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Ring-chain tautomerism of thirty-six aldehyde semicarbazones was studied by nmr spectroscopy. The 2,4-dimethylsemicarbazones of benzaldehyde, *p*-tolualdehyde, *p*-anisaldehyde, and *p*-chlorobenzaldehyde exist as chain forms in DMSO-d_6, but as both ring and chain forms in deuteriotrifluoroacetic acid. Unlike these semicarbazones, the aldehyde semicarbazones of *N*-unsubstituted semicarbazide, 2-methylsemicarbazide, and 4-methylsemicarbazide did not cycloisomerize in either DMSO-d_6 or deuteriotrifluoroacetic acid. These results indicate that protonation of the C=N nitrogen atom and steric hindrance of the 2-methyl group with an aromatic group at the C=N carbon atom in the chain form cause cycloisomerization to ring isomers.

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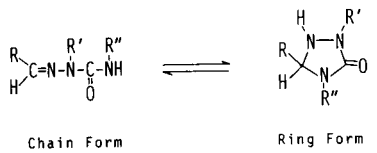
Cycloisomerism of visnaginone semicarbazones (1), khellinone semicarbazones (1), and acetone 2-phenylsemicarbazone (2) have been reported, but no cyclic isomers of aldehyde semicarbazones are known. It has recently been shown that ketone 4-alkyl-2-phenylsemicarbazones derived from aliphatic and alicyclic ketones isomerize to ring-tautomeric 1-phenyl-3,3,4-trialkyl-1,2,4-triazolin-5-ones in the presence of catalytic amounts of hydrochloric acid, whereas benzaldehyde 2-phenylsemicarbazones do not cyclize (3).

To assess whether cyclotautomerism is limited to ketone semicarbazones, various aldehyde semicarbazones were prepared and their ring-chain tautomerism was studied. Benzaldehyde, five *p*-substituted benzaldehydes and three pyridine aldehydes were used as parent carbonyl compounds to examine the electronic effects of substituents on tautomerism, since the steric effects around the carbonyl carbon atoms of these compounds are considered to be almost equal.

Scheme



Ring-chain tautomerism of the aldehyde semicarbazones was studied by nmr spectroscopy. Mayer and Lauerer (4) reported that aldehyde thiosemicarbazones exist in chain forms in hexadeuteriodimethylsulfoxide (DMSO-d_6) and the nmr signals of their methine protons appeared in a region of 7.5-8.0 ppm, whereas in deuteriotrifluoroacetic acid they exist in the ring form of 1,3,4-thiadiazoline derivatives and their signals appear in a region of 5.0-6.0 ppm. Therefore, it is possible to judge whether semicarbazones exist in ring or chain forms from the chemical shifts of their methine protons.

The nmr data in Table I show that all the semicarbazones (**1-9**) have signals of methine protons at about 7.7-8.0 ppm in DMSO-d_6. These signals were assigned to the methine protons of the chain isomers. The signals of the methine protons of the same compounds in deuteriotrifluoroacetic acid appeared in essentially the same region. Consequently, aldehyde *N*-unsubstituted semicarbazones were concluded to exist in chain forms in both DMSO-d_6 and deuteriotrifluoroacetic acid. These results are in contrast to the finding that aldehyde thiosemicarbazones exist in a ring form in deuteriotrifluoroacetic acid (4).

To study the effects of substituents at position 2 or 4 of semicarbazones on ring-chain tautomerism, various aldehyde 2-methylsemicarbazones (**10-18**) and aldehyde 4-methylsemicarbazones (**19-27**) were prepared. A methyl group at position 2 is thought to have an influence on cyclotautomerism, because many ketone 2-substituted semicarbazones have been reported to undergo cycloisomerization in the presence of catalytic amounts of hydrochloric acid (3). Methylation at position 4 is also

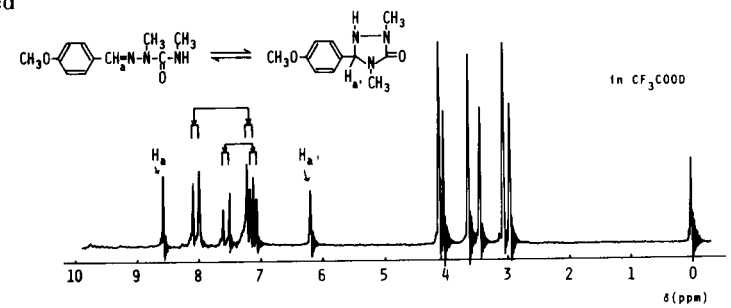


Figure 1. Pmr spectrum of *p*-anisaldehyde 2,4-dimethylsemicarbazone (**32**) in deuteriotrifluoroacetic acid.

