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STRUCTURAL STUDIES BY NUCLEAR MAGNETIC RESONANCE—XVI

CONFORMATIONS AND CONFIGURATIONS OF HYDRAZONES[1]

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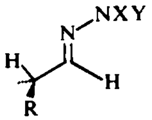
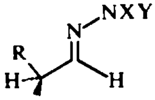
Abstract—Conformations and configurations were assigned to several hydrazones of aldehydes and ketones from analysis of their 60-Mc NMR spectra. Azines and hydrazone dimers were found to be frequent contaminants of the hydrazones, especially after the hydrazones, or their solutions, were let stand at room temperature. From the vicinal spin-spin coupling constants, $J_{H_1H_\alpha}$, the following conclusions were reached regarding the relative stabilities of rotamers I and II: (a) ΔG°_{40} for $V_a \rightleftarrows VI$ was +400, +500 and +700 cal/mole for R equal to methyl, isopropyl and phenyl, respectively. (b) ΔG°_{40} for $VII \rightleftarrows VIIIa$ was +200, +600 and +700 cal/mole for R equal to methyl, ethyl and isopropyl, respectively. Interpretation of the spin-spin coupling constants of the *trans* isomers (amino group *trans* to H_1) led to the conclusion that, whereas IX is the only significant rotamer of α,α-disubstituted acetaldehyde hydrazones, both X and XI—with a low barrier of interconversion between them—are significant rotamers of the α-monosubstituted compounds.

IN PREVIOUS publications we have commented on the problems of configurational isomerism about the C=N double bond and on the relative stabilities of rotamers I and II, when X is Me and Y is Ph;[2] when X is Ph and Y is H;[3] and when X is a substituted Ph,[4,5] a carbamido[5] or a thiocarbamido group.[5] In this paper we wish to discuss the results obtained from our investigations of hydrazones (X = H and Y = Me).



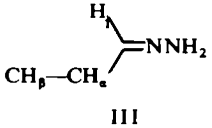
I



II

RESULTS

The chemical shifts, whose accuracy is about ±0·03 ppm, of a few representative hydrazones of aldehydes and ketones are summarized in Table 1. The notation used to distinguish the various protons is shown in III.



III

TABLE 1. CHEMICAL SHIFTS[a] (τ-VALUES) OF HYDRAZONES

$R_1R_2C{=}NNH_2$		Solvent	H_1		$H_\alpha(CH)$		$H_\alpha(CH_2)$		$H_\alpha(CH_3)$		$H_\beta(CH_3)$	
R_1	R_2		*cis*	*trans*	*cis*	*trans*	*cis*	*trans*	*cis*	*trans*	*cis*	*trans*
H	CH_3	Neat	2·88	3·42					8·32	8·23		
H	CH_3	C_6H_6							8·77	8·39		
H	CH_2CH_3	Neat	2·93	3·61				7·92			8·90	9·02
H	$CH_2C_6H_5$	Neat	3·02	3·40				6·63				
H	$CH_2C_6H_5$	CCl_4	2·96				6·35	6·55				
H	$CH_2C(CH_3)_3$	Neat[b]	2·85	3·45				7·99				
H	$CH(CH_3)_2$	Neat	2·97	3·75	6·94	7·67						8·97
H	$CH(CH_3)_2$	C_6H_6	3·40								9·20	9·04
CH_3	CH_3	Neat							8·35	8·20		
CH_3	CH_3	CCl_4							8·33	8·18		
CH_3	CH_3	C_6H_6							8·64	8·22		
CH_3	CH_2CH_3	Neat					7·84	7·87	8·34	8·21	8·92	9·01
CH_3	CH_2CH_3	CCl_4						7·85	8·34	8·21		8·97
CH_3	CH_2CH_3	C_6H_6						7·92	8·67	8·23		8·98
CH_3	$CH_2C_6H_5$	Neat						6·56	8·47	8·22		
CH_3	$CH_2C_6H_5$	CCl_4					6·55	6·61	8·45	8·18		
CH_3	$CH_2C_6H_5$	C_6H_6					6·84	6·88	8·77	8·22		
CH_3	$CH(CH_3)_2$	Neat			6·83	7·61			8·38	8·28	8·90	9·00
CH_3	$CH(CH_3)_2$	CCl_4				7·61			8·37	8·28	9·00	8·98
CH_3	$CH(CH_3)_2$	C_6H_6				7·62			8·65	8·28	9·21	8·97
CH_3	$C(CH_3)_3$	Neat							8·32			8·93
CH_3	$C(CH_3)_3$	CCl_4							8·34			8·93
CH_3	$C(CH_3)_3$	C_6H_6							8·63			8·93

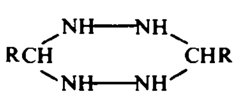
[a] The contamination of the hydrazones with azines and hydrazone dimers prevented accurate determination of several resonances. For this reason many chemical shifts are not reported in this Table.

