Geminal Proton Nonequivalences and Related Phenomena in Some N-Substituted Amides[1]

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Abstract: A number of N,N-disubstituted amides were synthesized and their proton magnetic resonance spectra were determined. When one N substituent is an *ortho*-substituted aryl group and the other contains an α-methylene group, the methylene protons are nonequivalent. The chemical shift between the nonequivalent protons is temperature dependent. The resonances of certain other protons are doubled. These phenomena are interpreted in terms of slow rotation around the aryl-to-nitrogen bond.

In the course of investigations of the structure of amides by proton magnetic resonance (pmr) spectroscopy, nonequivalence was observed for geminal protons in certain N-substituted N-arylamides.[2] The object of this paper is to report on these and related observations more fully.

Experimental Section

Whenever the intermediates were commercially available, the amides were synthesized by direct combination of amine with acid chloride in the presence of triethylamine as an HCl getter (method A) and dichloromethane as a solvent. In other cases the N-arylamide was synthesized as in A. The N-arylamide, in refluxing xylene, then was converted to its sodio derivative[3] by treatment with sodium hydride, the desired RBr or RI was added in excess, and reflux was continued for 2 or 3 hr (method B). A third method (C) was to treat the desired isocyanate with R'MgX to produce the N-arylamide[4] and then to proceed as in B. Interestingly enough, several of the sodio derivatives were found to be paramagnetic with definite electron paramagnetic spectra epr.[5] Further investigations of this phenomenon are in progress. In all methods the final product first was washed twice with water (after destroying NaH, if present, with ethanol), and then purified by crystallization or vacuum distillation. The proton resonances of all compounds were integrated and the infrared spectra of all compounds were obtained for verification of preparation.

The proton magnetic resonance (pmr) scans of all compounds were obtained at about 43° with a Varian A-60 spectrometer.[6] Selected compounds also were scanned with a Varian 3400B spectrometer of 40 Mc to aid in interpreting complex spectra. All temperature studies were made with the 40-Mc instrument.

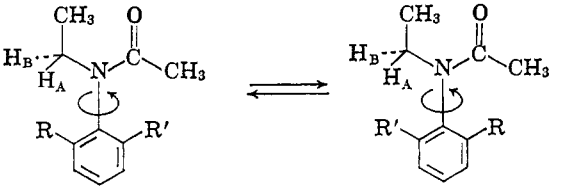
Results

The main body of results is tabulated in Table I. Illustrative spectrograms are given in Figures 1–3. The symbol $\langle \gamma_a - \gamma_b \rangle$ is used for the chemical shift between nonequivalent N-methylene protons in N-benzyl compounds. The symbols $\langle \gamma_1 - \gamma_9 \rangle$ and $\langle \gamma_1 - \gamma_5 \rangle$ are used for the measured instances between the first and third multiplets of the AB patterns of N-ethyl and N-isobutyl compounds. These are not true chemical shifts since they are not corrected for coupling. The center of the AB pattern is labeled Center, H_a, H_b in Table I. $\langle CH_{3a} - CH_{3b} \rangle$ is used as the symbol for the chemical shift between nonequivalent methyl groups. With N-isobutylamides the symbol J_{AC} denotes the coupling constant of the methylene proton at lower field with the methine proton while J_{BC} is the corresponding coupling constant for the methylene proton at higher field. The recorded values are the distance (cycles per second) between first and second (J_{AC}) and fifth and sixth (J_{BC}) peaks. The center of the methylene signals from the isobutyl radical has been taken as the midpoint between the high- and low-field sets (between the fourth and fifth signals).

All chemical shifts are given as parts per million from tetramethylsilane; all coupling constants are given in cycles per second. Except where otherwise noted all data are for a 25% solution of the compound in $CDCl_3$.

Discussion

Explanation of Nonequivalence. Examination of a Fischer–Taylor–Hirshfelder model suggests a reason for the nonequivalences listed in Table I. There is substantial hindrance to rotation around the benzene-to-nitrogen bond with two potential minima 180° apart. For a planar nitrogen atom this situation is demonstrated in the drawing below (for an N-ethylacetamide). The benzene ring occupies an average position perpendicular to the plane of the nitrogen atom



and its substituents. So long as $R \neq R'$, H_a and H_b, are nonequivalent, since the molecule has no symmetry element. However, when the benzene ring rotates, H_a and H_b interchange identities because only their orientation with respect to R and R' gives them separate identities. When the temperature is raised sufficiently, the rotation of the benzene ring increases and identity exchange becomes so rapid that nonequivalence is no longer observable (see Figure 4). If $R = R'$, there is never any nonequivalence, since the molecule has a symmetry plane that is also a mirror plane for the geminal protons. The same over-all argument applies to the geminal methyl groups in N-isopropyl derivatives and in isobutyramides.