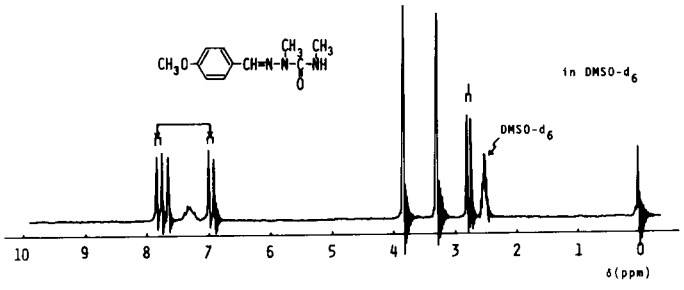
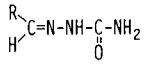
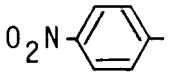
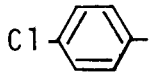
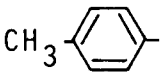
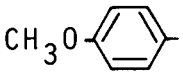
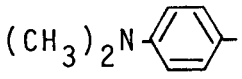


Figure 2. Pmr spectrum of *p*-anisaldehyde 2,4-dimethylsemicarbazone (**32**) in DMSO-d_6.

Table I

Chemical Shifts (ppm) of Methine-Protons in Semicarbazones (**1-9**)



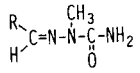
Compound No.	R	DMSO-d_6	Deuteriotrifluoroacetic Acid
1		7.92	8.14
2		7.85	8.04
3		7.82	8.20
4		7.81	8.50
5		7.78	8.55
6		7.70	8.11
7		7.96	8.32
8		7.94	8.32
9		7.96	8.28

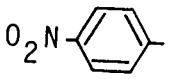
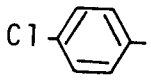
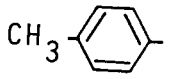
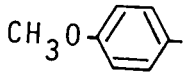
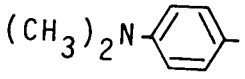
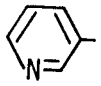
expected to be favorable for cycloisomerization by increasing nucleophilicity of the nitrogen atom. However, from the data in Tables II and III, all the 2- or 4-methylated semicarbazones were concluded to exist in a chain form in both DMSO-d_6 and deuteriotrifluoroacetic acid.

Next, ring-chain tautomerism of aldehyde 2,4-dimethylsemicarbazones was studied. The nmr data in Table IV show that all the 2,4-dimethylsemicarbazones (**28-36**) exist in a chain form in DMSO-d_6. However, these compounds except **28** and **33-36** exist in both ring and chain forms in deuteriotrifluoroacetic acid. That is, the nmr spectra of **29-32** in deuteriotrifluoroacetic acid have two singlets at about 8 ppm and 6 ppm. The upfield signals were assigned to the methine protons of the ring isomers and the downfield signals to those of the chain isomers. Other evidence supported the above conclusions. For example, the nmr spectrum of *p*-anisaldehyde 2,4-dimethylsemicarbazone (**32**) in deuteriotrifluoroacetic acid shows singlets at 2.96, 3.43, 4.03, and 6.20 ppm for the N^4-CH_3, N^2-CH_3, O-CH_3, and CH protons of the ring isomer, respectively, and at 3.06, 3.62, 4.10, and 8.56 ppm for those of the chain isomer, respectively (Figure 1). In the nmr spectrum of the same compound in DMSO-d_6, the signals of the N^4-CH_3 protons appeared at 2.79 ppm

Table II

Chemical Shifts (ppm) of Methine-Protons in 2-Methylsemicarbazones (**10-18**)



Compound No.	R	DMSO-d_6	Deuteriotrifluoroacetic Acid
10		7.78	8.04
11		7.68	7.98
12		7.66	8.05
13		7.63	8.15
14		7.62	8.35
15		7.55	8.03
16		7.60	7.97
17		7.71	8.04
18		7.63	7.99

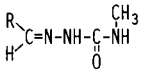
as a doublet and that of the NH proton appeared at 7.36 ppm as an unresolved quartet due to the chain isomer (Figure 2).

