## Notes

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# Studies on Organosulfur Compounds. IV.[1] Relative Strengths of 2-(2-Pyridyl)-3-phenyl-4(3H)-quinazolinone Series as Proton Acceptor in Hydrogen Bonding

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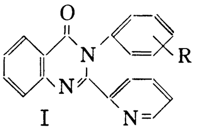
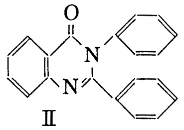
Earlier, Meyer, *et al.*[3] examined the Niementowski reaction of 3-phenyl-4(3H)-quinazolinone and showed that 4(3H)-quinazolinone is a strong enough base to form a salt, a carboxylate, when heated with a carboxylic acid, such as formic acid, phenylacetic acid, benzoic acid, salicylic acid, or anthranilic acid.

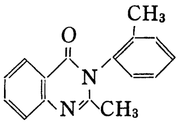
During the study on the Niementowski condensation of anthranilic acid with thiopicolinanilides,[1] we also found that an anthranilate of 4(3H)-quinazolinone is formed in the course of this reaction. In the present work, we would like to show that 4(3H)-quinazolinone[1] can act as a good proton acceptor and the frequency shift of hydrogen bonding, $\Delta\nu$ (in $cm^{-1}$), with the change of the bonded counterpart, OH···B.

## Experimental

**Materials**——Following 4(3H)-quinazolinones were employed in this work,


I


II


III

$I_a$: R=H, $I_b$: R=$o$-$CH_3$, $I_c$: R=$m$-$CH_3$, $I_d$: R=$p$-$CH_3$, $I_e$: R=$p$-$OCH_3$, $I_f$: R=$p$-$OC_2H_5$

Authentic samples of I and II were prepared according to the method described in the earlier report.[1] Commerical reagent grade of III is available.

**Enthalpy Changes and Spectral Shifts of Hydrogen Bonding**——Infrared spectra were measured on a Japan Spectroscopic Co., Model IR-G infrared spectrophotometer equipped with a grating. A pair of matched KRS-5 0.1-mm cells were used throughout the measurement and $CCl_4$, purified by distillation after drying over anhyd. $Na_2SO_4$, was used as a solvent. We believe our results to be accurate within ±2 $cm^{-1}$ for the sharp bands defined as a free stretching vibrational band of the hydroxyl group[4] and within ±4 $cm^{-1}$ for the broader absorption bands displaced to lower frequencies. All the spectral shifts of the bonded OH, OH···B, were measured at room temperature (25° on an average). The small variations in temperature had no noticable effect on absorption bands.[5]

In order to determine the hydrogen bonding energies, spectra were run at several different temperatures between 30 and 55°, and these band intensities were measured as a percentage transmission which was converted into an absorbance. All measurements were made at least twice. Excellent reproducibility was observed.

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[1] Part III: T. Hisano and M. Ichikawa, *Chem. Pharm. Bull.* (Tokyo), **91**, 2625 (1971).

[2] Location: *Oe-hon-machi, Kumamoto, 862, Japan.*

[3] J.F. Meyer and E.C. Wagner, *J. Org. Chem.*, **8**, 239 (1943).

[4] A. Allerhand and P.R. Schleyer, *J. Am. Chem. Soc.*, **85**, 371 (1963).

[5] Small variations in temperature may have a considerable effect on hydrogen bonded equilibria but the effect on infrared frequencies is very small. See E.D. Becker, *Spectrochim. Acta*, **17**, 436 (1961).

TABLE I. Hydrogen Bonding of Phenol, *p*-Chlorophenol, and Benzyl Alcohol to 4-Quinazolones[a)]

