Tautomeric Behavior of 3-(Arylhydrazono)methyl-2-oxo-1,2-dihydroquinoxalines Between the Hydrazone Imine and Diazenyl Enamine Forms in Acidic Media. Solvent and Substituent Effects

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The 3-(arylhydrazono)methyl-2-oxo-1,2-dihydroquinoxalines **1a-h** and **2a-e** showed tautomeric equilibria between the hydrazone imine **A** and diazenyl enamine **B** forms in a series of mixed trifluoroacetic acid/dimethyl sulfoxide media. The substituent and solvent effects on the tautomer ratios of **A** to **B** in a series of mixed media were studied for compounds **1a-h** and **2a-e** by the nmr spectroscopy. In compounds **1a-h** and **2a-e**, the ratios of the tautomer **B** gradually increased with elevation of acid concentration, and the tautomer **B** exclusively existed in trifluoroacetic acid media. The various acid concentrations (C v/v%, C' mol/l) giving the 1:1 tautomer ratios [C(A:B = 1:1), C'(A:B = 1:1)] were obtained from all compounds (Figures 1-13), and the linear correlation of the Hammett σ_p values with the log C'(A:B = 1:1) values were observed for compounds **1a-h**. The larger Hammett σ_p values brought about the larger acid concentrations C(A:B = 1:1) in compounds **1a-h** and **2a-e**, indicating that the higher acid concentration was required for the stabilization of tautomer **B** possessing the electron-withdrawing *p*-substituents R^1, which weakened the basicity of the azo nitrogen atom. Moreover, the ester group R^2 of compounds **2a-e** was found to decrease the electron density of the azo nitrogen atom, since the acid concentration C(A:B = 1:1) of compound **2c** (R^1 = H, R^2 = COOMe, σ_p = 0) was 52%, whose value was larger than that of compound **1b** (R^1 = CN, R^2 = H, σ_p = 0.66) [C(A:B = 1:1) = 42%].

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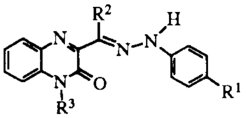
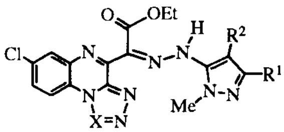
In previous papers [1,2], we reported the synthesis of the 3-(arylhydrazono)methyl-2-oxo-1,2-dihydroquinoxalines **1a-h** and **2a-e** (Chart 1), whose nmr spectra in dimethyl sulfoxide showed tautomeric equilibria between the hydrazone imine **A** and diazenyl enamine **B** forms (Schemes 1 and 2). Moreover, the linear correlation of the Hammett σ_p values with the tautomeric equilibrium constants K_T was found in compounds **1a-h**, although such a correlation was not observed in compounds **2a-e**. On the other hand, we have already reported that the tautomer ratios of **A** to **B** in compounds **3a-d** (Chart 2) change in a series of mixed trifluoroacetic acid/dimethyl sulfoxide media [3]. In the present investigation, we studied the solvent and substituent effects on the tautomer ratios of **A** to **B**, which were derived from the nmr spectral data of compounds **1a-h** and **2a-e** in a series of mixed trifluoroacetic acid/dimethyl sulfoxide media. As the result, it was found that the various acid concentrations (C v/v%, C' mol/l) giving a 1:1 tautomer ratio [C(A:B = 1:1), C'(A:B = 1:1)] were obtained in all compounds **1a-h** and **2a-e**, and the linear correlation of the Hammett σ_p values with the log C'(A:B = 1:1) values was observed in compounds **1a-h**. This paper describes the nmr spectral data and fluctuation

Chart 1



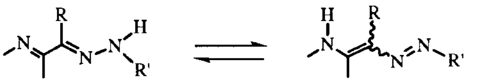
1a-h R^2 = H
2a-e R^2 = COOMe

Chart 2



3a X = CH, R^1 = H, R^2 = COOEt
3b X = CH, R^1 = Me, R^2 = CN
3c X = N, R^1 = H, R^2 = COOEt
3d X = N, R^1 = Me, R^2 = CN

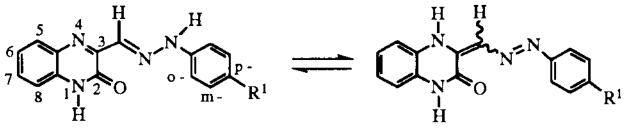
Scheme 1



A
Hydrazone Imine Form

B
Diazenyl Enamine Form

Scheme 2



A Compounds **1a-h** **B**

tendency for the tautomer ratios of **A** to **B** together with the correlation of the Hammett σ_p values with the log C'(A:B = 1:1) values.

