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CONFORMATIONAL BEHAVIOUR AND E/Z ISOMERIZATION OF N-ACYL AND N-AROYLHYDRAZONES

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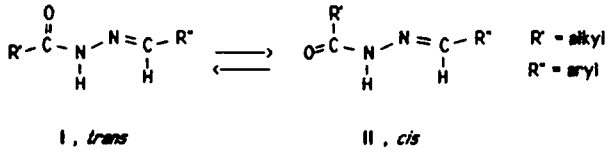
Abstract - The stereochemical behaviour of N-acyl and N-aroylhydrazones of aromatic aldehydes, of pyruvates and of acetone, in polar and less polar solvents, has been studied by HPLC and by NMR techniques. Z/E Geometrical isomers and cis/trans amide conformers have been found for N-acylhydrazones, while for N-aroylhydrazones only geometrical isomers were detected. Energy barriers of isomers are reported, and solvent effects are discussed with regard to hydrogen bond interactions.

N-Aroylhydrazones of methyl pyruvate and of aromatic aldehydes show considerable chelating power with transition metals[1,2], and can be used in analytical chemistry to recover and analyse metals selectively as hydrazone complexes[3,4]. We recently found, by chromatographic techniques, that several hydrazones of methyl pyruvate exist in solution as mixtures of E/Z geometrical isomers, whose ratio depends on the nature of the solvent and influences their chelating capability[5]. On the other hand we also found, by NMR studies, that N-acylhydrazones of aromatic aldehydes exist in solution as a mixture of the conformers I and II because of the hindered rotation on the C-N amide bond[6] (Scheme 1). This picture was confirmed by X-ray structural analyses carried out on two crystalline materials obtained from alcoholic solutions of 2-formylthiophene-N-acetylhydrazone (R' = CH_3, R'' = C_4H_3S) (7) and identified as the isomers I and II.

Scheme 1.



I, *trans* II, *cis*

However, during the same investigation[6], we ascertained that the aroylhydrazones of the same aromatic aldehydes possess only the less hindered trans form I.

In continuation of this research, we now report definitive results, obtained by NMR and HPLC techniques, on the behaviour of N-acyl- and N-aroylhydrazones of methyl pyruvate, which exhibit both configurational (E/Z) and conformational (cis/trans) isomers.

The corresponding hydrazones of acetone have also been studied, under the same conditions, for comparison. Moreover, we will start by discussing the behaviour in solution of pyridine-2-carbaldehyde-N-acetylhydrazone (R' = CH_3, R'' = C_5H_4N), which gives the same isomerization pattern as the methyl-pyruvate derivatives and differs from the other acetylhydrazones of aromatic aldehydes by also exhibiting E/Z geometrical isomers.

RESULTS AND DISCUSSION

It has been pointed out[6] that hydrazones derived from aldehydes and substituted hydrazides are present in solution in the E form. This is true in the case of $C_6H_5C(O)NH\text{-}N{=}CHR$ with R = phenyl or 2-thienyl, but when R = 2-pyridyl the Z form can be stabilized in less polar solvents by an intramolecular hydrogen bond and can be detected by reversed phase HPLC. The isomerization is induced by light, but can also be obtained thermally by warming the solution over 40°C. The equilibration rate is rather low, and the E/Z isomer ratio can be easily quantified by chromatography and by NMR techniques. Thus a chloroform solution of pyridine-2-carbaldehyde-N-acetylhydrazone, after E/Z isomerization, shows the four isomers III-VI, all distinguishable on the NMR time scale (Scheme 2). Geometrical Z isomers V and VI, carrying intramolecular hydrogen bonds, are more lipophilic than E isomers III and IV, in agreement with their higher retention volumes on reversed phase HPLC. The ratio of amide conformers III/IV and V/VI can be obtained only by ^1H NMR as they interconvert too fast to be detected by HPLC. The relative percentages of these isomers, thermally equilibrated in polar and less polar solvents (chloroform and dimethylsulphoxide), are reported in Table 1 together with ^1H NMR chemical shifts.

Scheme 2.

