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SIMULTANEOUS OBSERVATION OF MULTIPLE ISOMERISM IN SOME AMIDES*

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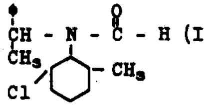
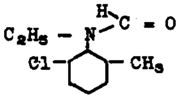
Multiple isomerism was deduced for certain amides from their proton magnetic resonance (PMR) spectrograms. The purpose of this letter is to report these observations. The amide,

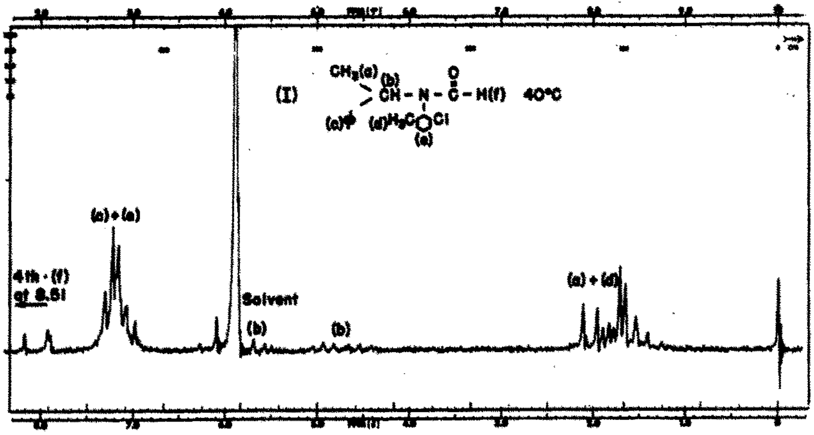


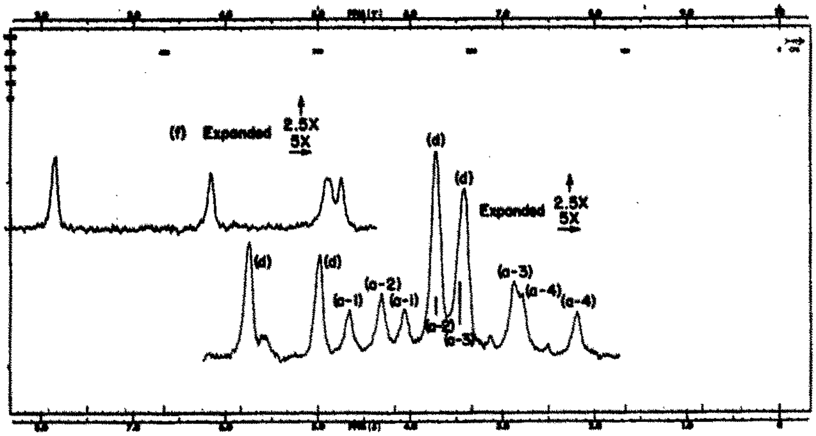
(I)

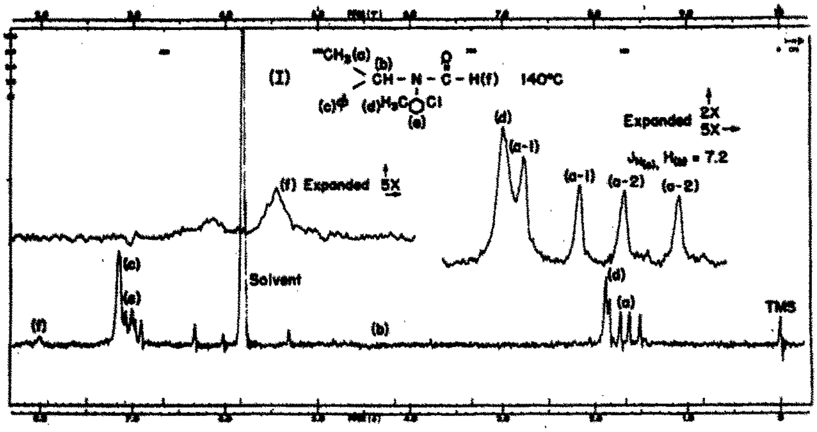
was prepared by 1) refluxing 2-chloro-6-methyl aniline in an excess of formic acid for four hours, 2) isolating the resulting secondary formamide (II) by crystallization, and 3) reacting II with sodium hydride and 1-phenyl-1-ethyl bromide in refluxing xylene. After washing with water and stripping off xylene, I was isolated by molecular distillation at <1 x 10^{-3} mm and 155°C. About two-thirds of I was distilled off and discarded as insurance against contamination by II, which distills at about 100°C. Theory: C = 70.3, H = 5.9, N = 5.1; found: C = 70.2, H = 6.2, N = 5.2. The ethyl derivative,



