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198. Shigeharu Inouye[*1]: Structure and Solution Equilibrium of N-Salicylidene-amino-sugars and Amino-alcohols.

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The structures and solution equilibria of twenty members of N-salicylidene-amino-sugars and -amino-alcohols were examined mainly in methanol, water and solid state. As the modeled compounds were examined simultaneously three members of N-salicylidene-alkylamines and eight members belonged to the *o*-methoxybenzylidene, 3-methoxysalicylidene, 3,5-dibromosalicylidene and 2-hydroxynaphthylidene derivatives. From the comparative studies on the electronic, infrared, NMR spectra and equilibrium position, it was shown that the solution equilibrium consisted of the phenolimine and the ketoamine species, the latter being stabilized by the intra- and intermolecular hydrogen bonding involving the alcoholic hydroxyl groups and protic solvents. The acid-base equilibria of the two tautomers in methanol and the ketoamine-ion-pair equilibrium in water were discussed.

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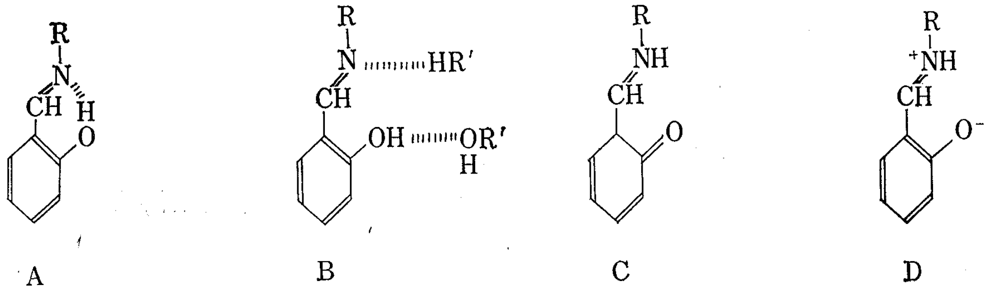
The Schiff bases derived from *o*-hydroxyaromatic aldehydes and primary amines have been widely utilized for the isolation and identification purposes of amino-sugars[1] and amino-alcohols,[2] but no paper has been devoted on the structures of these compounds. The work presented in this paper was carried out in connection with the optical rotatory dispersion studies on N-salicylidene-amino-sugars[3] with the purpose of disclosing the structure of N-salicylidene chromophore, which was the object of considerable discussion in the past.

It was known for many years that the electronic absorption spectra of N-salicylidene-alkylamines[4,5] and -aromatic amines[6] were extremely sensitive to solvents. The spectra in non-polar aprotic solvents displayed absorption bands at about 255 and 315 mμ, which were unambigiously attributed to the phenolimine species (A), supported by infrared[7] and nuclear magnetic resonance (NMR) evidence.[8,9] However, when measured in polar protic solvents, there appeared additional two new bands at about 280 and 405 mμ.



Chemical Structure I.

[*1] Morooka, Kohoku-ku, Yokohama-shi (井上重治).

1) R. Kuhn, H. J. Haas, A. Seeliger: Chem. Ber., **94**, 1259 (1961).
2) M. L. Wolfrom, F. Schafizadeh, J. O. Wehrmuller, R. K. Armstrong: J. Org. Chem., **23**, 571 (1958).
3) S. Inouye: This Bulltein, **15**, 1557 (1967).
4) J. Hires: C. A., **53**, 11985 (1959).
5) J. Charette, G. Faltlhand, Ph. Teyssie: Spectrochim. Acta, **20**, 597 (1964).
6) M. D. Cohen, Y. Hirshberg, G. M. J. Schmidt: J. Chem. Soc., 2051 (1964).
7) P. Teyssie, J. J. Charette: Spectrochim. Acta, **19**, 1407 (1963).
8) J. J. Charette: Spectrochim. Acta, **19**, 1275 (1963).
9) G. O. Dudek, R. H. Holm: J. Am. Chem. Soc., **84**, 2691 (1962).