[b] Some ethanol present.

Each proton is referred to as *cis* or *trans* with respect to the amino group, with assignments being made on the basis of arguments given in our previous publications.

The chemical shifts are typical of compounds of the general structure $R_1R_2C{=}NZ$. For example, H_1 resonates at lower fields when *cis* than when *trans* to the amino group; and *cis* α-methyl protons resonate at higher magnetic fields than *trans* α-methyl protons. As in compounds where X is hydrogen, benzene shifts the resonances of the *cis* groups to appreciably higher magnetic fields than it does those of the corresponding *trans* groups.

The spectra of freshly prepared neat liquid hydrazones, or of their solutions, are usually uncontaminated by the resonance signals of azines (H_1 of azines at τ about 2·2) or, as in the case of aldehyde hydrazones, of the dimers[6] of hydrazones, IV. The



IV

signals of the above mentioned species, however, often become strong within a few hours. Figure 1 shows the spectrum of a mixture of acetaldehyde hydrazone and its dimer.

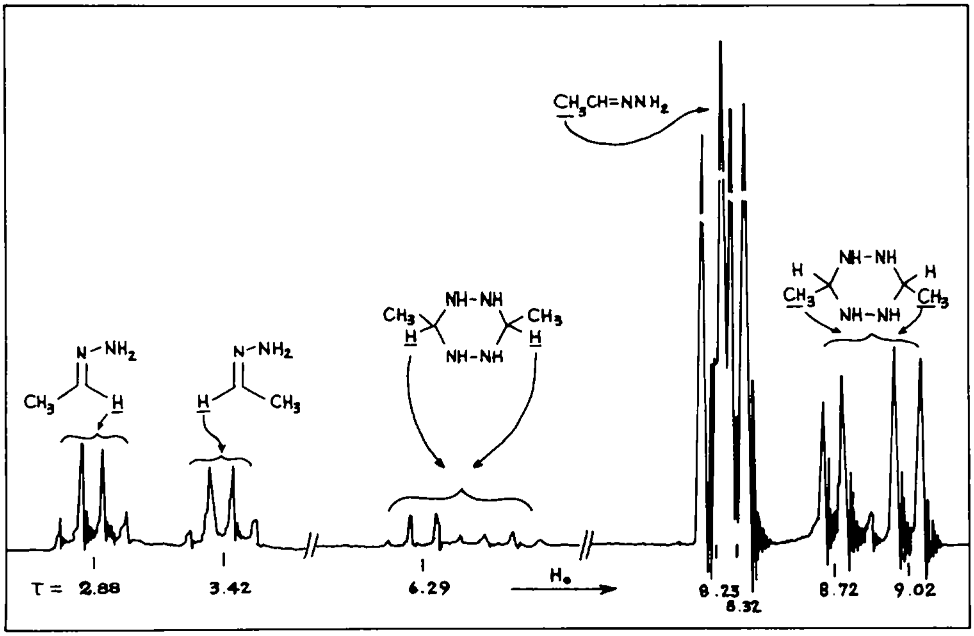


FIG. 1 NMR spectrum of acetaldehyde hydrazone and its dimer.

In Table 2 we have summarized the *syn* and *anti* isomer percentages, whose accuracy is about ±5%, and the free energy differences between these isomers. In

TABLE 2. *syn* AND *anti* PERCENTAGES AND ΔG°_{40} VALUES FOR *syn* ⇄ *anti* OF HYDRAZONES[a]

$R_1R_2C{=}NNH_2$ R_1	R_2	% *syn*[b]	% *anti*	ΔG°_{40} (Kcal/mole)
H	CH_3	51	49	+0·04
H	CH_2CH_3	64	36	0·35
H	$CH_2C_6H_5$	62	38	0·31
H	$CH_2CH(CH_3)_2$	64	36	0·35
H	$CH_2C(CH_3)_3$	73	27	0·61
H	$CH(CH_3)_2$	91	9	1·41
H	$CH(Et)_2$	87	13	1·2
H	$CH(i\text{-}Pr)_2$	84	16	1·0
CH_3	CH_2CH_3	78	22	0·78
CH_3	$CH_2C_6H_5$	79	21	0·80
CH_3	$CH(CH_3)_2$	93	7	1·58
CH_3	$C(CH_3)_3$	100	0	>2·7

[a] Data from neat liquids.

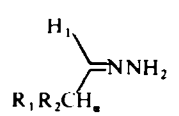
[b] *syn* is the isomer having the amino group *cis* to R_1.

all cases the predominant isomer is that in which the amino group is *cis* to the smaller group.

