which is particularly interesting in view of the nature of the procedures for peptide degradation.

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