(1) The information contained in this article was developed during the course of work under Contract AT(07-2)-1 with the U. S. Atomic Energy Commission.

(2) T. H. Siddall and C. A. Prohaska, *Nature*, 208, 582 (1965).

(3) W. S. Fones, *J. Org. Chem.*, 14, 1099 (1949).

(4) A. M. Schwartz and J. R. Johnson, *J. Am. Chem. Soc.*, 53, 1063 (1931).

(5) We are indebted to H. R. Tilley, Sr., of this laboratory for the epr work.

(6) We are indebted to W. O. Granade for operating this spectrometer and for his assistance in preparation of many of the compounds.

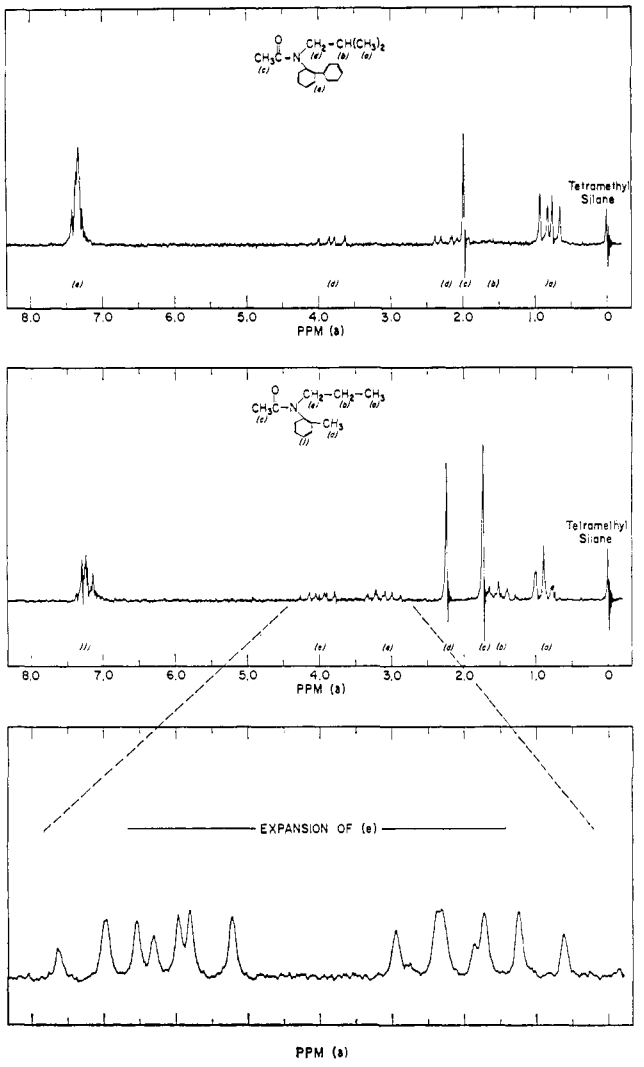


Figure 1.

