Notes

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Tautomeric Character of 3-Heteroarylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxalines¹⁾

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The proton nuclear magnetic resonance (¹H-NMR) spectra of some 3-(1,3,4-oxadiazol-5-ylmethylene)-2-oxo-1,2,3,4-tetrahydroquinoxalines and 3-(1,2,4-triazol-5-ylmethylene)-2-oxo-1,2,3,4-tetrahydroquinoxalines were measured in dimethylsulfoxide-*d*₆ (DMSO-*d*₆), trifluoroacetic acid (TFA), and TFA-*d*₁. The spectra in DMSO-*d*₆ indicated that **2**, **3**, **4**, and **5** existed as the two tautomers A and B, and **6**, **7**, and **8** as a single tautomer. From the spectra of **2**, **3**, **4**, and **5** in DMSO-*d*₆, it was elucidated that tautomer A was predominant over tautomer B at low temperature, while the ratio of the tautomer B gradually increased with increase of the temperature. The spectra in TFA indicated that **2** occurred as the three tautomers C, D, and E, while **3**, **4**, and **5** existed as a single tautomer, D. Compounds **6** and **7** also appeared to isomerize in TFA, that is, **6** existed as the two tautomers C and E, while **7** existed as two of the three tautomers C, E, and G. Compound **8** was predominantly present in the form of tautomer C or E.

Keywords—3-(1,3,4-oxadiazol-5-ylmethylene)-2-oxo-1,2,3,4-tetrahydroquinoxaline; 3-(1,2,4-triazol-5-ylmethylene)-2-oxo-1,2,3,4-tetrahydroquinoxaline; 3-(α -hydroxy-1,3,4-oxadiazol-5-ylmethylene)-2-oxo-1,2,3,4-tetrahydroquinoxaline; 3-(4-allyl- α -hydroxy-3-methylsulfinyl-4*H*-1,2,4-triazol-5-ylmethylene)-2-oxo-1,2,3,4-tetrahydroquinoxaline; 3-(α -hydroxyimino-4-methyl-4*H*-1,2,4-triazol-5-ylmethyl)-2-oxo-1,2-dihydroquinoxaline; prototropy; protonation; isomerization

The tautomerism of 3-methoxycarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxaline (**1a**) and related compounds (**1b**—**e**) has been studied by means of nuclear magnetic resonance (NMR) and ultraviolet (UV) spectroscopies by Mondelli and Merlini.²⁾ Namely, the proton nuclear magnetic resonance (¹H-NMR) spectra in dimethylsulfoxide-*d*₆ (DMSO-*d*₆) demonstrated that two tautomers A and B of **1a**, **1b**, and **1c** coexist, while the tautomer A predominates in the cases of **1d** and **1e**, as shown in Chart 1 and Table I. In addition, the ¹H-NMR spectra in trifluoroacetic acid (TFA) indicated that **1a** and **1b** existed as the tautomer B, while **1c**, **1d**, and **1e** existed as the tautomer A. Thus, compounds **1a**—**e** exist predominantly as the single tautomer A or B in TFA.

In previous studies,^{3–6)} we also synthesized compounds of type **1** having various heteroaryl groups at the 3-methylenic carbon, such as 3-(1,3,4-oxadiazol-5-ylmethylene)-2-oxo-1,2,3,4-tetrahydroquinoxalines (**2a**,³⁾ **2b**,³⁾ **2c**⁴⁾), 3-(2,3-dihydro-2-thioxo-1,3,4-oxadiazol-

Chart 1. Equilibria of **1** in DMSO or TFA

TABLE I. Tautomers of 1 Assigned on the Basis of $^1\text{H-NMR}$ Spectral Data

No.	Compound R	R'	Tautomers	
			in $\text{DMSO-}d_6$	in TFA
1a	COOMe	H	A B	B
1b	COOEt	H	A B	B
1c	CN	H	A B	A
1d	COMe	H	A	A
1e	COCOOEt	Me	A	A