In Table 3 are summarized the vicinal spin-spin coupling constants, whose accuracy is about ±0·03 c/s, between H_1 and H_α. These coupling constants are again typical of hydrazone-type compounds. For example, the coupling constants of the *syn* isomers increase as R increases in size; those of the *anti* monosubstituted acetaldehyde hydrazones behave irregularly; and those of the *anti* disubstituted acetaldehyde hydrazones are appreciably larger than all others.

Conformations of the syn isomers. The instability of the hydrazones prevented us

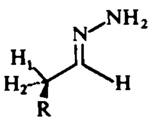
TABLE 3. SPIN–SPIN COUPLING CONSTANTS OF ALDEHYDE HYDRAZONES[a] AT 40°

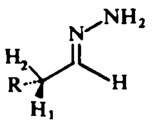


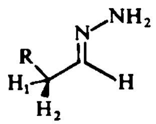
R_1	R_2	$J_{H_1H_\alpha}$ (c/s) *syn*[b] isomer	*anti* isomer
H	CH_3	5·40	5·50
H	CH_2CH_3	5·52	5·45
H	$CH_2CH(CH_3)_2$	5·60	4·93
H	$CH_2C_6H_5$	5·77	5·07
H	$CH_2C(CH_3)_3$[c]	6·23	5·35
H	$CH(CH_3)_2$	5·18	7·18
H	$CH(Et)_2$	6·32	8·10
H	$CH(i\text{-}Pr)_2$[c]	6·58	8·43

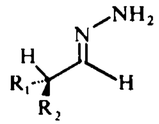
[a] Data from neat liquids. [b] *syn* is the isomer having the amino group *cis* to H_1. [c] Contaminated by ethanol.

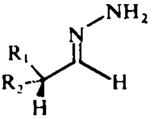
from studying the behavior of the coupling constants $J_{H_1H_\alpha}$ as a function of temperature, and, consequently, the only parameters that can be obtained on the relative stabilities of rotamers V vs. VI and VII vs. VIII is the free energy difference ΔG°, between them.

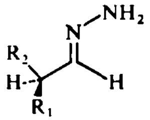

Va


Vb


VI


VII


VIIIa


VIIIb

Eqs (1) and (2) express the relevant free energy differences, where J_t is the *trans* coupling, J_g is the *gauche*, and J_{obs} is the experimentally

$$\Delta G^\circ_{Va \rightleftharpoons VI} = -RT \ln (J_t + J_g - 2\,J_{obs})/(J_{obs} - J_g) \tag{1}$$

$$\Delta G^\circ_{VII \rightleftharpoons VIIIa} = -RT \ln \tfrac{1}{2} (J_t - J_{obs})/(J_{obs} - J_g) \tag{2}$$

observed averaged coupling constant. J_t and J_g can be evaluated from Eqs (3) and (4), where equation (3) expresses the coupling of

$$J_{obs}(\text{acet.}) = \tfrac{1}{3}(J_t + 2\,J_g) \tag{3}$$

$$J_{obs}(\text{t-Bu}) + 0{\cdot}4 = \tfrac{1}{2}(J_t + J_g) \tag{4}$$

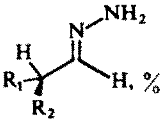
acetaldehyde hydrazone and Eq. (4) that of t-butylacetaldehyde hydrazone. The reasonable assumption is again made[2,7] that t-butylacetaldehyde hydrazone exists mainly in conformation V. The 0·4 term in Eq. (4) is the alkyl correction term.[7,8] The calculated values, $J_t = 10{\cdot}0$ c/s and $J_g = 3{\cdot}0$ c/s, compare favorably with those calculated for analogous systems.[2,7] In Table 4 are summarized the free energy differences between various rotamers and the relative populations of these rotamers as calculated from Eqs (5) and (6), where p is the population of V and of VII and $(1 - p)$ that of VII and of VIII.

$$J_{obs} = p(J_t + J_g)/2 + (1 - p)\,J_g \tag{5}$$

$$J_{obs} = pJ_t + (1 - p)\,J_g \tag{6}$$

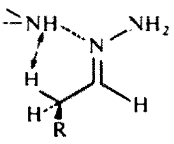
The ΔG° values presented in Table 4 are certainly comparable to those obtained for structurally similar compounds.[2,7,9] They may, however, be somewhat more positive than the true ΔG° values for the unassociated hydrazones. The rationale behind this statement is as follows: Consider V and VI and the corresponding hydrogen bonded species IX and X. The observed $J_{H_1H_\alpha}$ coupling constants, from which the ΔG° values are calculated, are weighted averages of all the $J_{H_1H_\alpha}$ coupling