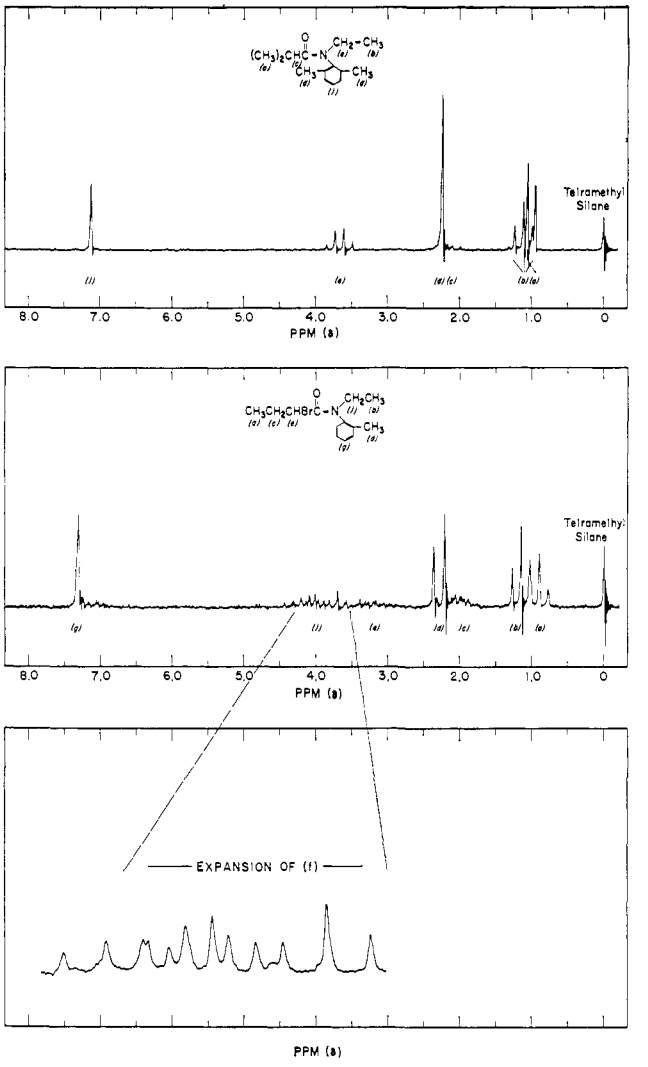
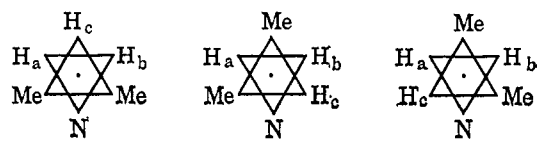


Figure 2.

If the nitrogen atom is pyramidal rather than planar, rotation around the benzene-to-nitrogen bond would still be the rate-limiting step in proton identity exchange. However, the complete set of internal molecular motions that accomplish this exchange would also include molecular inversion at the nitrogen atom. The over-all process might then be called "inversion–rotation."

N-Isobutyl Derivatives (XXXI–XXXIV). The isobutyl derivatives provide the opportunity for examining the effects of a single, third spin on the methylene protons. Although the spectra for the isobutyl derivatives (Figures 1–3) are complex ($ABCD_6$ or even $ABCD_3E_3$), it is approximately correct to view the indicated signals as AB, with chemical shifts as shown in Table I and $J_{BC} \sim 9$ cps and $J_{AC} \sim 5$ cps. The three rotamers are as shown.



1 **2** **3**

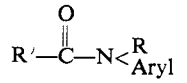
Now if the generally accepted proposal that $J_{HH}(gauche) < J_{HH}(trans)$ is also accepted here, then it must be that there is a deficiency of rotamer **3**. Only in this way can $J_{AC} > J_{BC}$. Yet within the limits of the above drawings, **2** and **3** are antipodes, have equal energies, and must have equal populations. However, with slow rotation around the benzene to nitrogen bond, **2** and **3** are *not* antipodes. This analysis predicts that the γ-methyl groups will also be nonequivalent, as indeed they are.

Other Derivatives. A more complicated situation is observed in the spectra of N-*n*-propyl compounds as can be seen in Figures 1–3. The pattern appears to be $ABCDE_3$. That part of the spectrum that is predominantly AB appears to consist of two sets of eight lines rather than two sets of six lines which would be the case in the ABX_2 approximation for the AB part of a ABC_2D_3 pattern. This suggests that there is a rotamer preference in the *n*-propyl radical analogous to that in isobutyl.

Consistent with other observations, the two methyl groups of the 2-propyl radical (XXXV) are also nonequivalent. However, $J_{AB} = J_{AC}$ because now the hydrocarbon radical must be regarded as a substituted methane instead of a substituted ethane.

The β-methyl signals obtained from isobutyramides (R′ = 2-propyl) follow the same pattern as that ob-