Chart 2

5-ylmethylene)-2-oxo-1,2,3,4-tetrahydroquinoxaline (3),⁴⁾ 3-(3,4-dihydro-3-thioxo-2H-1,2,4-triazol-5-ylmethylene)-2-oxo-1,2,3,4-tetrahydroquinoxalines (4a—c),^{5,6)} 3-(4H-1,2,4-triazol-5-ylmethylene)-2-oxo-1,2,3,4-tetrahydroquinoxalines (5a,^{5,6)} 5b,⁶⁾ 5c,⁶⁾ 3-(α -hydroxy-1,3,4-oxadiazol-5-ylmethylene)-2-oxo-1,2,3,4-tetrahydroquinoxaline (6),^{3b)} 3-(α -hydroxyimino-4-methyl-4H-1,2,4-triazol-5-ylmethyl)-2-oxo-1,2-dihydroquinoxaline (7),^{5,6)} and 3-(4-allyl- α -hydroxy-3-methylsulfinyl-4H-1,2,4-triazol-5-ylmethylene)-2-oxo-1,2,3,4-tetrahydroquinoxaline (8),⁶⁾ as shown in Chart 2. In contrast to the above tautomerism of 1, some of compounds 2—8 were found to exhibit interesting tautomeric behavior. That is, they existed as two or more tautomers in TFA and as two tautomers in $\text{DMSO-}d_6$. These tautomeric properties in TFA are presumably due to the presence of the heterocycles conjugated with the 3-methylenic carbon in place of the carbonyl or nitrile group of 1. This paper describes the tautomeric behavior of 3-(1,3,4-oxadiazol-5-ylmethylene)-2-oxo-1,2,3,4-tetrahydroquinoxalines and 3-(1,2,4-triazol-5-ylmethylene)-2-oxo-1,2,3,4-tetrahydroquinoxalines in $\text{DMSO-}d_6$, TFA, and $\text{TFA-}d_1$ based on $^1\text{H-NMR}$ spectral analyses.

Tautomeric Equilibria of 2, 3, 4, and 5

The $^1\text{H-NMR}$ spectrum of 1a in $\text{DMSO-}d_6$ exhibited vinyl and methylene proton signals due to the tautomers A and B at δ 5.52 and 3.83 ppm, respectively. The spectra of 2a, 2b, and 2c in $\text{DMSO-}d_6$ also showed the vinyl and methylene proton signals together with pairs of $\text{C}^{2'}\text{-H}$, $\text{C}^{2'}\text{-Me}$, and $\text{C}^{2'}\text{-SMe}$ proton signals (Table II). Similarly, the spectra of 3, 4a—c, and 5a—

TABLE II. ^1H -NMR Spectral Data for **2**

Solvent	Compound	Vinyl		Chemical shift δ (ppm)		
				Methylene	C ^{2'} -H, Me, SMe	
DMSO- <i>d</i> ₆	2a	6.12		4.47	9.20	9.13 (C ^{2'} -H)
	2b	6.02		4.37	2.50	2.49 (C ^{2'} -Me)
	2c	6.00		4.39	2.71	2.66 (C ^{2'} -SMe)
TFA	2a	6.63	6.03	4.97	— ^{a)}	— ^{a)} 8.44 (C ^{2'} -H)
	2b	6.52	5.97	4.93	2.92	2.80 2.62 (C ^{2'} -Me)
	2c	6.47	5.92	4.93	2.88	2.84 2.73 (C ^{2'} -SMe)
TFA- <i>d</i> ₁	2a	—	—	—	9.05	8.97 8.47 (C ^{2'} -H)
	2b	—	—	—	2.95	2.88 2.65 (C ^{2'} -Me)
	2c	—	—	—	2.93	2.86 2.73 (C ^{2'} -SMe)

a) Overlapping with TFA hydrogen.

TABLE III. ^1H -NMR Spectral Data for **3**, **4**, and **5**

Solvent	Compound	Vinyl	Chemical shift δ (ppm)	
			Methylene	Methyl
DMSO- <i>d</i> ₆	3	5.86	4.29	
	4a	5.88	4.18	
	4b	5.87	4.18	3.79 3.76 (N ^{2'} -Me)
	4c	5.93	4.27	3.53 3.50 (N ^{4'} -Me)
	5a	5.97	4.23	2.63 2.58 (C ^{3'} -SMe)
	5b	6.42	4.56	
	5c	6.42	4.56	3.60 3.56 (N ^{4'} -Me)
TFA	3	—	4.72	
	4a	—	4.90	
	4b	—	— ^{a)}	2.73 (N ^{2'} -Me)
	4c	—	4.83	3.90 (N ^{4'} -Me)
	5a	—	4.90	2.90 (C ^{3'} -SMe)
	5b	—	5.26	
	5c	—	5.25	3.88 (N ^{4'} -Me)
TFA- <i>d</i> ₁	3	—	—	
	4a	—	—	
	4b	—	—	2.73 (N ^{2'} -Me)
	4c	—	—	3.83 (N ^{4'} -Me)
	5a	—	—	2.87 (C ^{3'} -SMe)
	5c	—	—	3.87 (N ^{4'} -Me)

a) Overlapping with allylic H.

c in DMSO-*d*₆ showed the vinyl and methylene proton signals, and pairs of methyl proton signals were observed in **4b**, **4c**, **5a**, and **5c** (Table III). These results are shown in Chart 3. Furthermore, the spectra of **2a**, **2b**, **4c**, and **5a—c** were measured at various temperatures in order to estimate changes in the distribution of the tautomers A and B in DMSO-*d*₆. The results are shown in Table IV; it is clear that tautomer A predominates over tautomer B at low temperature, but the ratio of tautomer B gradually increased with elevation of the temperature.