The nmr spectral data and tautomer ratios of compounds **1a-h** and **2a-e** in dimethyl sulfoxide have already been described in previous papers [1,2] and also listed in this paper (Tables 1 and 2). The assignment of the hydrazone NH proton signals in compounds **1** (R^1 = Me) and **2** (R^1 = Me) was established by the C-H coupling data [1], and hence the hydrazone CH (**A** form), diazenyl CH (**B** form), N_4-H (**B** form) and C_5-H (**A**, **B** forms) proton signals were easily distinguishable from the other signals. In this study, the nmr spectra of compounds **1a-h** and **2a-e** were measured in a series of mixed trifluoroacetic acid/dimethyl sulfoxide media in order to clarify the fluctuation tendency for the tautomer ratios of **A** to **B**. The

Table 1

The NMR Spectral Data for Compounds **1a-h**

							Chemical Shift (δ ppm)			
				TFA %	Tautomer Ratio		Hydrazone CH	Diazenyl CH	C_5-H	
Compound	R^1	R^2	R^3	in DMSO	**A**	**B**	**A** Form	**B** Form	**A** Form	**B** Form
1a	NO_2	H	H	0	30	70	7.86	8.49	8.10	7.82
				25	50	50	7.85	8.42	7.77	7.89
				50	59	41	7.77	8.29	7.69	[a]
				75	26	74	7.80	8.06	[a]	7.66
				100	0	100	--	8.34	--	7.87
1b	CN	H	H	0	40	60	7.81	8.41	8.10	7.79
				25	50	50	7.78	8.35	7.81	7.89
				40	51	49	7.76	8.29	7.75	7.86
				50	38	62	7.70	8.20	7.64	7.85
				75	0	100	--	7.98	--	7.57
				100	0	100	--	8.24	--	7.79
1c	SO_2NH_2	H	H	0	44	56	7.78	8.41	8.08	7.79
				25	50	50	7.74	8.32	[a]	[a]
				35	50	50	7.72	8.27	[a]	7.85
				50	48	52	7.81	8.17	[a]	[a]
				75	33	67	7.82	7.99	[a]	[a]
				100	0	100	--	8.32	--	7.87
1d	COOEt	H	H	0	46	54	7.79	8.44	8.04	7.81
				15	47	53	7.78	8.38	7.92	7.82
				25	50	50	7.76	8.32	[a]	[a]
				50	31	69	7.70	8.21	7.66	7.82
				75	12	88	7.81	7.99	[a]	7.61
				100	0	100	--	8.08	--	7.62
1e	Cl	H	H	0	54	46	7.72	8.33	8.06	7.77
				10	51	49	7.73	8.28	7.86	7.98
				20	44	56	7.71	8.22	7.86	7.89
				25	32	68	7.68	8.19	[a]	[a]
				50	0	100	--	8.08	--	7.81
				75	0	100	--	7.95	--	[a]
				100	0	100	--	8.03	--	7.60
1f	F	H	H	0	60	40	7.68	8.31	8.04	7.75
				10	49	51	7.69	8.24	7.88	7.97
				25	30	70	7.66	8.16	7.83	7.88
				50	0	100	--	8.07	--	7.80
				75	0	100	--	7.88	--	7.52
				100	0	100	--	8.00	--	7.57
1g	H	H	H	0	62	38	7.70	8.33	8.02	7.76
				5	53	47	7.71	8.29	7.87	7.97
				25	29	71	7.66	8.18	7.80	7.89
				50	11	89	7.59	8.10	7.61	7.82
				75	0	100	--	7.87	--	7.52
				100	0	100	--	7.94	--	7.51
1h	Et	H	H	0	67	33	7.68	8.33	7.99	7.77
				5	50	50	7.68	8.23	7.88	7.96
				25	0	100	--	8.12	--	7.87
				50	0	100	--	8.06	--	7.81
				75	0	100	--	7.84	--	7.49
				100	0	100	--	7.89	--	7.48

[a] Overlapped with other signals.