Table I. Pmr Data[a] for Amides



Compd	R	Aryl	R′	Method[b]	$\langle\nu_1 - \nu_2\rangle$[c]	Center, H_a, H_b	CH_3 C=O	Center, ethyl CH_3	$C_6H_4(CH_3)$	Remarks
I	Ethyl	*o*-Methylphenyl	Methyl	A	0.82	3.69	1.72	1.13	2.25	
	Undiluted ethyl	*o*-Methylphenyl	Methyl		0.82	3.66	1.66	1.06	...	No internal reference, assume
	10% $CDCl_3$ ethyl	*o*-Methylphenyl	Methyl		0.83	3.68	1.73	1.12	2.23	$C_6H_4CH_3$ = 2.24
	25% CCl_4 ethyl	*o*-Methylphenyl	Methyl		0.83	3.62	1.62	1.09	2.25	
	10% CCl_4 ethyl	*o*-Methylphenyl	Methyl		0.85	3.59	1.62	1.09	2.23	
II	Ethyl	*p*-Methylphenyl	Methyl	A	0	3.72	1.82	1.12	...	*p*-CH_3, 2.40
III	Ethyl	2,6-Dimethylphenyl	Methyl	B	0	3.68	1.71	1.13	2.24	
IV	Propyl	*o*-Methylphenyl	Methyl	B	0.92	3.59	1.72	...	2.23	
V	Ethyl	*o*-Ethylphenyl	Methyl	B	0.98	3.68	1.73	1.12	...	$C_6H_4CH_2CH_3$, 1.25, 2.58
VI	Ethyl	*m*-Methylphenyl	2-Propyl	A	0	3.72	...	1.09	...	*m*-CH_3, 2.38; $(CH_3)_2C$, equivalent center, 1.02
VII	Ethyl	2,6-Dimethylphenyl	2-Propyl	B	0	3.67	...	1.14	2.23	$(CH_3)_2C$, equivalent center, 1.00
VIII	Ethyl	*o*-Methylphenyl	2-Propyl	A	0.85	3.66	...	1.18	2.28	$\langle CH_{3a} - CH_{3b}\rangle$ = 0.033, center, 1.00
IX	Ethyl	*o*-Methylphenyl	Ethyl	A	0.74	3.68	...	1.12	2.21	(O=)CCCH$_3$ center, 1.02; (O=)CCH$_2$C, not doubled highest component, 1.73
X	Ethyl	*o*-Methylphenyl	*t*-Butyl	A	1.33	3.57	...	1.12	2.25	$(CH_3)^-_3$, 1.02
XI	Ethyl	*o*-Methylphenyl	$ClCH_2$	A	0.88	3.72	...	1.16	2.27	CH_2Cl equivalent, 3.73
XII	Ethyl	*o*-Methylphenyl	$BrCH_2$	A	0.90	3.70	...	1.16	2.28	CH_2Br equivalent, 3.56
XIII	Ethyl	*o*-Methylphenyl	Cl_2CH	A	0.87	3.71	...	1.18	2.28	$CHCl_2$, 5.71
XIV	Ethyl	*o*-Methylphenyl	Cl	From $COCl_2$, A	0.58	3.69	...	1.09	2.27	(O=)CCCH$_3$, 1.56, each component doubled; 0.008, 0.015 ($\neq$); CHCl gives six peaks; center, 3.25
XV	Ethyl	*o*-Methylphenyl	CH_3CHCl	A	Complex	~4.1	...	1.15	Doublet, 2.19–2.32	
XVI	Ethyl	*o*-Methylphenyl	CH_3CH_2CHBr	A	Complex	~4.0	...	1.14	Doublet, 2.22–2.36	CHBr complex, center ~3.2; CCH_2C complex, center ~2.1; $CCCH_3$ center, 0.89
XVII	Ethyl	*o*-Methylphenyl	$(CH_3)_2CBr$	A	~1.2	~3.7	...	1.17	2.25	$\langle CH_{3a} - CH_{3b}\rangle$ = 0.28, center, 1.76; high-field broadened; high-field CH_2 badly blurred
XVIII	Ethyl	*o*-Methylphenyl	Phenyl	A	Complex	~3.8	...	1.20	2.16	
XIX	Ethyl	β-Naphthyl	Methyl	B	0	3.83	1.87	1.16	...	
XX	Ethyl	*o*-Biphenyl	2-Propyl	B	1.30	3.38	...	1.05	...	$\langle CH_{3a} - CH_{3b}\rangle$ = 0.18, center, 0.96
XXa	Ethyl	α-Naphthyl	Methyl	B	0.80	3.86	1.75	1.15	...	
XXI	Ethyl	*o*-Biphenyl	Methyl	B	1.37	3.29	1.88	0.97	...	
XXII	Methyl	*o*-Methylphenyl	2-Propyl	A	...	...	...	...	2.24	$\langle CH_{3a} - CH_{3b}\rangle$ = 0.019, center = 1.00 N-Methyl = 3.18