On the other hand, the spectrum of **1a** in TFA showed the methylene proton signal at δ 4.55 ppm, lacking the vinyl proton signal. Interestingly, however, the spectra of **2a—c** in TFA showed two vinyl and one methylene proton signals together with three C^{2'}-H, C^{2'}-Me,

Chart 3. Equilibria of 2, 3, 4, and 5 in DMSO

TABLE IV. Integral Ratios of Vinyl-Methylene Signals in DMSO- d_6 at Various Temperatures

Compound	Temperature (°C)	Vinyl-methylene	
2a	30	4	1
	50	4	1
	90	2	1
2b	30	3	1
	50	2.5	1
	70	2	1
	90	1	1
4c	30	1	0.7
	50	1	0.8
	70	1	1.3
	90	1	2.3
	110	1	2.5
5a	70	7	1
	90	3	1
	110	2	1
	110	2	1
5b	30	4.5	1
	50	2.5	1
	70	2	1
	90	1.7	1
	110	1	1
5c	30	4	1
	50	3	1
	70	2	1
	90	2	1
	110	1.5	1

and C^{2'}-SMe proton signals (Table II). These data indicate that **2a**—**c** occur as three tautomers, possibly as the protonated species⁷⁾ in TFA. As regards protonated azoles in TFA, 1,2,4-triazole,⁸⁾ imidazole,⁸⁾ oxazole,⁹⁾ and 1,2-benzisothiazole¹⁰⁾ derivatives have already been reported, as shown in Chart 4. In particular, protonations of 1,2,4-triazoles give cations stabilized by amidinium resonance, and the downfield shift of the proton conjugated with the positively charged carbon is larger than that of the other proton.⁸⁾ However, the C^{2'}-H proton signals of **2a** in TFA did not show a downfield shift compared with the C^{2'}-H proton signal in DMSO- d_6 , while the methylene proton signals of **2a**—**c** in TFA appeared at lower magnetic fields than those in DMSO- d_6 . The shift differences of the methylene proton signals are δ 0.5—0.6 ppm. These results support the occurrence of protonation on N^{4'} of **2a**—**c** in TFA. Moreover, taking prototropy into consideration, the species C, D, and E are proposed as the tautomers of **2** in TFA, as shown in Chart 5. In tautomer E, protonation was assumed to

Chart 4

Chart 5. Equilibria of **2** in TFA Chart 6. Tautomers of **3**, **4**, and **5** in TFA

occur on the N^{3'} atom on the basis of the relative basicity of the N^{3'} and N^{4'} atoms. In the literature,²⁾ the vinyl and methylene proton signals of **1** in TFA were reported to be at lower

TABLE V. Tautomers of **2**, **3**, **4**, and **5** Assigned on the Basis of ¹H-NMR Spectral Data

Compound	Tautomers				
	in DMSO- <i>d</i> ₆		in TFA		
2a	A	B	C	D	E
2b	A	B	C	D	E
2c	A	B	C	D	E
3	A	B		D	
4a	A	B		D	
4b	A	B		D	
4c	A	B		D	
5a	A	B		D	
5b	A	B		D	
5c	A	B		D	

magnetic fields than those in DMSO-*d*₆, and the shift differences between the solvents were δ 0.4–1.1 ppm in the vinyl proton signals and δ 0.6–0.7 ppm in the methylene proton signals. Accordingly, it was assumed that the vinyl proton signals [δ 6.63 (**2a**), 6.52 (**2b**), 6.47 (**2c**) ppm] were due to tautomer C, the methylene proton signals [δ 4.97 (**2a**), 4.93 (**2b**), 4.93 (**2c**) ppm] were due to tautomer D, and the remaining vinyl proton signals [δ 6.03 (**2a**), 5.97 (**2b**), 5.92 (**2c**) ppm] were due to tautomer E. In addition, the vinyl and methylene proton signals of **2a**—**c** disappeared on measurement in TFA-*d*₁,^{2,11)} while the C^{2'}-H proton signals of **2a** did not