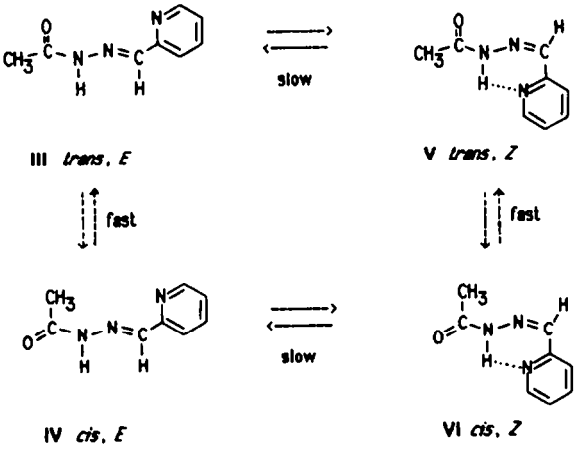


Table 1. ^1H NMR chemical shifts (δ, TMS) and percentages of hydrazones III-VI after thermal equilibration in $CDCl_3$ and in DMSO-d_6[a].

Isomer	%	CH_3	=CH-	arom	NH	solvent	T°C	Notes
III	6	2.16	8.23	7.2-8.7	10.67	$CDCl_3$	25	trans E
IV	34	2.42	8.07	7.2-8.7	10.43	$CDCl_3$	25	cis E
V	15	2.19	---[b]	7.2-8.7	14.40	$CDCl_3$	25	trans Z
VI	45	2.38	7.12	7.2-8.7	14.02	$CDCl_3$	25	cis Z
III	24	2.02	8.23	7.1-8.7	11.61	DMSO-d_6	30	trans E
IV	76	2.25	8.08	7.1-8.7	11.47	DMSO-d_6	30	cis E

[a] The signals of the more hindered Z forms in DMSO were not detected.

[b] Signal not assigned as it was covered by other aromatics.

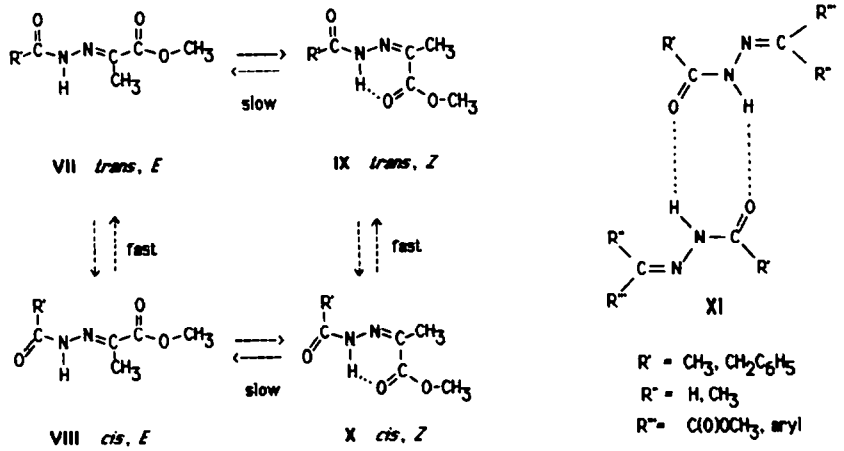
In deuterated chloroform a strong intramolecular hydrogen bond C(O)NH⟶N(pyr), producing a low-field shift of the NH lines (δ = 14.40, 14.02), stabilizes the more hindered Z forms V and VI. In dimethylsulphoxide, which forms competitive intermolecular hydrogen bonds (and also in chloroform when R'' = phenyl instead of 2-pyridyl) only the less hindered forms III and IV have been detected by both NMR and HPLC techniques.

The ^{1}H- signal of CH_3 in III (trans, δ = 2.16) falls upfield of the corresponding signal of IV (cis, δ = 2.42), whereas the singlet due to N=CH- shows a reverse pattern, with a line at 8.23 for form III (trans) and at 8.07 δ for form IV (cis). The correctness of the assignments was confirmed, for I and II, by monitoring the intensity ratio of the two signals of N=CH produced by introducing R' groups with increasing bulk (R' = methyl, ethyl, isopropyl)[6]. The structure I (trans) was assigned to the form whose lines increased with the steric hindrance of R', i.e. to the one with the N=CH line at higher field and methyl group at lower field.