The appearance of the red-shifted bands was interpreted by Ferguson[10] in terms of the intramolecular hydrogen bonding effect of the phenolimine (A). Charette, *et al.*[5] rationalized the solvent effect on the basis of the competitive hydrogen bonding between the internally bonded phenolimine species (A) and the solvated phenolimine species (B), and the bathochromic bands were assigned to the latter. Heinert and Martell,[11] on the other hand, discussed the spectrum of N-salicylidene-valine potassium salt on the ground of tautomerism between the phenolimine (A) and the ketoamine (C), the bathochromic bands being assigned to C. Dudek and Dudek,[12] based on the N^{15}-H coupling in the NMR spectrum of N-salicylideneaniline in ethanol at 0°, assigned the 396 mμ band to the quinoid form. One of the main difficulties in the previous investigations was that the N-salicylidene compounds in solution usually existed as a mixture of two or more species, which complicated the interpretation of the spectra. Evidently, further studies, in particular, the direct comparison of the spectra of the pure species was necessary to dissolve the discrepancy in the literatures.

Electronic spectra of N-salicylidene-amino-sugars and -amino-alcohols examined in this paper showed similar solvent effects as seen in the Schiff bases of simple primary amines, and the formation of isosbestic points[5] by the spectral curves measured in a variety of solvents indicated the existence of a solution equilibrium. It was found out, however, that the position of the solution equilibrium was largely shifted towards either side, depending upon the nature of substituents carried by amino-components and phenyl groups as well as solvents. Examination of the spectra of the respective equilibrates in a relatively pure state revealed that the solution equilibrium was best interpreted in terms of the tautomerism between the phenolimine and the ketoamine (D).*2 Furthermore, a comparative study on the effects of substituents and solvents on the equilibrium position indicated that most of the ketoamine species were in the intra- and intermolecular hydrogen bonded form involving alcoholic hydroxyl groups and solvents in solution and solid state. These results were described in this paper.

Experimental

The compounds studied in this paper were salicylidene Schiff bases derived from fifteen members of amino-sugars, five amino-alcohols and three alkylamines. The modeled compounds examined simultaneously for a comparison were *o*-methoxybenzylidene, 3-methoxysalicylidene, 3,5-dibromosalicylidene and 2-hydroxynaphthylidene Schiff bases derived from an alkylamine and two amino-alcohols. These compounds were listed in Table I.

The respective Schiff bases were prepared by mixing a free base in H_2O or EtOH and an aromatic aldehyde in EtOH at room temperature. The products obtained were purified by recrystallization or reprecipitation or vacuum distillation and the degree of purity was checked by the elemental analysis. Table II summarized the analysis for new compounds.

Electronic absorption spectra were recorded with Hitachi EPS-2U and EPU-2 spectrometers at 22~23° unless otherwise noted. The band positions were calibrated by the use of a niobium glass. For solution measurement, were used 0.2, 1.0, 10 and 50 mm. quartz cells with a thermistor located in a well in the 10 mm. cell. All the solvents used were spectro grade. For measurement of spectra in H_2O at $10^{-4}M$, the MeOH solution of $10^{-3}M$ was diluted with H_2O and the spectra were measured within 5 minutes to avoid hydrolysis. Use of the 10% MeOH solution enabled the measurement of the Schiff bases difficultly soluble in H_2O and the spectra were almost indistinguishable from those in pure H_2O so long as examined. The solid state spectra were obtained from the KBr pellet of 1 mm. thickness. The molar absorption coefficient

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*2 Although the exact electronic configuration of the ketoamine may be represented by the linear combination of various valence-bond structures, the dipolar form was conveniently employed in this paper and the subsequent paper.[3] The generic term ketoamine likewise did not imply the exact structure.

10) L. N. Ferguson: "The Modern Structural Theory of Organic Chemistry," 528 (1963). Prentice-Hall, Inc., New Jersey.

11) D. Heinert, A. E. Martell: J. Am. Chem. Soc., **85**, 183 (1963).

12) G. O. Dudek, E. P. Dudek: Chem. Comm., 464 (1965).