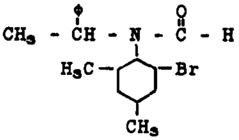
(III) was prepared by the conventional reaction of triethyl orthoformate with 2-chloro-6-methyl aniline and isolated by vacuum distillation at about 100°C and 0.2 mm. Theory: C = 60.8, H = 6.1, N = 7.1; found: C = 60.7, H = 6.0, N = 6.9. Amides V, VI, and VII (see structural formulas below) were prepared by similar methods. The PMR spectra (with sym-tetrachloroethane as the solvent), were obtained with a Varian A-60 spectrometer fitted with the Varian variable temperature accessory.


(I)
CH3(a) (b)
CH - N - C - H(f) 40°C
O
(c)ϕ (d)H3C Cl
(e)
(c)+(e)
4th·(f) at 8.51
Solvent
(b)
(b)
(a)+(d)
PPM (τ)
PPM (δ)


(f) Expanded 2.5X 5X
(d)
(d) Expanded 2.5X 5X
(d)
(d)
(a-1)
(a-2)
(a-1)
(a-2)
(a-3)
(a-3)
(a-4)
(a-4)
PPM (τ)
PPM (δ)

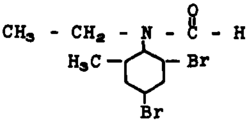

(I)
CH3(a) (b)
CH - N - C - H(f) 140°C
O
(c)ϕ (d)H3C Cl
(e)
(d)
(a-1)
Expanded 2X 5X
J H(a), H(b) = 7.2
(a-1)
(a-2)
(a-2)
(f) Expanded 5X
(c)
(e)
Solvent
(f)
(b)
(d)
(a)
TMS
PPM (τ)
PPM (δ)

Compound I at 40°C possesses four sets of signals for all except the ring protons. This over-all fourfold multiplicity can be attributed to the coexistence of epimers with the epimers in turn having cis and trans amide isomers. Rotation is slow enough around the benzene-to-nitrogen bond(1,2) to produce one asymmetry center that is recognizable on the PMR time scale, while the asymmetric carbon atom is the other. Slow rotation around the carbonyl to nitrogen (amide) bond is responsible for the cis-trans isomerism. It should be noted that cis-trans isomerism was not observed in similar epimeric amides(2) that had large carbonyl substituents. At 100°C the spectrum of I (not shown) is very badly blurred and largely unresolved. However, at 140° the spectrum is sharp and simple, and there is an over-all multiplicity of two. This behavior would be expected as rotation around the amide bond becomes rapid enough to cause coalescence of the cis-trans signals into a single set for each of the two epimers. The compound,

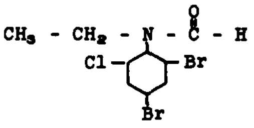


(IV), shows almost identical behavior. However, IV was not isolated in high purity, and its behavior is reported here only to corroborate observations with I.

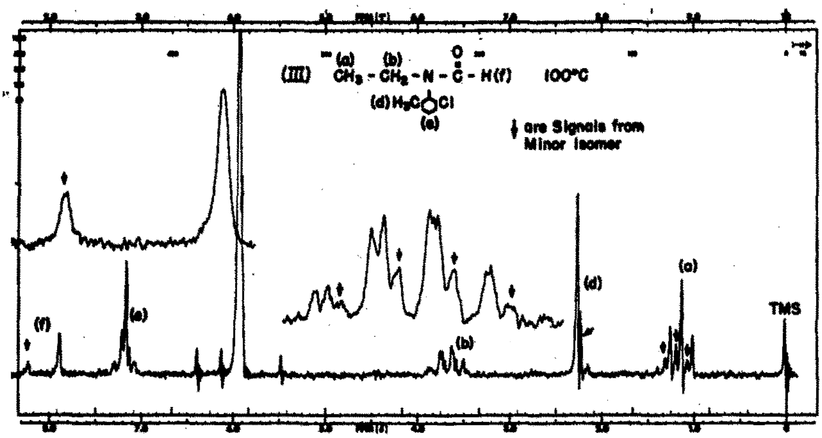
The behavior of III is that of a simple formamide (no diastereorsomers) except that the methylene protons (b) are non-equivalent. Even at 100°C the separate signals from the cis and trans isomers are visible (one isomer being about three times as abundant as the other). Nonequivalence in the methylene signals is clear for the major isomer only, but may be present also for the minor isomer. At 140° the signals from the separate isomers have almost entirely coalesced and nonequivalence is barely detectable. The very similar formamides (spectra not shown)