| Compound | Phenol OH bonded | $\Delta\nu$ | Spectral shift ($\mathrm{cm}^{-1}$) *p*-Chlorophenol OH bonded | $\Delta\nu$ | Benzyl alcohol OH bonded | $\Delta\nu$ (band I) | OH bonded | $\Delta\nu$ (band II) |
|---|---|---|---|---|---|---|---|---|
| $I_a$ | 3333 | 268 | 3344 | 251 | 3445 | 155 | 3356 | 244 |
| $I_b$ | 3350 | 250 | 3350 | 245 | 3470 | 130 | 3356 | 244 |
| $I_c$ | 3358 | 242 | 3356 | 239 | 3450 | 150 | 3344 | 256 |
| $I_d$ | 3348 | 252 | 3350 | 245 | | | | |
| $I_e$ | 3345 | 255 | | | | | | |
| $I_f$ | 3362 | 238 | | | | | | |
| II | 3340 | 260 | 3344 | 251 | 3431 | 169 | 3333 | 267 |
| III | 3350 | 250 | 3350 | 245 | 3470 | 130 | 3340 | 260 |
| DMF | 3344 | 256 | | | 3450 | 150 | — | — |
| Cyclohexanone | 3335 | 265 | | | — | — | — | — |
| Pyridine | — | — | — | — | — | — | 3285 | 315 |
| 2,2′-Bipyridyl | — | — | — | — | — | — | 3310 | 290 |
| Quinoline | — | — | — | — | — | — | 3275 | 325 |

a) approximate concentration: 4-quinazolones 0.07 M, phenol and *p*-chlorophenol 0.008 to 0.02 M Spectral shifts were measured from the free peaks of phenol at 3600 $\mathrm{cm}^{-1}$, *p*-chlorophenol at 3595 $\mathrm{cm}^{-1}$, and benzyl alcohol at 3600 $\mathrm{cm}^{-1}$. The reproducibility of these measurements was with in $\pm 2\ \mathrm{cm}^{-1}$. After standing the solution for a few hours, identical spectroscopic results were obtained, which indicate the stability of the instrument and samples during the measurement.

**Calculations**——The values of $\Delta H$ were calculated by the following equation[6)] as generally used for the determination of hydrogen bonding energy on the condition that a large excess of a proton acceptor exists in a very diluted solution of a proton donor:

$$\ln k'/k = -\Delta H/\mathrm{R}\cdot T + \mathrm{C}$$

$$\mathrm{C} = \Delta S/\mathrm{R} + \ln k_0'/k_0 + \ln \mathrm{C}_a$$

where $k$ is the apparent absorption coefficient at the absorption maximum of the free OH, $k'$ that of the bonded OH, $-\Delta H$ the enthalpy change at the formation of hydgogen bonding, R the gas constant, and the T the absolute temperature. In the C term, $k_0$ is the true absorption ceofficient of the free OH, $k'_0$ that of the bonded OH, $\mathrm{C}_a$ the concentration of the proton acceptor and $\Delta S$ the entropy change. This equation

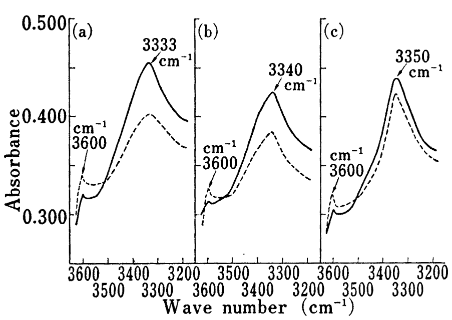

Fig. 2. Spectra of $\mathrm{CCl_4}$ Solutions Containing Benzyl Alcohol and 4-Quinazolones at Different Temperatures

(a) $\mathrm{I}_a$-benzyl alcohol, (b) II-benzyl alcohol, (c) III-benzyl alcohol concentration of benzyl alcohol 0.01M; concentration of 4-quinazolones 0.07M
—— : 30° ······ : 45°

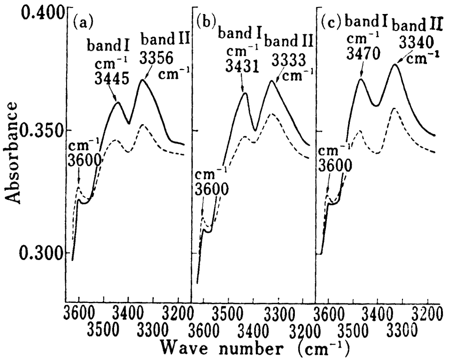

Fig. 1. Spectra of $\mathrm{CCl_4}$ Solutions Containing Phenol and 4-Quinazolones at Different Temperatures

(a) $\mathrm{I}_a$-phenol, (b) II-phenol, (c) III-phenol concentration of phenol 0.01 M; concentration of 4-quinazolones 0.07M
—— : 30° ······ : 45°

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6) M. Oka, "Jikken Kagaku Koza," (Experimental Chemistry, Suppl. 10), Maruzen, Tokyo, 1964, p. 407.

may be applied when the ratio obtained at the molar concentration of 4(3H)-quinazolinones is greater than seven-fold against that of the proton donors in this area.