Table I. Schiff Bases examined in This Paper

Compound No.	Schiff Base	M. P. (°C)
I	N-Salicylidenebenzylamine	25～27
II	N-Salicylidene-2-aminoethanol[a]	liq.
III	N-Salicylidene-3-amino-*n*-propanol[b]	liq.
IV	N-Salicylideneethylamine	liq.
V	N-Salicylidenecyclohexylamine	liq.
VI	N-Salicylidene-2-amino-2-deoxy-D-glucitol	154～155
VII	N-Salicylidene-2-amino-2-hydroxymethyl-1,3-propanediol	141～143
VIII	N-Salicylidene-2-deoxystreptamine	184～185
IX	N-Salicylidene-β-D-glucopyranosylamine	amorph.
X	N-Salicylidene-β-D-mannopyanosylamine	amorph.
XI	N-Salicylidene-2-amino-2-deoxy-D-glucose[c]	181～182
XII	N-Salicylidene-2-amino-2-deoxy-D-galactose	amorph.
XIII	N-Salicylidene-2-amino-2-deoxy-D-mannose	amorph.
XIV	Methyl N-Salicylidene-2-amino-2-deoxy-α-D-glucopyranoside	163～164
XV	Methyl N-Salicylidene-2-amino-2-deoxy-β-D-glucopyranoside[c]	118～119
XVI	Methyl N-Salicylidene-3-amino-3-deoxy-α-D-glucopyranoside	amorph.
XVII	Methyl N-Salicylidene-3-amino-3-deoxy-β-L-glucopyranoside	amorph.
XVIII	Methyl N-Salicylidene-3-amino-3-deoxy-α-D-mannopyranoside	148～150
XIX	Methyl N-Salicylidene-6-amino-6-deoxy-α-D-glucopyranoside	140 (decomp.)
XX	N-Salicylidene-5-amino-5-deoxy-1,2-O-isopropylidene-α-D-xylofuranose[2]	153～154
XXI	Methyl N-Salicylidene-3,6-diamino-3,6-dideoxy-α-D-altropyranoside[d]	118～120
XXII	Methyl N-Salicylidene-3,6-diamino-3,6-dideoxy-α-D-glucopyranoside[e]	243～244
XXIII	Methyl N-Salicylidene-3,6-diamino-3,6-dideoxy-α-D-mannopyranoside[e]	183～184
XXIV	N-*o*-Methoxybenzylidene-2-aminoethanol[a]	36～37
XXV	(N-3-Methoxysalicylidene)-2-aminoethanol	81～82
XXVI	(N-3-Methoxysalicylidene)-2-amino-2-hydroxymethyl-1,3-propanediol	178～179
XXVII	(N-3.5-Dibromosalicylidene)-2-aminoethanol	145
XXVIII	(N-3,5-Dibromosalicylidene)-2-amino-2-hydroxymethyl-1,3-propanediol	223～224
XXIX	(N-2-Hydroxynaphthylidene)-benzylamine[18]	99～100
XXX	(N-2-Hydroxynaphthylidene)-2-aminoethanol	152～153
XXXI	(N-2-Hydroxynaphthylidene)-2-amino-2-hydroxymethyl-1,3-propanediol	164～165

a) E.D. Bergmann, E. Zimkin, S. Pinchas: C.A., **47**, 6397 (1953).
b) A.J. Chalk, J.F. Smith: *Ibid.*, **52**, 10907 (1958).
c) C. Irvine, J.C. Earl: J. Chem. Soc., **121**, 2370 (1922).
d) S. Inouye: This Bulletin, **10**, 1112 (1966).
e) *Idem*: *Ibid.*, **10**, 902 (1966).

(ε) at about 315 mμ in the phenolimine form was estimated to be 4500±300 from the absorbances in cyclohexane of the compounds I～V. The ε_{315} values of the other compounds were estimated from the absorbances in dioxane at $10^{-4}M$, assuming the ketoamine contents of 1～3%. These values varied within the experimental error (7%) in all the N-salicylidene derivatives examined.

The ε_{405} value of the ketoamine in MeOH was calculated to be 6,500 from the absorbance around 405 mμ after subtracting the phenolimine content estimated from the absorbance at 315 mμ and the ε_{315} value. The maximum deviation from the means were ±600 in all the compounds, which was close to the experimental error. It was assumed from this that the molar absorption coefficients (ε) of the individual species were not so largely changed with compounds and solvents, which was somewhat supported by the presence of the sharp isosbestic points at 265 mμ, 295 mμ and 345 mμ in MeOH-dioxane[5] and in MeOH carbon tetrachloride systems. The ε_{400} values obtained in H_2O were *ca.* 10% smaller than those in MeOH. But, since the precise correction for hydrolysis was difficult to do, the ε_{405} value in MeOH was used as such for the calculation of the equilibrium position in H_2O. The variation of the ε values with temperature was also neglected in the enthalpy calculation. Treating the spectra of the 3-methoxysalicylidene, 3,5-dibromosalicylidene and 2-hydroxynaphthylidene derivatives in a similar manner gave the ε values of the characteristic bands of two tautomers, which were shown under the footnote in Table IV.

