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Structure of Cyanoacetylhydrazones of Aldehydes and Ketones

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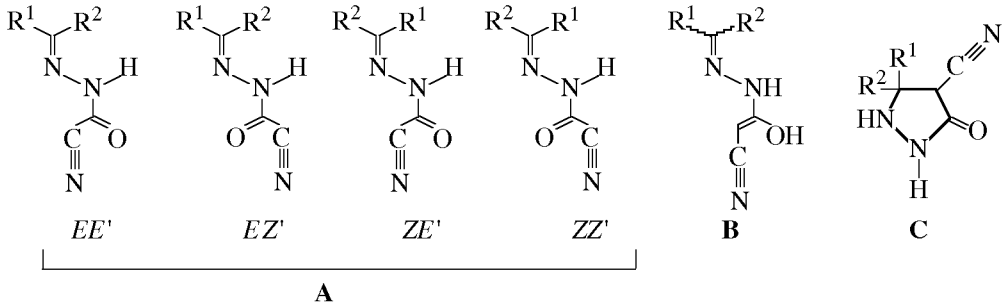
Abstract — 1D ^{1}H and ^{13}C, and 2D ^{1}H NOESY NMR were used to establish that cyanoacetylhydrazones of aliphatic and aromatic aldehydes and ketones in $CDCl_3$ and $(CD_3)_2SO$ solutions have a linear structure, exist as a mixture of geometric isomers by the C=N bond, and exhibit hindered amide rotation.

Cyanoacetylhydrazones exhibit a broad-spectrum biological activity (antimicrobial [1], antihelmintal [2], antiviral [3], modification of activity of brain mitochondrial monoaminoxidase [4], and inhibition of cell prolipheration [5, 6], which is valuable for therapy of cancer and atherosclerosis).

Reliable data on their structure are necessary for correct interpretation of biological properties. At the same time, the available information is controversial. In detail, cyanoacetylhydrazones of benzaldehyde and anisaldehyde [7] (by IR data), as well as *para*-chlorobenzaldehyde [8] and acetophenone [9] (by ^{1}H NMR data) were proposed to exist exclusively in hydrazone form **A**. Zommer [10], based on ^{1}H NMR, UV, and IR data, stated that cyanoacetylhydrazones of acetone and *para*-hydroxybenzaldehyde are present as two tautomers due to the keto-enol equilibrium **A** $\rightleftarrows$ **B**.



$R^1 = CH_3$ (**I**), C_2H_5 (**II**), C_3H_7 (**III**), C_3H_7-*i* (**IV**), C_6H_5 (**V**), $C_6H_4OCH_3$-*p* (**VI**), $R^2 = H$ (**I**–**VI**); $R^1 = CH_3$ (**VII**), C_4H_9-*t* (**VIII**), $R^2 = CH_3$ (**VII, VIII**); R^1, $R^2 = (CH_2)_4$ (**IX**); $R^1 = C_6H_5$ (**X**), $C_6H_4OCH_3$-p (**XI**), $C_6H_4NO_2$-*p* (**XII**), $R^2 = CH_3$ (**X**–**XII**); $R^1 = R^2 = C_6H_5$ (**XIII**).

Avetisyan *et al.* [11] reported the ^{1}H NMR evidence showing that cyanoacetylhydrazones of acetone, butan-2-one, 3-methylbutan-2-one, and pentan-3-one undergo irreversible cycloisomerization to the corresponding pyrazolidin-3-one derivatives **C** under reflux in triethylamine. Nevertheless, the authors did not present complete ^{1}H NMR data underlying their structural assessments. In [11], Avetisyan *et al.* obtained pyrazolidin-3-ones **C** isomeric to cyanoacetylhydrazones **A** by reactions of cyanoacetylhydrazine with acetaldehyde, propionaldehyde, butyraldehyde, and isobutyraldehyde [12], but the ^{1}H NMR data presented in this work are doubtful. Later the same authors stated that cyanoacetylhydrazones of propionaldehyde and acetone [13], as well as of other aliphatic aldehydes and ketones [14] exhibit the ring-chain tautomerism **A** $\rightleftarrows$ **C** in solutions. On the one hand, this contradicts the above data on isomerization, and on the other, is not substantiated by convincing spectral evidence. In [14], the authors only conclude that ^{1}H NMR spectra are not enough informative. At the same time, the cited work contains complete ^{1}H NMR spectra of those cyanoacetylhydrazones (of benzaldehyde, acetophenone, and some of their *para* derivatives) which have a single hydrazone form **A**.