Compd	R	Aryl	R′	Method[b]	$\langle\nu_a - \nu_b\rangle$[d]	Center, H_a, H_b	Intensity ratio (H_a, H_b) inner to outer signals Calcd	Obsd	C_6H_4-(CH_3)	CH_3 C=O	$J_{H_aH_b}$ = 14.0–14.2 cps for all benzyl compounds
XXIII	Benzyl	*o*-Methylphenyl	Methyl	B	0.83	4.77	1.74	1.67		1.74	
XXIV	Benzyl	2,6-Dimethylphenyl	Methyl	B	0	4.73	...	...		1.72	
XXV	Benzyl	Phenyl	Methyl	A	0	4.87	...	...		1.86	
XXVI	*o*-Methylbenzyl	*o*-Methylphenyl	Methyl	B	0.63	4.88	2.06	2.1		1.77	
XXVII	Benzyl	*o*-Biphenyl	Methyl	B	1.82	4.44	Not measured		...	1.93	
XXVIIa	Benzyl	*o*-Biphenyl	Ethyl	B	1.85	4.45	1.27	1.21	...	...	(O=)CCH$_2$CH$_3$ 1.98 (highest), 0.93 (center, CH_2 equivalent)

Compd	R	Aryl	R′	Method[b]	$\langle\nu_a - \nu_b\rangle$[d]	Center, H_a, H_b	CH_3 C=O	Center, ethyl CH_3	C_6H_3-(CH_3)	CH_3 C=O	Remarks
XXVIII	Benzyl	*o*-Biphenyl	2-Propyl	B	1.83	4.55	1.29	1.26	...	...	$\langle CH_{3a} - CH_{3b}\rangle$ = 0.17, center, 1.08
	10% CCl_4 benzyl	*o*-Biphenyl	2-Propyl		1.91	4.46	Not measured		...	...	$\langle CH_{3a} - CH_{3b}\rangle$ = 0.19, center, 1.05
XXIX	Benzyl	*o*-Biphenyl	Benzyl	B	1.83	4.57	Not measured		...	...	$C_6H_5CH_2$, singlet at 3.50
	10% CCl_4 benzyl	*o*-Biphenyl	Benzyl		1.9	4.3	Not measured		...	...	$C_6H_5CH_2$, singlet at 3.41
XXX	Benzyl	α-Naphthyl	2-Propyl	C	1.53	4.92	1.35	1.35	...	...	$\langle CH_{3a} - CH_{3b}\rangle$ = 0.08, center, 1.00
	25% CCl_4 benzyl	α-Naphthyl	2-Propyl		1.58	4.77	Not measured		...	...	$\langle CH_{3a} - CH_{3b}\rangle$ = 0.07, center, 0.96
	25% Acetone benzyl	α-Naphthyl	2-Propyl		1.37	4.84	Not measured		...	...	$\langle CH_{3a} - CH_{3b}\rangle$ = 0.11, center, 0.94

Table I (*Continued*)

Compd	R	Aryl	R′	Method[b]	$\langle\nu_1 - \nu_5\rangle$[e]	Center, H_a, H_b	$\langle CH_{3a} - CH_{3b}\rangle$	Center, CH_{3a}, CH_{3b}	C_6H_4-(CH_3)	CH_3 | C=O	J_{AC}, J_{BC}
XXXI	Isobutyl	*o*-Methylphenyl	Methyl	B	1.24	3.44	0.09	0.94	2.22	1.73	8.6, 5.6
XXXII	Isobutyl	*o*-Ethylphenyl	Methyl	B	1.37	3.46	0.11	0.93	...	1.74	9.0, 5.4 $C_6H_5CH_2CH_3$ (centers) 2.58 1.25
XXXIII	Isobutyl	Phenyl	Methyl	A	0	3.59	0	0.91	...	1.85	...
XXXIV	Isobutyl	*o*-Biphenyl	Methyl	B	1.60	3.00	0.17	0.79	...	1.97	9.0, 5.4
	~15% CCl_4 isobutyl	*o*-Biphenyl	Methyl		1.95	2.99	0.19	0.75	...	1.88	8.4, 5.4
XXXV	2-Propyl	*o*-Biphenyl	Methyl	B	...	...	0.30	0.87	...	1.88	C, C>CH center 4.28
XXXVI	Methyl	*o*-Methylphenyl	$C_6H_5C(H)Cl$	A	...	...	...	...	Doublet, 1.64–2.38		N-methyl, a doublet (separation 0.022) center, 3.20; CH, a doublet (separation 0.11) center, 5.20