TABLE 4. ROTAMER POPULATIONS[a] AND ΔG VALUES OF HYDRAZONES

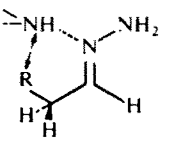
$R_1R_2C{=}NNH_2$			ΔG°_{40} for Va ⇌ VI (cal/mole)
R_1	R_2		
H	CH_3	80	+400
H	$CH(CH_3)_2$	83	+500
H	C_6H_5	87	+700
H	$C(CH_3)_3$	100[b]	> +3,000[b]
			ΔG°_{40} for VII ⇌ VIIIa
CH_3	CH_3	40	+200
CH_2CH_3	CH_2CH_3	56	+600
$CH(CH_3)_2$	$CH(CH_3)_2$	60	+700

[a] Calculated at 40°. [b] Value was assumed.

constants of the various species present in solution. As a result of stronger nonbonded repulsions (R ↔ H) in X than in IX (H ↔ H), the ratio IX/X ought to be larger than the ratio V/VI of the unassociated species. The greater the concentration of the hydrogen bonded species, the more positive, therefore, the ΔG° is.

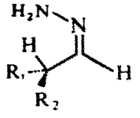


IX

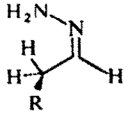


X

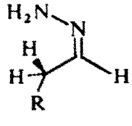
Conformations of the anti isomers. From the parallel behavior between the $J_{H_1H_\alpha}$ of the *anti* isomers of hydrazones and those of analogous compounds[7,9] we can draw conclusions on the conformations of the *anti* isomers that are similar to those previously drawn. Namely, that the most stable conformation of the disubstituted acetaldehyde hydrazones is XI; and that XII and XIII are reasonably accurate representations of the minimum energy conformations of the monosubstituted acetaldehyde hydrazones. Again, the irregular behavior of $J_{H_1H_\alpha}$ of the monostituted derivatives suggests that the barrier to interconversion between XII and XIII is probably low.[9]



XI

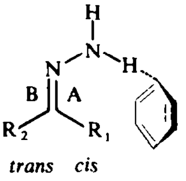


XII



XIII

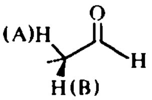
Chemical shifts and solvent effects. The larger upfield shift of the *cis* over the *trans* protons on dilution with benzene (Table 1) suggests specific orientation of benzene by interaction with the hydrazone. A weakly bonded complex, XIV, that has been suggested for similar compounds,[3,4] adequately accommodates the data. For example, as a consequence of its being closer to the ring center, the *cis* group R_1 is



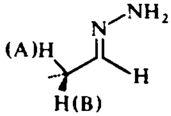
XIV

more strongly shielded than the *trans* group R_2. As in so many other compounds of the general structure $R_1R_2C{=}NZ$, region A is deshielded with respect to B (both A and B in the plane of the molecule). This conclusion is strongly supported by the lower field absorption of *cis*-H_1 over *trans*-H_1 (about 0·5 ppm) of *cis* α-methine over *trans* α-methine (about 0·8 ppm).

Recently it was pointed out[10] that position A (XV), in the plane of the carbonyl, is shielded, rather than deshielded, with respect to position B (XV). It is of interest to note that the same is true in hydrazones, i.e. position A (XVI), in the plane of the



XV



XVI

carbon-nitrogen double bond, is also shielded with respect to position B (XVI) that is outside the plane. For example, whereas the *trans* α-methylene of propionaldehyde hydrazone resonates at τ = 7·92, that of the t-butylacetaldehyde hydrazone, which spends more time in position A, resonates at τ = 7·99 (higher). Similarly, whereas the *trans* α-methine of dimethylacetaldehyde hydrazone resonates τ = 7·67, that of diethylacetaldehyde hydrazone resonates at τ about 8·05. Analogous results were observed with the oxime O-methyl ethers,[7] oximes,[9] and N-methylphenylhydrazones.[2] In this respect, therefore, the anisotropic effect of the carbon-nitrogen double bond parallels that of the carbonyl group.

EXPERIMENTAL

Preparation of hydrazones. The following is a typical preparation of a hydrazone. About 4 g (0·08 mole) 100% hydrazine hydrate, 5 ml EtOH and 15·3 g (0·10 mole) BaO were placed in a 100 ml round-bottomed flask and cooled to 0°. To the magnetically stirred soln was added, over a period of a ½ hr, a soln of 4·53 g (0·08 mole) acetone in 5 ml EtOH. After the addition was completed, the reaction mixture was stirred for an additional 10 min. The reaction mixture was then cooled, shaken with added ether, and distilled under vacuum. The above procedure was used for the preparation of all other hydrazones. In general, the reaction time required for the preparation of the other ketone hydrazones was longer. For example, stirring was continued for 3 hr at room temp.

NMR spectra were determined at 60-Mc on a Model A-60 spectrometer (Varian Associates, Palo Alto, Calif.). Undegassed solns were used with TMS as internal reference standard.

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