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Table 1. Physicochemical characteristics of first prepared compounds

Comp. no.	mp, °C	R_f[a]	Found, %			Formula	Calculated, %		
			C	H	N		C	H	N
IV	110–111	0.74	54.96	7.18	27.59	$C_7H_{11}N_3O$	54.89	7.24	27.43
VIII	102–104	0.71	59.43	8.51	23.24	$C_9H_{15}N_3O$	59.64	8.34	23.19
IX	159–161	0.63	57.96	6.86	25.33	$C_8H_{11}N_3O$	58.17	6.71	25.44
XI	185–187	0.86	62.48	5.47	18.31	$C_{12}H_{13}N_3O_2$	62.33	5.67	18.17
XII	233–234	0.76	53.74	3.85	22.89	$C_{11}H_{10}N_4O_3$	53.66	4.09	22.75
XIII	178–180	0.82	72.76	4.79	16.10	$C_{16}H_{13}N_3O$	72.99	4.98	15.96

[a] Benzene–acetonitrile, 1 : 1.

Table 2. ^{1}H NMR spectra of compounds **I**–**XIII** in $CDCl_3$

Comp. no.	Form, %	δ, ppm (*J*, Hz)			
		R^1	R^2	CH_2, s	NH, br.s
I	*EE*', 53	1.98 d (5.5)	7.36 q (5.5)	3.82	10.33
	EZ', 30	1.98 d (5.5)	7.36 q (5.5)	3.82	10.26
	ZE', 13	1.95 d (5.6)	6.82 q (5.6)	3.84	9.86
	ZZ', 4	2.06 d (5.6)	7.63 q (5.6)	3.52	9.77
II	*E*, 87	1.10 m (CH_3), 2.30 m (CH_2)	7.40 t (4.9)	3.82	10.53
	ZE', 6	1.10 m (CH_3), 2.30 m (CH_2)	6.63 t (5.3)	3.83	10.04
	ZZ', 7	1.10 m (CH_3), 2.30 m (CH_2)	7.57 t (5.3)	3.54	10.02
III	*E*, 84	0.95 m (CH_3), 1.55 m (CH_2CH_3), 2.23 m (CH_2CH=N)	7.36 t (5.2)	3.80	10.52
	ZE', 8	0.95 m (CH_3), 1.55 m (CH_2CH_3), 2.23 m (CH_2CH=N)	6.64 t (5.6)	3.83	10.18
	ZZ', 8	0.95 m (CH_3), 1.55 m (CH_2CH_3), 2.23 m (CH_2CH=N)	7.54 t (5.6)	3.55	10.13
IV	*E*, 92	1.08 d (6.8) ($2CH_3$), 2.50 m [$(CH_3)_2CH$]	7.29 d (4.8)	3.79	10.47
	ZE', 3	1.08 d (6.8) ($2CH_3$), 2.86 m [$(CH_3)_2CH$]	6.44 d (7.9)	3.81	10.12
	ZZ', 5	1.08 d (6.8) ($2CH_3$), 2.50 m [$(CH_3)_2CH$]	7.43 d (6.0)	3.51	9.84
V	*E*, 100	7.2–7.8 m (H_{Ar})	7.88 s	3.95	9.57
VI	*E*, 100	3.88 s (CH_3O), 6.9–7.7 m (H_{Ar})	7.73 s	3.90	8.65
VII	100	1.95 br.s (CH_3), 2.01 br.s (CH_3)		3.82	9.72
VIII	*E*, 100	1.11 s	1.89 s	3.79	9.96
IX	100	1.69–1.95 m (H^β), 2.25–2.45 m (H^α)		3.79	9.69
X	*E*, 100	7.3–7.9 m	2.38 s	3.97	10.12
XI	*E*, 100	3.87 s (CH_3O), 6.9–7.8 m (H_{Ar})	2.28 s	3.93	9.20
XII	*E*, 100	7.9–8.3 m	2.34 s	3.92	8.85
XIII	100	7.2–7.8 m		3.99	8.57

Note that the **A** $\rightleftarrows$ **B** tautomerism is an extremely rare case of ring–chain tautomerism involving C–H bond. Therefore, it is not surprising that the above-mentioned results [13, 14] were included in the review on the modern state of the problem of ring–chain tautomerism [15].