As shown in Fig. 1 and 2 for a typical illustration, the frequency shifts, $\Delta\nu$, upon hydogen bond formation can be measured accurately and their band intensities are considerably affected by temperature change. Three 4(3H)-quinazolinone derivatives, $I_a$, II and III, whose substituents at the C-2 position are of a different nature, were empolyed for the thermodynamic measurements. Fig. 3 shows the $\Delta H$ values form a ln $k'/k$ against $1/T$ plot.

## Result and Discussion

Table I summarizes results on hydrogen bonded OH stretching frequencies. To avoid the association of proton donors themselves the lowest possible concentration of the proton donors was used in accord with suggestions in the literature.[4,7] All of the quinazolinones were found to be responsible for one broad spectral shift by interaction with the phenolic proton donors and two broad spectral shifts by interaction with the alcoholic proton donor in the environment. The bonding site for the phenolic protons appears most certainly to be the carbonyl group at the C-4 position of the 4(3H)-quinazolinone ring, because the spectrum of phenol on mixing with N,N-dimethylformamide (DMF) shows a band with a napparent maximum at 3344 cm$^{-1}$ and also shows such a band at 3355 cm$^{-1}$ (Fig. 1) on mixing with cyclohexanone. On the other hand, all the spectra of benzyl alcohol when mixed with 4-(3H)-quinazolinones show two partially overlapped but well-defined bands with apparent maxima at near 3450 and 3330 cm$^{-1}$ (Fig. 2). One band near 3450 cm$^{-1}$ (band I) appears to be due to the hydrogen bond formed between the carbonyl group of 4(3H)-quinazolinone and the alcoholic proton donor group, because benzyl alcohol gives a broad band at 3450 cm$^{-1}$ due to hydrogen bonding with DMF. Another band near 3330 cm$^{-1}$ (band II) appears to be

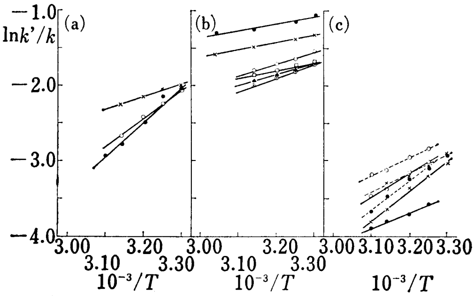

Fig. 3. Correlation between Temperature and Hydrogen Bonded OH stretching Fraquencies[a] caused by (a) Phenol 4-quinazolones[b]; (b) $p$-Chlorophenol 4-quinazolones[c]; (c) Benzyl Alcohol 4-Quinazolones[d]

[a] approximate concentrations: 4-quinazolones 0.07M (near maximum solubility at 25°); phenol and $p$-chlorophenol 0.008 to 0.015M; benzyl alcohol 0.01 to 0.02 M At the concentration used, the proton donor peaks followed the Lambert–Beer's law.

[b] —●—: $I_a$, —○—: II, and —×—: III

[c] —●—: $I_a$, —▲—: $I_b$, —□—: $I_c$, —◎—: $I_d$, —○—: II, —×—: III

[d] —●—: $I_a$, —○—: II, —×—: III in band I; ···●···: $I_a$, ···○···: II, ···×···: III in band II

