Transannular Interactions in Difunctional Medium Rings. Part 3.[1] ^{13}C and ^{17}O Nuclear Magnetic Resonance Studies on Cyclic Amino Ketones

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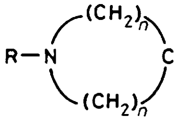
Transannular interactions of alkylamino and carbonyl groups in medium rings have been studied by ^{13}C and ^{17}O n.m.r. spectroscopy. In amino ketones with six-, eight-, ten-, and twelve-membered rings ^{13}C and ^{17}O chemical shifts of the carbonyl group are changed up to 11 (^{13}C) or 81 p.p.m. (^{17}O) relative to the signals of the corresponding cycloalkanone. The observed effects, $\Delta\delta_C$ and $\Delta\delta_O$, are linearly correlated and are obviously not only caused by transannular homoconjugation. Therefore, in contrast to i.r. and p.e. spectroscopic data, only qualitative conclusions regarding transannular interactions are possible. $\Delta\delta_C$ Values of 1-alkylhexahydroazocin-5-ones (**2a**—**d**) are linearly correlated with the first ionization potentials of these compounds.

In the preceding papers of this series[1,2] it has been shown that electronic interactions between functional groups in medium rings can be studied by photoelectron (p.e.) spectroscopy. In amino ketones (**1**)—(**4**) the n_0 orbital is a good measure of transannular interaction. Its energy changes linearly with the distance between the two functional groups in the range from 270 to 480 pm.[3] This behaviour corresponds well to the analogous bimolecular interaction of monofunctional molecules. Thus, from studies on this type of compound, information about reacting molecules close to the transition state can be obtained.



n	2	3	3	3	3	4	5
R	Me	Me	Et	Pr^i	Bu^t	Me	Me
	(**1**)	(**2a**)	(**2b**)	(**2c**)	(**2d**)	(**3**)	(**4**)

Although p.e. spectroscopy probably is the method of choice for the study of transannular interactions in molecules such as (**1**)—(**4**),[1-4] we found it also appropriate to investigate these compounds by other experimental methods. In this communication we wish to report our ^{13}C and ^{17}O n.m.r. studies with special emphasis on the question of how transannular effects can be ascertained by these methods. For this purpose chemical shifts of the nuclei of the carbonyl group in amino ketones (**1**)—(**4**) have been investigated.

Results and Discussion

^{13}C *N.m.r. Spectra.*—Nakashima and Maciel have shown that transannular interactions in heterocyclic eight-membered ketones can be detected by ^{13}C n.m.r. spectroscopy.[5] In Table 1 chemical shift data for the carbonyl group of the 1-alkylazacycloalkanones (**1**)—(**4**) are summarized together with the data of the corresponding cycloalkanones. ^{13}C N.m.r. spectra of the latter compounds and of 1-methylpiperidin-4-one (**1**) have already been studied by other authors,[6,7] but we have repeated these measurements under identical conditions as for (**2**)—(**4**), in order to obtain accurate values for the variation in chemical shifts due to electronic interactions.

Relative chemical shifts, defined as $\Delta\delta = \delta(\text{ketone}) - \delta(\text{amino ketone})$, are also given in Table 1. The parent cycloalkanones are used as reference compounds although it would have been preferable to refer to the corresponding alkylated cyclic ketones as 'isosteric' compounds. However, only marginal effects ($<|0.1|$ p.p.m.) on the $\Delta\delta$ values are to be expected since the substituents are at least four bonds away from the carbonyl group, but long-range effects due to geometrical distortions cannot completely be excluded.[8]

Table 1. ^{13}C And ^{17}O n.m.r. data (p.p.m.) of the carbonyl group for the amino ketones (**1**)—(**4**) and cyclic ketones (25% solutions in C_6H_{12})