[a] All data for 25% solution in $CDCl_3$ except where noted. [b] See text for methods of preparation. [c] Measured distance between corresponding signals of the halves of the AB spectrum (*i.e.*, first and ninth signals) in ppm. [d] Chemical shift between methylene protons. [e] Measured distance between first and fifth lines of AB spectrum.

served for the methylene protons that are α to nitrogen. Whenever this is one *ortho* substituent on the aryl group and only in this case, two sets of signals are obtained from these β-methyl protons.

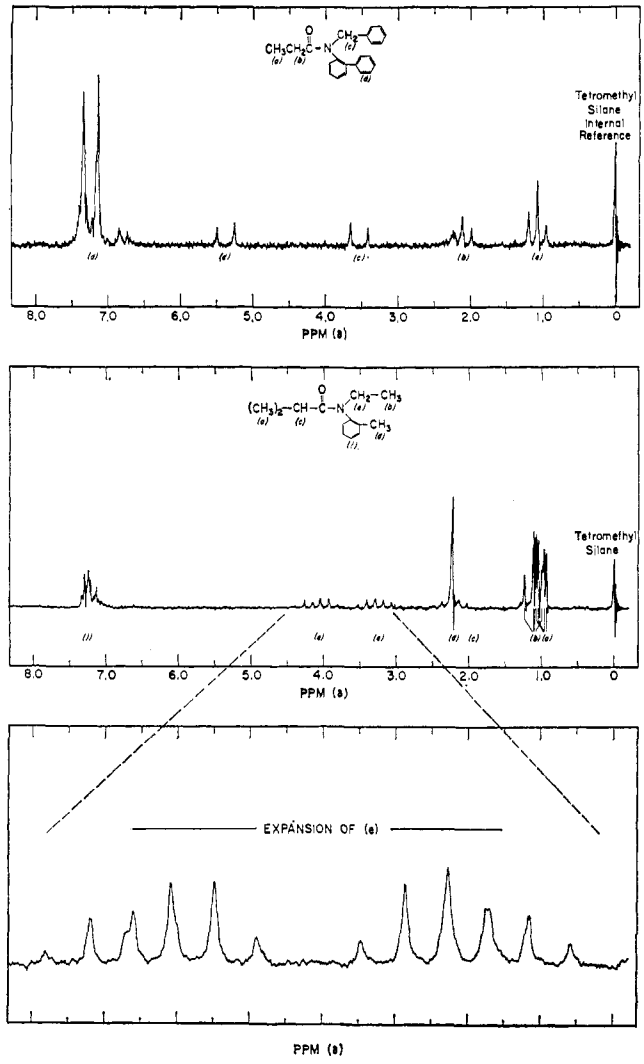


Figure 3.

There is pronounced interaction of N-substituent with carbonyl substituent and *vice versa*. For example with the N-ethyl-N-(*o*-methyl)phenylamides, although the values of $\langle\nu_1 - \nu_9\rangle$ for acetamide (I), propionamide (IX), and isobutyramide (VIII) are very close, the value for pivalamide (X) is significantly larger. With the benzamide (XVIII) $\langle\nu_a - \nu_b\rangle$ becomes small enough (probably 0.2–0.4 ppm) that the AB pattern can no longer be analyzed, even approximately, by simple inspection. We presume that the effect in the series I, IX, VIII, H is primarily steric, but that with benzamide there are also electronic effects.