Hence, the question on the structure of cyanoacetylhydrazones in solutions have still remained open. To fill this gap, we synthesized a series of cyanoacetylhydrazones of typical representatives of aldehydes and ketones (compounds **I**–**XIII**, see Table 1) and studied their structure by means of ^{1}H and ^{13}C NMR spectroscopy in $CDCl_3$ and $(CD_3)_2SO$ solutions (see Tables 2–4).

To make sure that we deal with an established equilibrium, we measured NMR spectra of the solutions just after their preparation, after handling for two weeks at room temperature, and, finally, after heating for a day at 70°C. With all the compounds under study, the spectra showed no alterations with time.

Table 3. ^{1}H NMR spectra of compounds **I**–**XIII** in $(CD_3)_2SO$

Comp. no.	Form, %	δ, ppm (*J*, Hz)			
		R^1	R^2	CH_2, s	NH, br.s
I	*EE'*, 61	1.85 m	7.33 q (5.3)	3.96	11.30
	EZ', 28	1.85 m	7.47 q (5.3)	3.65	11.30
	ZE', 8	1.85 m	6.73 q (5.5)	4.00	10.86
	ZZ', 3	1.85 m	6.92 q (5.5)	3.79	10.58
II	*EE'*, 68	1.01 t (7.3) (CH_3), 2.21 m (CH_3CH_2)	7.35 t (4.8)	3.98	11.35
	EZ', 28	1.01 t (7.3) (CH_3), 2.21 m (CH_3CH_2)	7.48 t (4.8)	3.66	11.27
	ZE', 3	1.01 t (7.3) (CH_3), 2.21 m (CH_3CH_2)	6.58 t (5.3)	4.03	10.92
	ZZ', 1	1.01 t (7.3) (CH_3), 2.21 m (CH_3CH_2)	6.76 t (5.3)	3.79	10.60
III	*EE'*, 66	0.89 t (7.5) (CH_3), 1.48 m (CH_3CH_2), 2.16 m (CCH_2CH=N)	7.33 t (5.3)	3.96	11.33
	EZ', 27	0.89 t (7.5) (CH_3), 1.48 m (CH_3CH_2), 2.16 m (CCH_2CH=N)	7.46 t (5.3)	3.66	11.26
	ZE', 5	0.89 t (7.5) (CH_3), 1.48 m (CH_3CH_2), 2.16 m (CCH_2CH=N)	6.61 t (5.6)	4.02	10.92
	ZZ', 2	0.89 t (7.5) (CH_3), 1.48 m (CH_3CH_2), 2.16 m (CCH_2CH=N)	6.77 t (5.6)	3.79	10.59
IV	*EE'*, 74	1.06 m [$(CH_3)_2C$], 2.46 m [$(CH_3)_2CH$]	7.27 d (4.8)	3.90	11.29
	EZ', 25	1.06 m [$(CH_3)_2C$], 2.46 m [$(CH_3)_2CH$]	7.40 d (5.2)	3.60	11.15
	ZE', 0.7	1.06 m [$(CH_3)_2C$], 2.46 m [$(CH_3)_2CH$]	6.38 d (8.1)	3.95	10.96
	ZZ', 0.3	1.06 m [$(CH_3)_2C$], 2.46 m [$(CH_3)_2CH$]	6.55 d (8.1)	3.74	10.57
V	*EE'*, 80	7.3–7.8 m	8.00 s	4.13	11.78
	EZ', 20	7.3–7.8 m	8.18 s	3.82	11.78
VI	*EE'*, 78	3.80 s (CH_3O), 6.9–7.7 m (H_{Ar})	7.95 s	4.17	11.66
	EZ', 22	3.80 s (CH_3O), 6.9–7.7 m (H_{Ar})	8.11 s	3.78	11.66
VII	*E'*, 67	1.86 s (CH_3), 1.92 s (CH_3)		3.89	10.51
	Z', 33	1.86 s (CH_3), 1.95 s (CH_3)		3.68	10.25
VIII	*EE'*, 80	1.06 s	1.81 s	3.94	10.53
	EZ', 20	1.06 s	1.83 s	3.74	10.33
IX	*E'*, 67	1.59–1.83 m ($H^{3,4}$), 2.18–2.38 m ($H^{2,5}$)		3.97	10.46
	Z', 33	1.59–1.83 m ($H^{3,4}$), 2.18–2.38 m ($H^{2,5}$)		3.74	10.20
X	*EE'*, 78	7.3–7.9 m	2.26 s	4.23	11.04
	EZ', 22	7.3–7.9 m	2.28 s	3.90	10.70
XI	*EE'*, 78	3.77 s (CH_3O), 6.8–7.9 m (H_{Ar})	2.21 s	4.17	10.93
	EZ', 22	3.77 s (CH_3O), 6.8–7.9 m (H_{Ar})	2.23 s	3.89	10.62
XII	*EE'*, 80	7.9–8.4 m	2.31 s	4.30	11.27
	EZ', 20	7.9–8.4 m	2.33 s	3.95	10.91
XIII	*E'*, 67	7.2–7.7 m		4.34	10.24
	Z', 33	7.2–7.7 m		3.82	10.38