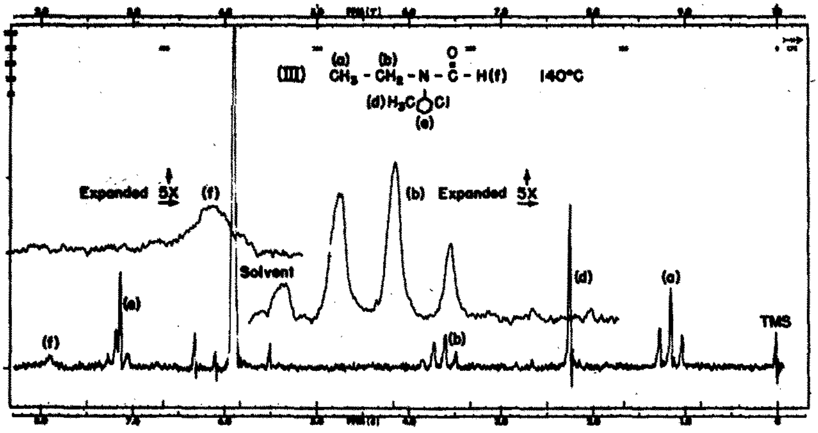


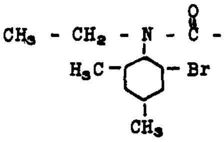
(V),



(VI), and


(III) CH₃ - CH₂ - N - C(=O) - H(f)
(a) (b)
(d) H₃C⬡Cl
(e)
100°C
are Signals from Minor Isomer
(f)
(e)
(b)
(d)
(a)
TMS
PPM (τ)
PPM (δ)


(III) CH₃ - CH₂ - N - C(=O) - H(f)
(a) (b)
(d) H₃C⬡Cl
(e)
140°C
Expanded 5X
(f)
(b) Expanded 5X
Solvent
(e)
(f)
(b)
(d)
(a)
TMS
PPM (τ)
PPM (δ)



(VII) do not exhibit clear methylene proton nonequivalence even at -40°C, though there is some broadening for V and VI.

These observations point up two quite variable patterns of behavior in tertiary amides that contain an unsymmetrically 2,6-substituted benzene ring attached to nitrogen. One of these variable patterns is the observation of cis-trans isomerism in certain epimer pairs, but not in others. The lack of apparent cis-trans isomerism in amides(3) might be due to (a) rapid rotation around the amide bond at the lowest accessible temperatures or (b) the great preponderance of one isomer for thermodynamic reasons. Factor (b) would seem to cause lack of observable cis-trans isomerism.(2) From work in progress in this Laboratory as well as from other data(4), it is unlikely that replacement of the formyl proton with a bulky group would decrease the temperature for the onset of rapid rotation around the amide bond by 150°C or more [factor (a)]. It is unlikely that the coexistence of four isomers in nearly equal abundance as we observed in I and IV is very common.

The other variable pattern is the seemingly random nonequivalence of the methylene protons of the N-ethyl formamides (III, V, VI, and VII). The absence of clear nonequivalence (in V, VI, and VII) could be ascribed to a rapid rate of rotation around the benzene to nitrogen bond. Since the ethyl group is small compared to the 1-phenylethyl group, steric factors might favor rapid rotation around the benzene to nitrogen bond more in the N-ethyl formamides than in I and IV. However, this seems unlikely since V and VII with the larger bromine atom replacing chlorine and VI with bromine (about equal size) replacing the methyl group do not show the methylene proton nonequivalence observed for III. A more likely explanation is that the methylene protons in V, VI, and VII are very nearly equivalent despite their lack of a symmetry element. Perhaps the methylene protons are <u>geometrically</u> nonequivalent, but because the field gradient is so small, they are magnetically equivalent. Alternatively, there may be rapid molecular motions that produce such a good approximation of symmetry that geometric nonequivalence is too small to be detected. This last consideration carries additional weight in view of the diminution of the degree of nonequivalence in III with increasing temperature.

Whatever the underlying structural factors may be, the coexistence of cis-trans isomers in coexisting epimers should be investigated. Mannschreck(5) recently isolated a pure amide isomer; epimers similar to those of I and IV were separated in this Laboratory(2). Therefore, it may be possible to isolate individuals of the four isomers for compounds such as I and IV. This could, among other things lead to a direct study of the effect of diastereoisomerism on the rate of rotation around the amide bond. Even in the absence of separation of cis-trans isomers, this information could be obtained indirectly by signal shape analysis(3).

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