Compound	δ_C	$\Delta\delta^a$	δ_O	$\Delta\delta^a$
Cyclohexanone	206.7		572.5	
1-Methylpiperidinone (**1**)	204.3	2.4	576.1	−3.6
Cyclo-octanone	212.5		578.8	
1-Methylhexahydroazocin-5-one (**2a**)	204.1	8.4	522.5	56.3
1-Ethylhexahydroazocin-5-one (**2b**)	205.7	6.8	534.7	44.1
1-Isopropylhexahydroazocin-5-one (**2c**)	206.5	6.0	534.2	44.6
1-(t-Butyl)hexahydroazocin-5-one (**2d**)	207.1	5.4	536.6	42.2
Cyclodecanone	209.7		575.7	
1-Methyloctahydroazecin-6-one (**3**)	198.6	11.1	494.3	81.4
Cyclododecanone	207.7		581.4	
1-Methyl-1-azacyclododecan-7-one (**4**)	207.4	0.3	585.8	−4.4

[a] $\Delta\delta = \delta(\text{ketone}) - \delta(\text{amino ketone})$.

From Table 1 variations of $\Delta\delta$ (*i*) with ring size [compounds (**1**), (**2a**), (**3**), (**4**)] and (*ii*) with substituent size (**2a**—**d**) are recognizable. The difunctional six- and twelve-membered-ring compounds [(**1**) and (**4**)] show only minor changes in the ^{13}C n.m.r. signals, whereas the eight- and ten-membered rings [(**2**) and (**3**)] reveal substantial $\Delta\delta$ values. This is in accordance with small to non-existent transannular interactions in the former and sizable effects in the latter ring systems.[1-3] However, there is no quantitative correlation between the ^{13}C n.m.r. and p.e.[2] or i.r.[9] spectroscopic data: according to the $\Delta\delta$ values, in the ten-membered-ring compound (**3**) there should be stronger interaction of the functional groups than in the eight-membered one (**2a**). It is, however, well established that the opposite is actually true.[1-3,9]

In order to explain these findings, several possibilities have to be considered. δ_C Values are dependent on various parameters, and often it is very difficult to evaluate their individual contributions.[10] Moreover, it is unknown whether these contributions are additive, co-operative, or counteracting.[8] There is a marked variation of CO-carbon shielding in cycloalkanones with ring size.[6] For some cyclic and acyclic

Table 2. Strain energies per ring atom (E_S/n, kJ mol^{-1}) for the most stable conformation of amino ketones (**1**), (**2a**), (**3**), (**4**) and cyclic ketones (MM2 results)

Compound	Conformation[a]	E_S/n
Cyclohexanone	C	2.45
1-Methylpiperidin-4-one (**1**)	C	2.46
Cyclo-octanone	BC	5.91
1-Methylhexahydroazocin-5-one (**2a**)	BC	7.09
Cyclodecanone	BCB	5.73
1-Methyloctahydroazecin-6-one (**3**)	BCB	4.70
Cyclododecanone	[3333]	3.56
1-Methyl-1-azacyclododecan-7-one (**4**)	[3333]	3.84

[a] Ref. 14.

ketones a linear correlation has been observed for δ_C values of the carbonyl group and n/π^* transition energies ΔE.[11] Stothers and co-workers[6] proposed conformational factors (α-bond eclipsing) to be responsible for the shielding of the carbonyl group. Langford *et al.*[12] suggested that additional factors such as angle strain should be taken into account. For these reasons we have investigated the strain energies of *N*-methylamino ketones [(**1**), (**2a**), (**3**), and (**4**)] and the corresponding ketones by MM2 calculations.[13] The results are given in Table 2.

For the cyclic ketones the chemical shifts of the carbonyl carbon atom (Table 1) and the calculated strain energies per ring atom (E_S/n) for the most stable conformation[1,3,14] show a rough linear correlation (r = 0.87), so undoubtedly a clear trend exists: high strain energy (E_S/n) leads to large δ_C values. Moreover, the data in Table 2 indicate that the amino ketone (**2a**) is more strained than cyclo-octanone, while (**4**) is less strained than cyclodecanone. Therefore, the variation of $\Delta\delta_C$ with ring size (Table 1) may be explained by a combination of through-space and strain effects.