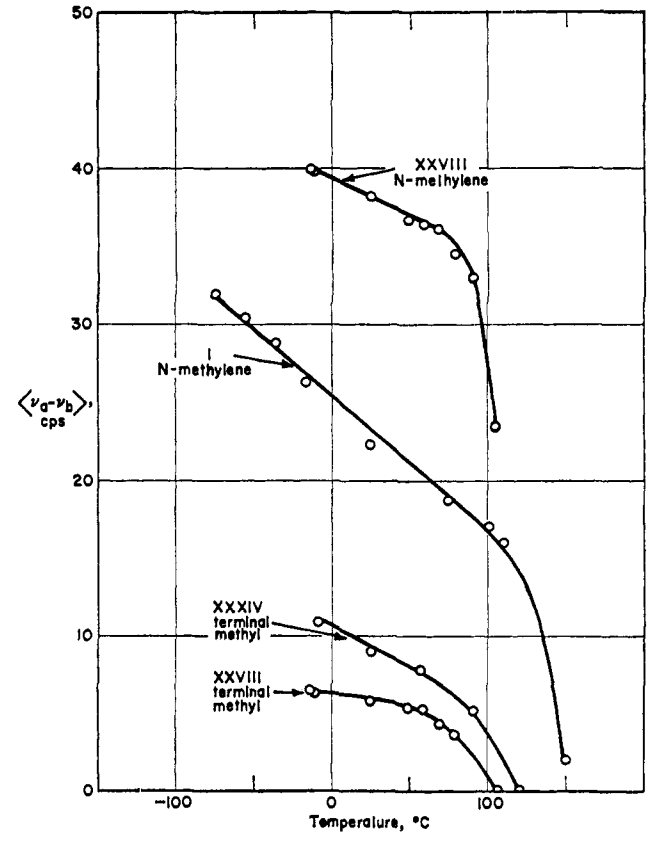


Figure 4. $\langle\nu_a - \nu_b\rangle$ *vs.* temperature.

Compound XVII has an interesting spectrogram. The lower half of the N spectrum is normal, but the half at higher field is a broad hump with no particular structure. There are two signals from the $CBr(CH_3)_2$

protons, but the high-field signal is much less sharp than the low-field signal. The same or similar phenomenon of a blurred signal set has been noted by others.[7,8] Possibly this phenomenon is evidence of crowding with several very closely spaced states.

The most striking effect is achieved when the α-carbon atom in the carbonyl substituent is asymmetric (XV, XVI, XXXVI). Nearly all of the signals are altered—even the pattern of signals from the ring protons. Compare the spectrum of XVI with others in Figures 1–3; the *o*-methyl signal is a doublet, the N-methylene signals form a very complex pattern.

An obvious interpretation of the effect of an asymmetric α-carbon atom (α to carbonyl) on the pmr spectra is that there are now two diastereoisomers of each compound. With two diastereoisomers there is always a potential for two complete sets of signals. All that is required to develop this potential into two distinct sets are groups with large enough electric and/or magnetic fields within the molecules. Observation of diastereoisomerism by nmr in compounds of this type when both asymmetry centers are nitrogen atoms also should be possible. We are currently investigating this possibility.

Effects of Solvent and Temperature. Effects of solvent are small, but detectable. Such effects are expected, since molecular shape must be a function of the nature of the solvent, at least in some details. However, none of these effects alter the conclusion based on the work in $CDCl_3$. For at least one reported case[9] in which nonequivalence was ascribed entirely to solvent effect, an alternative explanation is available. If, as the author suggests in his footnote,[10] there is intramolecular hydrogen bonding, the ring formed in this manner could lead to nonequivalence. The equilibrium constant for such hydrogen bonding would be expected to follow the polarity of the solvent, which in turn would lead to nonequivalence that is, indeed, a function of the solvent; however invoking magnetic properties of solvent as the primary cause of nonequivalences would not be necessary.

The temperature effect was studied for compounds I, XXVIII, and XXXIV. The data are summarized in Figure 4. The N-methylene signals for all three compounds had converged at 170°, but, except for I, were still considerably broadened at this temperature. The terminal methyl proton signals converge at a much lower temperature. At 106° for XXVIII and 120° for XXXIV, these signals are sharp doublets with no appreciable broadening.

Interpretation of these temperature data is difficult, and about the only conclusion we can draw is that the reorientation of these protons cannot be treated in the simplest manner as a typical rate process.[11] Potential barriers and frequency factors calculated from these data assuming a typical rate process can only be rough approximations at best. One probable source of very large error is that the value of $\langle \nu_a - \nu_b \rangle$, the chemical shift, for infinite lifetime must itself be a function of temperature. This complication can be taken into account with the proper computer program, but we prefer to postpone the computer analysis to another time.

(7) J. C. Randall, J. J. McLeskey, III, P. Smith, and M. E. Hobbs, *J. Am. Chem. Soc.*, **86**, 3229 (1964).
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(9) E. I. Snyder, *J. Am. Chem. Soc.*, **85**, 2624 (1963).
(10) See ref 9, footnote 21.
(11) H. S. Gutowsky and C. H. Holm, *J. Chem. Phys.*, **25**, 1228 (1956).