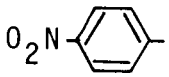
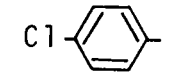
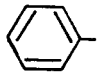
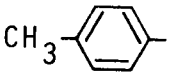
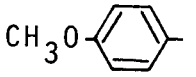
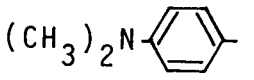
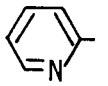
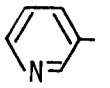
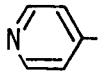
The finding that only 2,4-dimethylsemicarbazones can exist in ring forms indicates that the presence of substituents at positions 2 and 4 is essential for cycloisomerization of aldehyde semicarbazones. We conclude that steric hindrance between the 2-methyl group and the aromatic ring in the chain isomers favors isomerization to ring isomers and that the methyl group at position 4 also aids cycloisomerization by increasing the nucleophilicity of the N^4-atom.

The ring/chain ratios of **29-32** were determined by measuring the relative intensities of the methine or *N*-methyl signals (Table IV). These data indicate that the ring/chain ratio decreased as electron-attracting or electron-releasing effects of the *p*-substituents in phenyl group increased. This observation was unexpected, because substitution of the electron-attracting group at *p*-position in phenyl group causes electron-deficiency of the C=N

Table III

Chemical Shifts (ppm) of Methine-Protons in 4-Methylsemicarbazones (**19-27**)



Compound No.	R	DMSO-d_6	Deuteriotrifluoroacetic Acid
19		7.91	8.21
20		7.80	8.20
21		7.82	8.43
22		7.80	8.58
23		7.77	8.58
24		7.72	8.18
25		7.88	8.22
26		7,86	8.28
27		7.80	8.20

carbon atom and so might be favorable for cycloisomerization. However, this unexpected results can be explained by the following mechanism. Since the ring isomers of the 2,4-dimethylsemicarbazones can exist only in deuteriotrifluoroacetic acid, the first step of cyclotautomerization seems to involve protonation of the C=N nitrogen atom and then attack of the N^4-atom on the polarized C=N carbon atom. Protonation of other positions would prevent protonation of the C=N group: for example, protonation of the dimethylamino group in compound **33** would be unfavorable for protonation of the C=N group. This mechanism would explain why *p*-nitrobenzaldehyde semicarbazone (**28**), *p*-dimethylaminobenzaldehyde semicarbazone (**33**), and the three pyridinealdehyde semicarbazones (**34-36**) did not cycloisomerize in deuteriotrifluoroacetic acid.

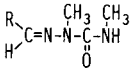
EXPERIMENTAL

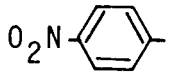
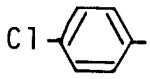
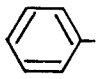
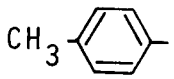
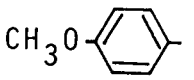
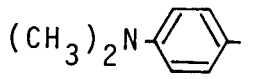
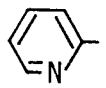
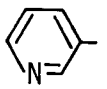
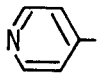
Nmr spectra were recorded with a JEOL PS-100 spectrometer at 100 MHz using tetramethylsilane as an internal standard. All melting points were determined by the capillary method and were uncorrected.

General Method for Preparation of the Semicarbazones (Table V).

Table IV

Chemical Shifts (ppm) of Methine-Protons in 2,4-Dimethylsemicarbazones (**28-36**)



Compound No.	R	DMSO-d_6	Deuteriotrifluoroacetic Acid
28		7.81	7.94
29		7.67	7.76 + 6.18 (65% 35%)
30		7.67	8.07 + 6.16 (22% 78%)
31		7.64	8.23 + 6.12 (25% 75%)
32		7.62	8.56 + 6.20 (62% 38%)
33		7.55	7.94
34		7.62	7.88
35		7.71	7.94
36		7.65	7.89

The appropriate aldehyde (5 mmoles) was added to a solution of the corresponding semicarbazide (5 mmoles) in ethanol (5-10 ml.), and the mixture was refluxed for 2-3 hours. The semicarbazone precipitated on cooling was recrystallized from ethanol. In preparation of 2,4-dimethylsemicarbazones, several drops of acetic acid were added to the reaction mixtures. The starting materials, 2-methylsemicarbazide (5), 4-methylsemicarbazide (6), and 2,4-dimethylsemicarbazide (6), were prepared by published methods.