Table 2

The NMR Spectral Data for Compounds **2a-e**

							Chemical Shift (δ ppm)					
				TFA%	Tautomer Ratio		C_5-H		COOMe		N_1-Me	
Compound	R^1	R^2	R^3	in DMSO	A	B	A Form	B Form	A Form	B Form	A Form	B Form
2a	NO_2	COOMe	H	0	100	0	7.89	--	3.77	--		
				25	93	7	7.79	[a]	3.69	3.71		
				50	87	13	7.68	[a]	3.60	3.58		
				75	79	21	7.72	7.64	3.55	3.57		
				100	0	100	--	7.88	--	3.90		
2b	NO_2	COOMe	Me	0	100	0	7.96	--	3.78	--	3.70	--
				25	89	11	7.86	7.80	3.69	3.71	3.61	3.59
				50	88	12	7.72	[a]	3.60	3.57	3.48	3.50
				75	79	21	7.76	7.66	3.57	3.66	3.54	3.48
				100	0	100	--	7.93	--	3.83	--	3.83
2c	H	COOMe	Me	0	100	0	7.92	--	3.71	--	3.66	--
				25	100	0	7.84	--	3.66	--	3.59	--
				50	71	29	7.67	[a]	3.58	3.55	3.43	3.48
				75	0	100	--	7.70	--	3.58	--	3.55
				100	0	100	--	7.75	--	3.90	--	3.79
2d	Me	COOMe	H	0	100	0	7.88	--	3.73	--		
				25	100	0	7.77	--	3.65	--		
				50	85	15	7.65	[a]	3.58	3.47		
				75	0	100	--	7.64	--	3.62		
				100	0	100	--	7.60	--	3.90		
2e	Me	COOMe	Me	0	100	0	7.94	--	3.72	--	3.67	--
				25	100	0	7.82	--	3.64	--	3.57	--
				50	78	22	7.70	[a]	3.58	3.56	3.48	3.50
				75	0	100	--	7.67	--	3.60	--	3.54
				100	0	100	--	7.71	--	3.91	--	3.77

[a] Overlapped with other signals.

Table 3

Data of the Hammett σ_p, C(A:B = 1:1), C'(A:B = 1:1) and log C'(A:B = 1:1) Values for Compounds **1** and **2**

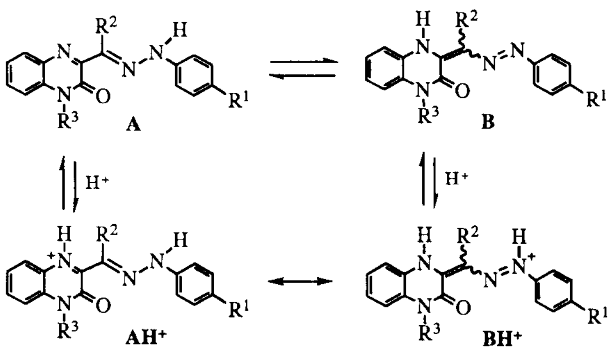
Compound	R^1	R^2	R^3	σ_p [a]	C(A:B = 1:1) (v/v %)	C'(A:B = 1:1) (mol/l)	log C'(A:B = 1:1)
1a	NO_2	H	H	+0.78 (*p*-NO_2)	57	7.70	0.89
1b	CN	H	H	+0.66 (*p*-CN)	42	5.67	0.75
1c	SO_2NH_2	H	H	+0.58 (*p*-SO_2NH_2)	35	4.73	0.67
1d	COOEt	H	H	+0.45 (*p*-COOEt)	25	3.38	0.53
1e	Cl	H	H	+0.23 (*p*-Cl)	13	1.76	0.25
1f	F	H	H	+0.06 (*p*-F)	9	1.22	0.09
1g	H	H	H	0 (*p*-H)	7	0.95	-0.02
1h	Et	H	H	-0.15 (*p*-Et)	5	0.68	-0.17
2a	NO_2	COOMe	H	+0.78 (*p*-NO_2)	94		
2b	NO_2	COOMe	Me	+0.78 (*p*-NO_2)	96		
2c	H	COOMe	Me	0 (*p*-H)	52		
2d	Me	COOMe	H	-0.17 (*p*-Me)	55		
2e	Me	COOMe	Me	-0.17 (*p*-Me)	51		

[a] The values shown herein were selected from several literature references [7-12].

hydrazone CH, diazenyl CH and C_5-H proton signals (compounds **1a-h**) and the C_5-H, ester methyl and N_1-methyl proton signals (compounds **2a-e**) in a series of mixed media could be easily assigned by analogy with those in dimethyl sulfoxide media, although the chemical shifts of the respective proton signals were slightly changed in a series of mixed media. Accordingly, the tautomer ratios of **A** to **B** in compounds **1a-h** and **2a-e** were calculated from the integral ratios of the signals due to the hydrazone CH, diazenyl CH, C_5-H, ester methyl, N_1-methyl or other CH proton signals (Tables 1 and 2).