Infrared absorption spectra were measured on a Koken 401 grating spectrometer in nujol mull or KBr tablet (solid), in KBr cells of 0.1, 5 and 50 mm. layers and a RKS cell of 0.05 mm. Calibration of the wave-

Table II. Elemental Analysis of Schiff Bases

Compound No.	Molecular formula	Analysis (%)					
		Calcd.			Found		
		C	H	N	C	H	N
VI	$C_{13}H_{19}O_6N$	54.8	6.7	4.9	55.0	6.9	5.0
VII	$C_{11}H_{15}O_4N$	58.7	6.7	6.2	58.8	6.8	6.1
VIII	$C_{20}H_{22}O_5N_2$	64.9	6.0	7.6	64.7	6.3	7.6
IX	$C_{13}H_{17}O_6N$	55.1	6.1	4.9	54.5	6.8	5.2
X	$C_{13}H_{17}O_6N$	55.1	6.1	4.9	54.1	6.2	4.7
XII	$C_{13}H_{17}O_6N$	55.1	6.1	4.9	54.0	6.7	4.6
XIII	$C_{13}H_{17}O_6N$	55.1	6.1	4.9	54.4	6.3	4.5
XIV	$C_{14}H_{19}O_6N$	56.6	6.4	4.7	55.6	6.9	4.9
XVI	$C_{14}H_{19}O_6N$	56.6	6.4	4.7	57.6	6.9	4.4
XVII	$C_{14}H_{19}O_6N$	56.6	6.4	4.7	56.2	6.9	4.4
XVIII	$C_{14}H_{19}O_6N$	56.6	6.4	4.7	57.0	7.0	4.8
XIX	$C_{14}H_{19}O_6N$	56.6	6.4	4.7	55.8	6.5	4.8
XXV	$C_{10}H_{13}O_3N$	61.5	6.7	7.2	61.6	6.6	7.1
XXVI	$C_{12}H_{17}O_5N$	56.5	6.7	5.5	56.4	6.9	5.3
XXVII	$C_9H_9O_2NBr_2$	33.5	2.8	4.3	33.9	3.2	4.4
XXVIII	$C_{11}H_{13}O_4NBr_2$	34.5	3.4	3.7	34.2	3.7	3.6
XXX	$C_{13}H_{13}O_2N$	72.5	6.1	6.5	72.6	6.4	6.3
XXXI	$C_{15}H_{17}O_4N$	65.4	6.2	5.1	65.6	6.7	5.2

a) For numbering of the compounds see Table I.

numbers was performed with a polystyrene film. The apparent absorption coefficient defined by $\varepsilon = 1/cl\ (\log T_0/T)$ ($cm^{-1}M^{-1}$) was obtained by the use of the base line method[13] and uncorrected for the use of finite slit width.

NMR Spectra were obtained with JNM C-60 and 3H-60 spectrometers at 23°, with an internal standard (DSS in D_2O and TMS in other solvents). Acid dissociation constants of Schiff bases, parent amines and aldehydes in MeOH were measured at 23±1° according to the procedure reported by Ritchie and Heffley[14] except for the use of HCl and NaOH instead of $HClO_4$ and NaOMe. A Metrohm autotitrator with a EA 107 UX glass electrode and a EA 245 silver-silver chloride electrode filled with MeOH saturated with KCl were used. The standardization potentials used for the calibration of pH in MeOH were those of γ-picoline (p*K*a 6.09 at 25°)[14] and N,N-dimethylaniline (p*K*a 5.02 at 25°).[15] The titration in 50% MeOH was carried out similarly with a same combination of the electrodes described above, filled with 50% MeOH saturated with KCl. The pH was calibrated with the usual aqueous phosphate buffer of pH 7.01.

Results and Discussion

Structure of Two Species equilibrated in Solution

The problem of the structure of the Schiff base is the exact nature of the tautomeric form which may be inferred from the spectroscopic examination of the Schiff bases. We have analyzed the spectra of Schiff bases by comparison with those of the parent aldehydes whose structures were established. The validity of this comparison was shown by the fact that *o*-methoxybenzaldehyde and its Schiff base of 2-aminoethanol (XXIV) displayed striking resemblances in the electronic spectra (200～400 mμ) (Table III) and the infrared spectra (1610～1240 cm⁻¹) (Fig. 1).