TABLE VI. ^1H -NMR Spectral Data for **6**, **7**, and **8**

Compound	Solvent	Chemical shift δ (ppm)
6	DMSO- d_6	9.34 (C $^{2'}$ -H)
	TFA	9.02 8.53 (C $^{2'}$ -H)
	TFA- d_1	8.97 8.54 (C $^{2'}$ -H)
7	DMSO- d_6	8.57 (C $^{3'}$ -H) 3.87 (N $^{4'}$ -Me)
	TFA	9.60 9.52 (C $^{3'}$ -H) 4.32 4.13 (N $^{4'}$ -Me)
	TFA- d_1	9.60 9.52 (C $^{3'}$ -H) 4.32 4.13 (N $^{4'}$ -Me)
8	DMSO- d_6	3.20 (C $^{3'}$ -SMe)
	TFA	3.47 (C $^{3'}$ -SMe)
	TFA- d_1	3.45 (C $^{3'}$ -SMe)

Chart 7. Equilibria of **6** in TFA Chart 8. Equilibria of **7** in TFA

disappear, and the C $^{2'}$ -Me proton signals of **2b** were observed as three singlet signals.

In contrast to the above tautomeric behavior of **2** in TFA, **3**, **4**, and **5** showed no vinyl proton signal, but showed a single methylene proton signal on measurement in TFA (Table III). Moreover, the methylene proton signals of **3**, **4**, and **5** disappeared on measurement in TFA- d_1 , and the methyl proton signals of **4b**, **4c**, **5a**, and **5c** became singlets on measurements in TFA and in TFA- d_1 . These data indicate that **3**, **4**, and **5** occur as tautomer D in TFA, as shown in Chart 6.

Thus, the compounds (**2**) having the 1,3,4-oxadiazole ring were found to exist in the three tautomers C, D, and E, while the compounds (**3**, **4**, **5**) possessing the 2,3-dihydro-1,3,4-oxadiazole, 2,3-dihydro-1,2,4-triazole, and 4H-1,2,4-triazole rings existed predominantly as tautomer D, as shown in Table V.

Tautomeric Equilibria of **6**, **7**, and **8**

Compounds **2**, **3**, **4**, and **5** existed as the two tautomers A and B in DMSO- d_6 , but compounds **6**, **7**, and **8** existed as only one species, as shown in Chart 2. However, **6** and **7** were found to isomerize in TFA (Table VI). Namely, the ^1H -NMR spectra of **6** in both TFA and TFA- d_1 exhibited two C $^{2'}$ -H proton signals without the methine proton signal, excluding the D type of tautomer. In addition, the two C $^{2'}$ -H proton signals in TFA did not show any downfield shift in comparison with the one C $^{2'}$ -H proton signal in DMSO- d_6 . These results indicate that tautomers C and E are present in the case of **6**, as shown in Chart 7. In the spectra of **7** in both TFA and TFA- d_1 , two C $^{3'}$ -H proton signals were observed together with

Chart 9. Protonated Species of **8** in TFATABLE VII. Tautomers of **6**, **7**, and **8** in TFA Assigned on the Basis of ^1H -NMR Spectral Data

Compound	Tautomers
6	C and E
7	Two of C, E, and G
8	C or E

two $\text{N}^{4'}$ -Me proton signals. Interestingly, the two $\text{C}^{3'}$ -H proton signals in TFA appeared at lower magnetic fields than the one $\text{C}^{3'}$ -H proton signal in $\text{DMSO}-d_6$, supporting protonation on the $\text{N}^{2'}$ atom of **7**. The above results provide evidence that **7** occurs as two tautomers. Two of the tautomers C, E, and G may be involved in this case, as shown in Chart 8. On the other hand, the spectra of **8** in both TFA and $\text{TFA}-d_1$ exhibited one methyl proton signal, indicating that **8** exists predominantly as the single tautomer C or E, as shown in Chart 9.

Thus, the isomerization in TFA was also confirmed to occur in **6** and **7**, which were functionalized with hydroxyl and hydroxyimino groups, respectively, at the 3-methylenic carbon. However, no data have yet been obtained to identify the one tautomer of **8**, although spectral measurement at high temperature could provide a clue. The above results are shown in Table VII.

Experimental

^1H -NMR spectra were measured with an EM-390 spectrometer at 90 MHz using tetramethylsilane as an internal reference. Accuracy in the chemical shifts is within 1–3 Hz. The spectra in TFA and $\text{TFA}-d_1$ were measured at near 30°C . The concentrations of the samples in $\text{DMSO}-d_6$ varied between 4–10% because of poor solubility in some cases. No appreciable variation in chemical shifts in $\text{DMSO}-d_6$ was found within the range of temperatures measured.

The structural assignments of all samples employed were described previously.^{3–6)}

References and Notes

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