Figures 1-13 exhibiting the change in the tautomer ratios of **A** to **B** were constructed from the data in Tables 1 and 2. In all compounds, the ratios of tautomer **B** were found to increase with elevation of the acid concentration in a series of mixed media, and tautomer **B** existed exclu-

Scheme 3



Behavior of Compounds **1** and **2** in the Dimethyl Sulfoxide or Acidic Media

sively in trifluoroacetic acid media. Since the increase of the acid concentration augmented the ratio of tautomer **B**, the mechanism of the transformation from tautomer **A** to tautomer **B** in a series of mixed media was postulated as shown in Scheme 3. Namely, the protonation of tautomer **A** or **B** would give the tautomer **AH**$^+$ or **BH**$^+$ [4,5], respectively, and the increment of the acid concentration would stabilize the tautomer **BH**$^+$ [4a,4b] rather than its resonance isomer **AH**$^+$ [4c].

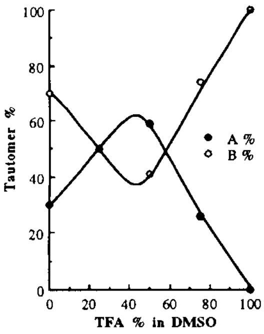


Figure 1. Plots of Tautomer Ratios **A/B** for Compound **1a**.

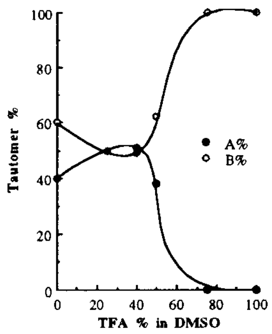


Figure 2. Plots of Tautomer Ratios **A/B** for Compound **1b**.

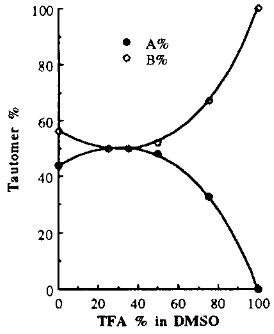


Figure 3. Plots of Tautomer Ratios **A/B** for Compound **1c**.

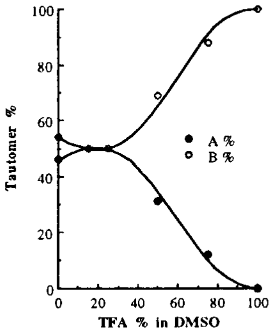


Figure 4. Plots of Tautomer Ratios **A/B** for Compound **1d**.

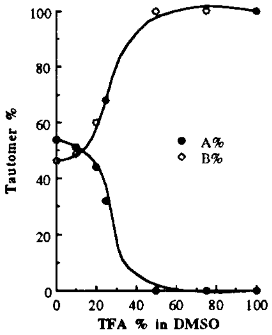


Figure 5. Plots of Tautomer Ratios **A/B** for Compound **1e**.

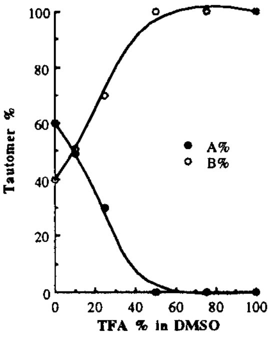


Figure 6. Plots of Tautomer Ratios **A/B** for Compound **1f**.

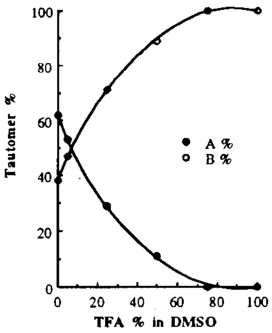


Figure 7. Plots of Tautomer Ratios **A/B** for Compound **1g**.

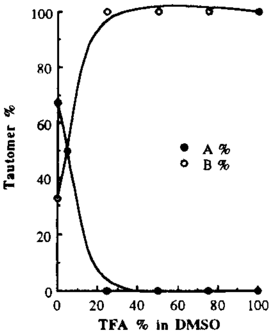


Figure 8. Plots of Tautomer Ratios **A/B** for Compound **1h**.