The rate of E⟶Z isomerization of 2-pyridylhydrazone III in chloroform has been followed by ^{1}H NMR at several temperatures (20, 30, 40°C) in order to evaluate the energy barriers of E⟶Z conversion. The increasing intensities of ^{1}H signals at 2.19, 2.38, 14.40, and 14.02 δ have us allowed measurement of the isomerization rate constants, from which the $\Delta G^{\neq}$ value has been calculated by considering the reaction as unimolecular and reversible.

The $\Delta G^{\neq}$ value of 24.5 Kcal/mole, found for III, falls in the range previously observed for E⟶Z isomerization of aroylhydrazones of methylpyruvate (22-25 Kcal/mole).[5] On the other hand the $\Delta G^{\neq}$ values of cis/trans amide conformers in 2-formylthiophene-N-acetylhydrazone (I: R' = CH_3, R'' = C_4H_3S), calculated by dynamic NMR (T_c of 79°C in DMSO-d_6), were 18.1 and 18.3 kcal/mole[7]. Even lower values of $\Delta G^{\neq}$ have been obtained for cis/trans conversion of pyruvate hydrazones VII-VIII, reported in the Scheme 3.

Scheme 3.



$\Delta G^{\neq}$ Values of 15.3 and 15.9 kcal/mole were found by dynamic NMR in the case of methyl pyruvate N-acetylhydrazone VII (R' = methyl), using the well known coalescence-temperature method[8]. Coalescence of methyl groups of VII and VIII conformers dissolved in a DMSO-d_6/$CDCl_3$ solvent mixture (5/2, v/v), occurred at 30°C. The lower T_c values exhibited by the amide conformers of pyruvate hydrazones with respect to those of aromatic aldehyde hydrazones could be explained in terms of electronic effects. The greater electron withdrawing power of pyruvate, compared with that of aryl groups, can reduce the contribution of polar structures such as $R'-C(O^-)=N^+H-N=C(CH_3)-C(O)OCH_3$ in favour of structures such as $R'C(O)-N^+H=N-C(CH_3)=C(O^-)OCH_3$ reducing the double-bond character of the amide C-N linkage and favouring rotation.

The pyruvate conformers were more successfully resolved by ^{13}C NMR than by ^{1}H NMR, owing to

the greater resolution of the carbon signals and to our ability to examine both C=O and C=N-lines, which differ greatly in cis and trans conformers. The more informative lines of ^{13}C-spectra, recorded for a series of selected compounds, are summarized in Table 2. The temperature was sometimes lowered to avoid coalescence, and the low solubility of products in chloroform was increased, when necessary, by adding DMSO; however, in many cases it was not possible to assign all the carbon lines.

Table 2. ^{13}C NMR assignments for N-acyl and N-aroylhydrazones of methyl pyruvate (VII-X, Scheme 3) in polar and less polar solvents (TMS as internal standard).

Isomer	R'	$\underline{C}H_3CO$	$-CH_2-$	N-C=O	N=C-	C-$\underline{C}H_3$	O-C=O	OCH_3	%[d]	T°C	solvent(v/v), notes
VII	CH_3	21.17	----	168.0	142.5	12.8	165.1	52.6	20	- 6	$CDCl_3$/DMSO-d_6 (5/1)
VIII	CH_3	20.7	----	174.5	139.3	12.3	165.1	52.6	80		
VIII	CH_3	20.6	----	174.8	140.1	11.9	164.9	53.1	100	-10	$CDCl_3$
VIII	CH_3	20.2	----	173.9	138.9	11.4	165.0	52.1	65	+20	$CDCl_3$ after thermal
X	CH_3	20.4	----	n.a.	n.a.	n.a.	n.a.	51.7	35		isomerization of VII[5]
VII-VIII	CH_3	20.5[a]	----	173.2[a]	139.0[a]	12.5	164.7	52.1	--	+30	DMSO-d_6
VII	$CH_2C_6H_5$	----	40.6	168.1	142.7	13.1	164.7	52.2	30	+ 0	$CDCl_3$/DMSO-d_6 (5/1)
VIII	$CH_2C_6H_5$	----	39.1	173.9	138.8	12.5	164.7	52.2	70		
VIII	$CH_2C_6H_5$	----	39.5	175.2	139.8	11.9	164.9	52.9	100	-10	$CDCl_3$
VIII	$CH_2C_6H_5$	----	38.9	175.0	140.0	11.7	164.9	52.7	50	+ 0	$CDCl_3$ after thermal
X	$CH_2C_6H_5$	----	43.0	173.8	140.0	20.4	162.3	52.4	50		isomerization of VII
VII-VIII	$CH_2C_6H_5$	--	n.a.[b]	173.6[a]	139.1	12.6	164.7	52.1	--	+30	DMSO-d_6
VII	C_6H_5	----	----	165.3[c]	144.1	13.0	164.7	52.1	82	+30	DMSO-$d_6$after thermal
IX	C_6H_5	----	----	n.a.	n.a.	20.1	n.a.	52.5	18		isomerization of VII
VII	C_6H_5	----	----	n.a.	n.a.	11.6	n.a.	52.7	16	+30	$CDCl_3$ after thermal
IX	C_6H_5	----	----	164.3[c]	137.3	20.0	163.3	52.5	84		isomerization of VII