The spectral data show that in solutions of compounds **I**–**XIII** no **B** and **C** forms are present. Form **B** is expected to give the CH= proton signal near 6–7 ppm in ^{1}H NMR spectrum and double-bond carbon signals at 85–90 and 175–180 ppm in the ^{13}C NMR spectrum [16]. Cyclic tautomer **B** can be easily found knowing that the H^4 proton signal in the ^{1}H NMR spectrum should be observed at 3.5–4.5 ppm and the C^3 carbon signals atom in the ^{13}C NMR, at 65–70 ppm [18]. In this case, the observation of multiple (up to four) sets of signals in the spectra of compounds **I**–**XIII** should be related to stereoisomerism: *E/Z* isomerism and hindered amide rotation (*E'*/*Z'* isomerism).

In structural assessments of stereoisomeric forms we used previously established rules and criteria [17–22]. Compounds **VII, IX**, and **XIII** in which the *E'*/*Z'* isomerism is impossible and compounds **V, VI, VIII**, and **X**–**XII** which are known to be present as a single *E'* isomer all exist in $CDCl_3$ solutions exclusively in hydrazone form **A**. In $(CD_3)_2SO$ solutions of these compounds an appreciable amount (from 20 to 33%) of another form appears. From a comparison of the chemical shifts of this form with those of the