By p.e. spectroscopy it has been shown that in 1-alkylhexahydroazocin-5-ones (**2**) transannular interaction is independent on the size of the substituent.[1] The relevant ^{13}C n.m.r. data of (**2a**—**d**) are included in Table 1. It is obvious that $\Delta\delta$ values decrease with increasing substituent size, which at first sight might be contradictory to the p.e. spectroscopic results. It has been supposed that the variation of the $\Delta\delta$ values of (**2a**—**d**) in C_6D_6 solution might at least partly be caused by solvent effects.[1] However, comparison with the results given in Table 1 indicates that the decrease of $\Delta\delta$ with substituent size is not solvent dependent.

As has been pointed out, a linear correlation was observed for δ_C values of the carbonyl group and n/π^* transitions of some cyclic and acylic ketones.[11] For difunctional medium rings it has been shown that transannular interactions of the functional groups lead to a strong absorption band in the 220—240 nm region.[15] This band is called a photodesmotic band, because the transition leads to a weak bond in the excited state between atoms not bonded in the ground state.[16] The wavelength of this band should be related to the energy of the highest occupied MO. Therefore, the $\Delta\delta_C$ values of (**2**) are supposed to be dependent on the energy of the n_N orbital.[17] Indeed, an excellent linear correlation (r = 0.99) between the first ionization potentials $E_i(n_N)$ [(**2a**) 8.13, (**2b**) 8.02, (**2c**) 7.96, and (**2d**) 7.88 eV][1] and $\Delta\delta_C$ values emerges indicating that for these compounds the variation of $\Delta\delta_C$ most likely is not caused by different transannular interactions:

$$E_i(n_N) = 0.08 \times \Delta\delta_C + 7.46\,(\mathrm{eV}).$$

Our MM2 calculations indicate that the non-bonded N···CO distance in compound (**3**) is *ca.* 45 pm longer than in (**2a**) and that this distance varies only slightly (max. 4.1 pm) in (**2a**—**d**). Since homoconjugation is distance-dependent, these findings support the argument that the $\Delta\delta$ values (Table 1) cannot be linearly proportional to the size of the transannular interaction.

In summary, it can be stated that δ_C data in a qualitative manner can be taken as a probe of homoconjugative transannular electron donation to the carbonyl group. Quantitative conclusions are not possible, because δ_C values are also dependent on other parameters.

^{17}O *N.m.r. Spectra.*—In a very qualitative manner ^{17}O chemical shifts can be taken as a probe of electronic density modifications in homologous series of compounds.[18] ^{17}O N.m.r. spectra of some cyclic amino ketones with six- and eight-membered rings, including compound (**2b**), have been investigated by Dahn *et al.*[19] Significant shifts of the ^{17}O signals relative to the ketones with equal ring size were observed and interpreted by transannular interactions.

The ^{17}O n.m.r. data of the amino ketones (**1**)—(**4**) as well as of the analogous ketones are collected in Table 1. The data of the latter compounds and of (**2b**) differ slightly from those given by Dahn *et al.*[19] because other solvents were used.

Relative chemical shifts, defined as $\Delta\delta = \delta(\text{ketone}) - \delta(\text{amino ketone})$, range from *ca.* -4 to *ca.* $+80$ p.p.m. The small values found for (**1**) and (**4**) reveal non-interacting functional groups, while from the large values for (**2**) and (**3**) strong transannular effects are indicated. As is already the case for the ^{13}C chemical shifts of the carbonyl carbon atom, the ^{17}O data also show a maximum for the ten-membered ring (**3**), although homoconjugation is greatest in the eight-ring homologue.[1—3,9] The explanation for this observation is most likely the same as in the former case (see above).

The data in Table 1 indicate that neither for the cycloalkanones nor for the amino ketones is there a linear correlation of δ_C with δ_O values.[18] However, the $\Delta\delta_O$ data are linearly correlated with the corresponding $\Delta\delta_C$ values:

$$\Delta\delta_O = 8.5 \times \Delta\delta_C - 11.5\,(\text{p.p.m.})$$

The correlation coefficient is r = 0.97. Hence, the results of both methods, as far as transannular interaction is concerned, are equivalent.

In summary, the same reservations concerning the significance of chemical-shift data for transannular interactions already mentioned for ^{13}C n.m.r. spectroscopy also are valid for ^{17}O n.m.r. spectroscopy.