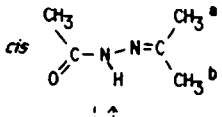
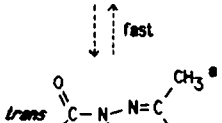
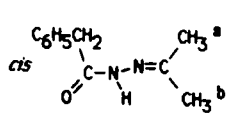
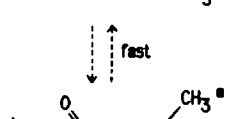
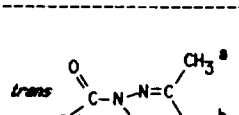
n.a.: not assigned. [a] Broad lines due to coalescence. [b] Covered by DMSO-d_6 carbon lines. [c] The broader line of carbonyls was assigned to the amide carbonyl. [d] The relative percentage of E/Z isomers VII-IX and VIII-X was determined by HPLC.

According to the assignments made for the hydrazones of aromatic aldehydes[6], the upfield lines of C=O and the lowfield lines of methyl and -C=N have been assigned to conformer VII (trans). Moreover it is known that steric hindrance in acetamides shifts the methyl group upfield and the carbonyl downfield.[9] The benzoyl hydrazone of methyl pyruvate apparently shows, both in polar and less polar solvents, only one amide conformer, to which the form VII (trans) has been assigned, as only this one was found in the purified solid state and identified by single-crystal X-ray analysis.[10]

The solvent polarity dramatically influences the ratio of cis/trans amide conformers and E/Z geometrical isomers. In polar aprotic solvents (DMSO), which are able to form strong intermolecular hydrogen bonds with NH groups, cis and trans amide conformers are present in about the same amount with the cis form (IV, VIII) prevailing slightly, while the unfavoured hindered geometrical Z isomers are present in small amounts (IX, X)[5] or not detected at all (V, VI). In less polar solvents ($CHCl_3$) intramolecular hydrogen bonds play a major role and stabilize the more hindered Z forms V-VI and IX-X, which consequently are usually more favoured than the corresponding E isomers. Hydrogen bonding interactions could also explain the greater stability of cis amide conformers (IV,VIII) in respect to trans ones (III, VII). Cis amide conformers are probably associated as dimers (Scheme 3, XI) by formation of pairs of hydrogen bonds, as has previously been reported for amides.[11]

The conformational behaviour of N-acyl and N-aroylhydrazones in solution and the effects of polar and less polar solvents on amide conformers were confirmed by a ^1H and ^{13}C NMR study on a series of hydrazones of acetone, which show simpler spectra, as they lack the possibility of E/Z geometrical isomers. Chemical shifts and percentage of conformers in DMSO-d_6 and in $CDCl_3$ are summarized in Table 3.

Table 3. ^1H NMR and ^{13}C NMR assignments for N-acetyl, N-phenylacetyl and N-benzoylhydrazones of acetone in polar and less polar solvents at 20°C (TMS as reference).