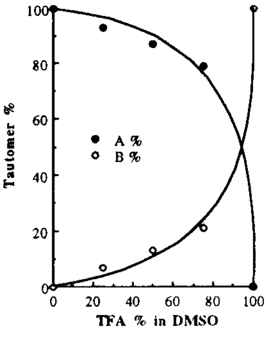


Figure 9. Plots of Tautomer Ratios **A/B** for Compound **2a**.

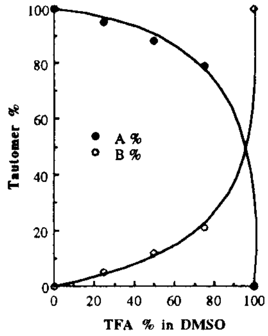


Figure 10. Plots of Tautomer Ratios **A/B** for Compound **2b**.

Figures 1-13 provided the intersections, which corresponded to the acid concentration (C v/v%) giving the 1:1 tautomer ratio [C(A:B = 1:1)] (Table 3) [6]. The values of the acid concentration C(A:B = 1:1) gradually increased with the stepwise elevation of the Hammett σ_p values, suggesting the correlation of the Hammett σ_p values with the acid concentrations in a series of acidic media. The values of the acid concentrations C'(A:B = 1:1) (mol/l) and log C'(A:B = 1:1) were derived from the acid concentrations C(A:B = 1:1) in order to inspect the above correlation. Consequently, the linear correlation of the

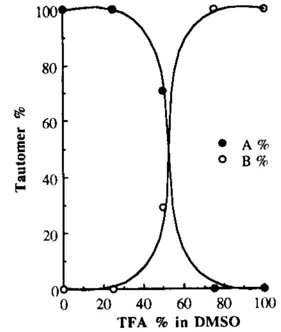


Figure 11. Plots of Tautomer Ratios **A/B** for Compound **2c**.

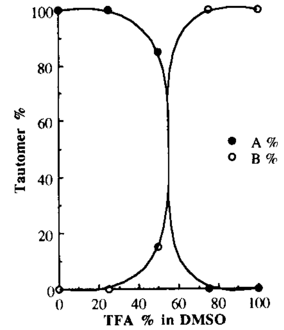


Figure 12. Plots of Tautomer Ratios **A/B** for Compound **2d**.

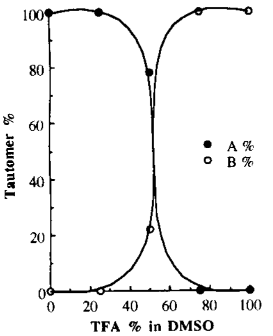


Figure 13. Plots of Tautomer Ratios **A/B** for Compound **2e**.

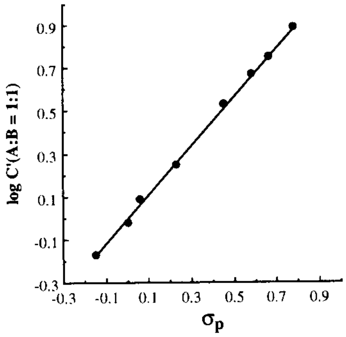


Figure 14. Correlation of the Hammett σ_p Values with the log C'(A:B = 1:1) Values in Compounds **1a-h**.

Hammett σ_p values with the log C'(A:B = 1:1) values was found in compounds **1a-h** (Figure 14) (correlation coefficient r = 0.999). Figure 14 indicated that the higher acid concentration was required for the stabilization of the tautomer **B** having the electron-withdrawing *p*-substituents R^1, which weakened the basicity of the azo nitrogen atom. In addition, the ester group R^2 of compounds **2a-e** was found to decrease the electron density of the azo nitrogen atom from the results that the acid concentration C(A:B = 1:1) of compound **2c** (R^1 = H, R^2 = COOMe, σ_p = 0) was 52% whose value was larger than that of compound **1b** (R^1 = CN, R^2 = H, σ_p = 0.66) [C(A:B = 1:1) = 42%].

EXPERIMENTAL

All nmr spectra were measured at 25° with a VXR-300 spectrometer at 300 MHz. The following solvents were employed for the measurement of the nmr spectra: 0 v/v% TFA in DMSO-deuteriodimethyl sulfoxide; 5-75 v/v% TFA in DMSO-trifluoroacetic acid and deuteriodimethyl sulfoxide; 100 v/v% TFA in DMSO-deuteriotrifluoroacetic acid.

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[6] When there were two intersections (Figures 1-4), the larger values C(A:B = 1:1) were adopted in order to obtain the common C(A:B = 1:1) values where tautomer **B** increased toward 100%.

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