Table 4. ^{13}C NMR spectra of compounds **I**–**XIII** in $(CD_3)_2SO$

Comp. no.	Form	δ_C, ppm					
		R^1	R^2	CH_2	C≡N	C=N	C=O
I	*EE*'	19.0	–	24.9	116.8	146.5	166.4
	EZ'	19.0	–	25.4	116.8	149.7	159.2
	ZE'	15.0	–	25.5	116.6	145.2	164.7
	ZZ'	15.2	–	24.4	116.6	148.6	162.6
II[a]	*EE*'	11.0 (CH_3), 24.9 (CH_3CH_2)	–	26.0	116.8	150.9	164.9
	EZ'	11.2 (CH_3), 25.4 (CH_3CH_2)	–	26.1	116.6	154.2	159.2
III[a]	*EE*'	14.3 (CH_3), 19.9 ($CH_3CH_2CH_2$), 34.5 ($CH_3CH_2CH_2$)	–	24.9	116.7	149.9	164.8
	EZ'	14.3 (CH_3), 20.1 ($CH_3CH_2CH_2$), 34.5 ($CH_3CH_2CH_2$)	–	25.4	116.5	153.2	159.2
IV[a]	*EE*'	20.1 (CH_3), 31.6 [$(CH_3)_2CH$]	–	24.7	116.4	154.1	164.7
	EZ'	20.3 (CH_3), 31.8 [$(CH_3)_2CH$]	–	25.4	116.2	157.5	159.1
V	*EE*'	127–135	–	25.2	116.8	145.4	165.6
	EZ'	127–135	–	25.8	116.5	148.8	159.9
VI	*EE*'	56.1 (CH_3O), 127–130, 159–162 (C_{Ar})	–	25.1	116.9	145.2	165.3
	EZ'	56.1 (CH_3O), 127–130, 159–162 (C_{Ar})	–	25.6	116.6	148.6	161.9
VII	*E*'	18.1 (CH_3), 25.9 (CH_3)		25.0	116.4	152.9	165.3
	Z'	18.4 (CH_3), 25. 6 (CH_3)		25.2	116.4	157.5	159.3
VIII	*EE*'	28.1 [$CH_3)_3C$], 39.2 [$(CH_3)_3C$]	13.0	25.3	116.7	160.8	166.1
	EZ'	28.2 [$CH_3)_3C$], 39.3 [$(CH_3)_3C$]	13.4	25.4	116.7	159.6	165.3
IX	*E*'	25.3 ($C^{3,4}$), 29.3 (*anti*-C^2), 33.9 (*syn*-C^5)		25.2	116.8	165.4	165.3
	Z'	25.1 ($C^{3,4}$), 29.4 (*anti*-C^2), 33.7 (*syn*-C^5)		25.4	116.7	168.9	159.5
X	*EE*'	126–140	14.8	25.8	117.1	150.0	166.7
	EZ'	126–140	15.2	25.8	116.8	154.0	160.2
XI	*EE*'	56.0 (CH_3O), 114–150 (C_{Ar})	14.5	25.7	117.1	149.8	166.4
	EZ'	56.0 (CH_3O), 114–150 (C_{Ar})	14.9	25.7	116.9	153.9	160.0
XII	*EE*'	123–145 (C_{Ar})	14.7	25.8	116.9	147.9	167.1
	EZ'	123–145 (C_{Ar})	15.1	25.8	116.7	151.5	160.7
XIII	*E*'	128–139 (C_{Ar})		25.8	116.9	152.4	166.1
	Z'	128–139 (C_{Ar})		25.7	116.7	155.3	160.6

[a] The signals of the *ZE*' and *ZZ*' forms are very weak (Table 2).

major isomer (a single form in $CDCl_3$) with regard to the known solvent effect on the isomer ratio [18–22] we can conclude that it is a *Z*' isomer.

For compounds **I**–**IV**, derivatives of aliphatic aldehydes, which were expected to exist as *E/Z* mixtures with prevalence of the *E* isomers, already in $CDCl_3$ solutions we observed up to 4 stereoisomeric forms. At first glance the signals of these forms were difficult to assign. But here we made use of 2D NOESY spectroscopy [23] in $(CD_3)_2SO$ to reliably assess the structure of acetaldehyde and acetone cyanoacetylhydrazones (**I, VII**) whose 1D ^1H NMR spectrum contain four and two sets of signal groups, respectively. Both for major and for minor pairs of NH, CH, and CH_2 signals on the dimetric matrix of ^1H NMR signals both intense and minor pairs of positive cross peaks were observed, implying exchange between the *E*' and *Z*' forms. From the negative cross peaks caused by NOE we gained a qualitative information on the distances between various groups in the molecule. The combined data allow a conclusion that the more intense sets of signals in the ^1H NMR spectra belong to the *E* form in relation to the C=N bond, while the minor pairs, to the *Z* isomer. In these pairs, the more intense signal is assignable to the *E*' form in relation to the amide NH–CO bond, while the minor one, to the *Z*' form.

Basing on the signal assignment for separate stereoisomeric forms of acetaldehyde cyanoacetylhydrazone (**I**), we made assignments for the other aliphatic aldehyde derivatives in both solvents. Note that the geminal coupling constant ^3J of the methine proton in aliphatic aldehydes is larger for the *Z* isomers as compared to the *E* isomers.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were registered at 300 K on a Bruker DPX-300 spectrometer [300.130 (^{1}H) and 75.47 MHz (^{13}C)]. The delay time in the NOESY experiment was 2 s. The chemical shifts were measured in δ, ppm, against TMS. The concentrations of the solutions were 5–15%.

Alkylidene derivatives of cyanoacetylhydrazine were prepared by boiling 10 mmol of carbonyl compound with 10 mmol of cyanoacetylhydrazine in 10 ml of methanol for 30 min. The resulting needle-like crystals were crystaliized from methanol.

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