Isomer	Confor.	NMR	CH_3CO	$-CH_2-$	N-C=O	H-N=C-	CH_3^a	CH_3^b	%	Solvent
	cis	H-	2.03	----	-----	9.80	1.80	1.87	60	DMSO-d_6
		C-	20.5	----	171.9	149.5	16.8	25.0		
	trans	H-	1.87	----	-----	9.80	1.80	1.87	40	DMSO-d_6
		C-	21.3	----	165.4	154.0	17.3	24.8		
	cis	H-	2.22	----	-----	9.25	1.88	1.95	86	$CDCl_3$
		C-	20.4	----	173.9	149.8	16.5	25.4		
	trans	H-	2.05	----	-----	8.85	1.88	1.88	14	$CDCl_3$
		C-	21.7	----	166.5	154.8	16.8	24.8		
	cis	H-	----	3.82	-----	10.12	1.83	1.90	52	DMSO-d_6
		C-	----	38.9	172.2	150.0	16.9	25.1		
	trans	H-	----	3.50	----	10.02	1.83	1.90	48	DMSO-d_6
		C-	----	42.7	166.3	155.4	17.4	24.8		
	cis	H-	----	3.92	-----	9.30	1.75	1.95	80	$CDCl_3$
		C-	----	39.4	173.6	149.8	16.3	25.4		
	trans	H-	----	3.58	-----	8.55	1.55	1.95	20	$CDCl_3$
		C-	----	42.5	167.6	155.6	17.8	24.8		
	trans	H-	----	----	-----	10.33	1.83	1.86	100	DMSO-d_6
		C-	----	----	163.2	160.1	17.9	25.0		
	trans	H-	----	----	-----	8.27	1.88	1.96	100	$CDCl_3$
		C-	----	----	164.4	156.9	16.9	25.4		

The prevalence of cis conformer (C=O syn to NH) in less polar solvents is evident. Moreover, in the case of the other N-aroylhydrazones previously studied, the N-benzoylhydrazone of acetone apparently shows only one conformer (trans), as even spectra recorded at low temperature always show only one carbon line for each of C=O, C=N and methyl groups.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra of N-acyl and N-aroylhydrazones were recorded on a Varian XL-100 instrument. The carbon spectra of hydrazones of acetone (Table 3) were recorded on a Varian CFT-20 instrument at 20 MHz. HPLC was carried out on a Waters instrument using a U6K septumless injector, a 6000 A pump and a dual wavelength (254, 280) UV detector.

General procedure for the synthesis of hydrazones. N-acyl and N-aroylhydrazides were prepared by refluxing overnight the commercial methyl esters of aliphatic and aromatic acids (0.1 mol) dissolved in ethanol (100 ml) in presence of hydrazine hydrate (99%, 0.11 mol). After cooling, the solid hydrazide was recovered by filtration in almost quantitative yield, then dissolved in dichloromethane (100 ml), mixed with 0.1 moles of acetone, aldehyde or pyruvate and gently warmed. The hydrazone crystallized in few hours. The identification was made by IR, NMR, and mass spectrometry. All the compounds gave satisfactory C, H, and N analyses.

E → Z Isomerization of the pyridine-2-carbaldehyde-N-acetylhydrazone III. Kinetic experiments were carried out in duplicate in the dark at 20, 30 and 40°C on 1 M solutions in $CDCl_3$. The conversion of E to Z was periodically checked by ^{1}H NMR (Varian A 60), following the change of peak intensity of $-CH_3$, CH- and -NH lines. The isomerization at 40°C required few hours.
$\Delta G^{\neq}$ Values were calculated from kinetic constants, considering the isomerization as a first order, reversible reaction and applying the Arrhenius equation as previously reported for isomerization of methyl pyruvate hydrazones.[5]

HPLC. Acyl and aroyl hydrazones were dissolved in $CHCl_3$ or DMSO (1% solution) and injected (10 µl) into a 5 µm RP 18 column (25 x 0.4 cm, Merck). Elution was carried out with a methanol/water mixture (7/3, v/v), working at 1.0 ml/min and at about 2000 psi. The percentages of E and Z isomers were calculated from the ratio of UV absorption peaks recorded at 254 and 280 nm, as already reported.[5]

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