Conclusions

^{13}C and ^{17}O chemical shifts of the carbonyl group in cyclic amino ketones can be used in a qualitative manner to determine transannular (homoconjugative) interactions. Owing to the rather complex nature of chemical shifts, it is difficult to explain in detail by which mechanism the observed effects are caused. Quantitative evidence is not possible. In this respect n.m.r. spectroscopy seems to rank behind p.e. and i.r. spectroscopy.

Experimental

General.—N.m.r. spectra ^{1}H and ^{13}C were recorded on a Varian XL200 with reference to the solvent (^{1}H, C_6D_5H: 7.15 p.p.m.; ^{13}C, C_6D_6: 128.0 p.p.m.; ^{13}C, C_6H_{12}: 27.0 p.p.m.). For ^{17}O n.m.r. spectra (solvent: C_6H_{12}; external standard: D_2O) a Bruker AM400 was used. Mass spectra were obtained with a Finnigan MAT 312/118. I.r. spectra were run on a Perkin-Elmer 397. Elemental analyses were carried out on a Heraeus EA301

C, H, N analyser. Melting points are uncorrected. MM2 calculations[20] were run on an Olivetti M24 personal computer.

Syntheses.—The ketones and 1-methylpiperidin-4-one (**1**) were obtained from 'Aldrich.' Compounds (**2**)—(**4**) were synthesized by the method of Leonard.[21] Syntheses of the amino ketones (**1**)—(**3**) have been reported previously.[1,19,21] Compound (**4**) is new. The purity of all compounds was checked by analytical g.c.

1-*Methyl*-1-*azacyclododecan*-7-*one* (**4**).—In a 4 l round-bottomed flask fitted with a Vögtle dilution principle apparatus (NORMAG), a mechanical stirrer, and a packed distillation column (30 cm) with a distillation head, a solution of potassium t-butoxide (161.4 g, 1.44 mol) in absolute xylene (2 l) was refluxed under argon. A solution of diethyl 6,6′-methyliminodihexanoate[22] (150 g, 0.48 mmol) in absolute xylene (1 l) was added through a dosing pump over a period of 250 h. Heating was continued for an additional 12 h to complete the reaction. During the whole period the temperature at the distillation head was kept at 135 °C by continuous removal of ethanol. The solution was cooled in an ice-bath and conc. HCl (250 ml) followed by water (250 ml) were added. The aqueous layer was separated and the organic solution was extracted nine times with 100-ml portions of conc. HCl. The combined aqueous phases were refluxed for 24 h and then concentrated to *ca.* 250 ml. The solution was made strongly alkaline by the cautious addition of cold saturated aqueous KOH and then extracted ten times with 100-ml portions of ether. The combined extracts were then dried (Na_2SO_4). The solvent was evaporated and the product remained as a white waxy solid, which could be purified by sublimation (63.7 g, 67.9%), m.p. 33 °C (Found: C, 73.45; H, 11.7; N, 7.1. $C_{12}H_{23}NO$ requires C, 73.04; H, 11.75; N, 7.10%); $\nu_{max.}$(neat) 2 790 (NCH_3, NCH_2), and 1 700 cm^{-1} (C=O); δ_H(200 MHz; C_6D_6) 2.15—2.00 (m, 8 H, CH_2), 1.98 (s, 3 H, CH_3), 1.60—1.30 (m, 8 H, CH_2), and 1.20—1.05 (m, 4 H, CH_2); δ_C (50.3 MHz; C_6D_6) 208.8 (s), 54.8 (t), 43.5 (q), 40.3 (t), 26.0 (t), 23.9 (t), and 23.0 (t); *m/z* 197 (M^+).

The corresponding picrate derivative had m.p. 159 °C (ethanol) (Found: C, 50.7; H, 6.45; N, 13.3. $C_{18}H_{26}N_4O_8$ requires C, 50.70; H, 6.15; N, 13.14%); $\nu_{max.}$(KBr) 2 850—2 600 ($H-NR_3^+$) and 1 705 cm^{-1} (C=O).

Acknowledgements

We are grateful to Mr. H. Bandmann for measurements of ^1H and ^{13}C n.m.r. spectra.

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Received 3rd *March* 1988; *Paper* 8/00859