The other semicarbazones, **1-3** (6), **4** (7), **5** (6), **6** (8), **7-8** (9), **9** (10), **10** (6), **12** (6), **14** (6), **19-21** (6), **23** (6), **28** (6), **30** (6), and **32** (6), used in this study were prepared as described in the literature.

Acknowledgments.

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(5) G. von Brüning, *ibid.*, **253**, 5 (1889).

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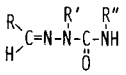
Table V

N-Methylated Semicarbazones



Compound No.	R	R′	R″	Appearance	Yield (%)	M.p. (°C)	Formula	Analyses Found (Calcd.) C	H	N
11	*p*-ClC_6H_4	CH_3	H	colorless needles	79	170-171	$C_9H_{10}ClN_3O$	50.90 (51.07)	4.71 (4.76)	19.81 (19.85)
13	*p*-$CH_3C_6H_4$	CH_3	H	colorless plates	86	178-179	$C_{10}H_{13}N_3O$	62.72 (62.81)	6.89 (6.85)	21.76 (21.97)
15	*p*-$(CH_3)_2NC_6H_4$	CH_3	H	pale yellow fine needles	83	199-200 (dec.)	$C_{11}H_{16}N_4O$	59.80 (59.98)	7.36 (7.32)	25.28 (25.44)
16	2-Pyridyl	CH_3	H	colorless plates	73	159-160	$C_8H_{10}N_4O$	53.97 (53.92)	5.72 (5.66)	31.45 (31.44)
17	3-Pyridyl	CH_3	H	colorless needles	85	200-201	$C_8H_{10}N_4O$	54.10 (53.92)	5.60 (5.66)	31.29 (31.44)
18	4-Pyridyl	CH_3	H	colorless needles	86	167-168	$C_8H_{10}N_4O$	53.75 (53.92)	5.65 (5.66)	31.68 (31.44)
22	*p*-$CH_3C_6H_4$	H	CH_3	colorless fine needles	95	192-193	$C_{10}H_{13}N_3O$	62.56 (62.81)	6.91 (6.85)	21.84 (21.97)
24	*p*-$(CH_3)_2NC_6H_4$	H	CH_3	pale yellow needles	87	194-195 (dec.)	$C_{11}H_{16}N_4O$	60.04 (59.98)	7.46 (7.32)	25.37 (25.44)
25	2-Pyridyl	H	CH_3	colorless needles	75	179-180	$C_8H_{10}N_4O$	53.67 (53.92)	5.68 (5.66)	(31.44) (31.44)
26	3-Pyridyl	H	CH_3	colorless needles	94	167-168	$C_8H_{10}N_4O$	53.71 (53.92)	5.63 (5.66)	31.25 (31.44)
27	4-Pyridyl	H	CH_3	colorless needles	91	187-188	$C_8H_{10}N_4O$	53.77 (53.99)	5.73 (5.66)	31.29 (31.49)
29	*p*-ClC_6H_4	CH_3	CH_3	colorless fine needles	80	163-164	$C_{10}H_{12}ClN_3O$	53.47 (53.22)	5.48 (5.36)	18.46 (18.62)
31	*p*-$CH_3C_6H_4$	CH_3	CH_3	colorless rods	78	113-114	$C_{11}H_{15}N_3O$	64.13 (64.37)	7.44 (7.37)	20.53 (20.47)
33	*p*-$(CH_3)_2NC_6H_4$	CH_3	CH_3	colorless plates	87	136-137	$C_{12}H_{18}N_4O$	61.32 (61.52)	7.73 (7.74)	24.03 (23.91)
34	2-Pyridyl	CH_3	CH_3	colorless plates	76	112-113	$C_9H_{12}N_4O$	56.01 (56.24)	6.10 (6.29)	29.02 (29.15)
35	3-Pyridyl	CH_3	CH_3	colorless fine needles	81	137-138	$C_9H_{12}N_4O$	56.16 (56.24)	6.27 (6.29)	28.97 (29.15)
36	4-Pyridyl	CH_3	CH_3	colorless fine needles	78	184-185	$C_9H_{12}N_4O$	56.08 (56.24)	6.15 (6.29)	28.98 (29.15)