Table II. Enthalpy Changes and Spectral Shifts[a] of Hydrogen Bonds of Phenol, $p$-Chlorophenol and Benzyl Alcohol to 4-Quinazolones

| Compound | Phenol | | $p$-Chlorophenol | | Benzyl acholol | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Band I | | Band II | |
| | $\Delta\nu$ cm$^{-1}$ | -$\Delta$H kcal/mole | $\Delta\nu$ cm$^{-1}$ | -$\Delta$H kcal/mole | $\Delta\nu$ cm$^{-1}$ | -$\Delta$H kcal/mole | $\Delta\nu$ cm$^{-1}$ | -$\Delta$H kcal/mole |
| $I_a$ | 268 | 8.5 | 251 | 2.0 | 155 | 4.2 | 244 | 7.4 |
| $I_b$ | | | 245 | 3.0 | | | | |
| $I_c$ | | | 239 | 2.0 | | | | |
| $I_d$ | | | 245 | 3.4 | | | | |
| II | 260 | 7.8 | 251 | 3.4 | 169 | 6.6 | 267 | 4.2 |
| III | 250 | 3.2 | 245 | 2.0 | 130 | 7.9 | 260 | 5.6 |

[a] Measured at an average room temperature of 25°, the frequency shifts caused by the change of temperatures from 30 to 55° are within ±4 cm$^{-1}$.

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[7] M.L. Josien and N. Fuson, *J. Chem. Phys.*, 22, 1169 (1954).

due to the hydrogen bond formed with the basic nitrogen of 4(3H)-quinazolinone, since mixing with a basic nitrogen such as pyridine, 2,2′-bipyridyl, or quinoline produces a broad band near 3300 cm$^{-1}$. Interaction of the carbon $\pi$-electron system with either the phenolic proton donor or the alcoholic proton could not be observed as a spectral shift in our examinations.

As shown in Table II, 2-(2-pyridyl)-3-phenyl-4(3H)-quinazolinone series seems to be able to function as a proton acceptor more uniquely than III.

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# Studies on the Pyridazine Derivatives. XVI.[1] Reaction of 3-Alkoxy-4-nitro-(and 4,6-dinitro)pyridazine 1-Oxides with Amines[2]

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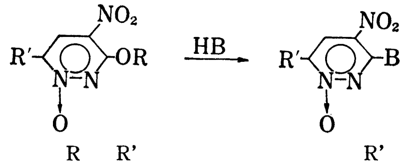
There are several reports on the reaction of alkoxy aromatic amine oxides with amines.[4] The authors attempt the amination of 3-alkoxy-4-nitro(and 4,6-dinitro)pyridazine 1-oxides for the synthesis of 3,4-diamino compounds which are intermediate to imidazo[4,5-*c*]-, *v*-triazolo[4,5-*c*]pyridazines.

General reaction formula of 3-alkoxy-4-nitro(and 4,6-dinitro)pyridazines with amines were shown in Chart 1 and the results were summarized in Table I. Reaction with alcoholic ammonia gave rise to the aminated compounds over 90% yield in any cases. Particularly, dinitro compounds reacted with amines easily. Thus, the present method provides useful synthetic means of triamino compounds. In the reactivity of alkoxy groups, ethoxyl is more active than methoxyl. This tendency is distinct in the reaction with 2-hydroxyethylamine. The reactivity of secondary amines is less active than that of primary amines.



| | R | R' |
|---|---|---|
| I: | $CH_3$, | H |
| II: | $CH_3$, | $NO_2$ |
| III: | $CH_3$, | $CH_3$ |
| IV: | $C_2H_5$, | H |
| V: | $C_2H_5$, | $NO_2$ |

| | R' |
|---|---|
| VI: | H |
| VII: | $NO_2$ |
| VIII: | $CH_3$ |

HB: a; ammonia b; hydrazine hydrate c; methylamine d; ethylamine e; 2-hydroxyethylamine f; benzylamine g; dimethylamine h; diethylamine i; piperidine j; morpholine

When compound V was treated with dimethylamine under mild condition (at room temperature for one hour), a mixture of 3-dimethylamino-4,6-dinitropyridazine 1-oxide

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1) Part XV: M. Yanai, T. Kinoshita and S. Takeda, *Chem. Pharm. Bull.* (Tokyo), **19**, 2181 (1971).

2) This work was presented at Kyushu Branch Meeting of Pharmaceutical Society of Japan, Nagasaki, Sept. 28, 1968.

3) Location: *1-14 Bunkyo-machi, Nagasaki, 852, Japan.*

4) *a*) E. Ochiai, "Aromatic Amine Oxides," Elsevier Publishing Co., Amsterdam, 1967, p. 401; *b*) E. Ochiai, *ibid.*, p. 381.