The electronic spectra of N-salicylidene-amino-sugars and -amino-alcohols measured in the dilute solution (less than 3%) of dioxane, tetrahydrofuran, and acetonitrile were

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13) H. A. Szymanski: "Theory and Practice of Infrared Spectroscopy," 320 (1964). Plenum Press, New York.

14) C. D. Ritchie, P. D. Heffley: J. Am. Chem. Soc., **87**, 5402 (1965).

15) A. L. Bacarella, E. Grunwald, H. P. Marshall, E. L. Purlee: J. Org. Chem., **20**, 748 (1955).

Table III. Electronic Absorption Data on Various Schiff Bases and Parent *o*-Hydroxy-aromatic Aldehydes at $10^{-4}M$ (22~23°)

Compound (Schiff base No.)	Solvent	Ketoamine (%)	λ_{max} mμ ($\varepsilon \times 10^{-4}$)			
N-Salicylidene (VII)	KBr	99	219 (1.95)	244 (1.05)	279 (1.10)	402 (0.58)
N-Salicylidene (VII)	$H_2O^{a)}$	82	218 (1.91)	242 (0.97)	279 (1.38)	398 (0.59)
N-Salicylidene (VII)	Dioxane	3	256 (1.32)	318 (0.45)		
N-Salicylidene (VII)	0.1*N* HCl-MeOH	Cation	225 (1.25)	278 (1.93)	350 (0.51)	
N-Salicylidene (VII)	0.1*N* NaOH-MeOH	Anion		360 (0.45)		
N-Salicylidene (V)	Cyclohexane	<1	216 (2.68)	256 (1.29)	318 (0.45)	
Salicylaldehyde	$H_2O^{a)}$		213 (1.83)	256 (1.29)	325 (0.35)	
Salicylaldehyde Na Salt	0.1*N* NaOH-H_2O		227 (1.73)	266 (0.71)	378 (0.64)	
o-Methoxybenzylidene (XXIV)	MeOH	0	213 (2.20)	251 (1.41)	308 (0.59)	
o-Methoxybenzylidene (XXIV)	0.1*N* HCl-MeOH	Cation	223 (1.35)	277 (2.00)	350 (0.55)	
3-Methoxysalicylidene (XXVI)	$H_2O^{a)}$	100	239 (1.59)	294 (1.27)	418 (0.45)	
3-Methoxysalicylidene (XXV)	CCl_4	<1	264 (1.21)	335 (0.25)		
3-Methoxysalicylaldehyde	$H_2O^{a)}$		218 (1.83)	265 (1.07)	344 (0.25)	
3-Methoxysalicylaldehyde Na Salt	0.1*N* NaOH-H_2O		236 (1.79)	282 (0.57)	391 (0.56)	
3,5-Dibromosalicylidene (XXVIII)	$H_2O^{a)}$	100	234 (2.14)	286 (1.26)	420 (0.75)	
3,5-Dibromosalicylidene (XXVII)	$CCl_4^{b)}$	2	263 (0.82)	339 (0.39)	441 (0.02)	
3,5-Dibromosalicylaldehyde	$H_2O^{a)}$		223 (2.42)	264 (0.71)	345 (0.31)	
3,5-Dibromosalicylaldehyde Na Salt	0.1*N* NaOH-H_2O		238 (2.14)	399 (0.63)		
2-Hydroxynaphthylidene (XXIX)	KBr	95	310 (0.63)	410 (0.89)	429 (1.00)	
2-Hydroxynaphthylidene (XXIX)	$H_2O^{a)}$	100	231 (4.00)	250 (1.90)	307 (0.75)	412 (1.06)
2-Hydroxynaphthylidene (XXIX)	Cyclohexane	8	233 (5.88)	301 (0.88)	313 (1.30)	361 (0.64) 407 (0.09)
2-Hydroxynaphthaldehyde	$H_2O^{a)}$		220 (5.15)	321 (0.60)	359 (0.45)	
2-Hydroxynaphthaldehyde Na Salt	0.1*N* NaOH-H_2O		230 (2.50)	249 (2.50)	316 (0.46)	394 (0.75)

a) Contained 10% MeOH. *b*) Contained 10% $CHCl_3$.

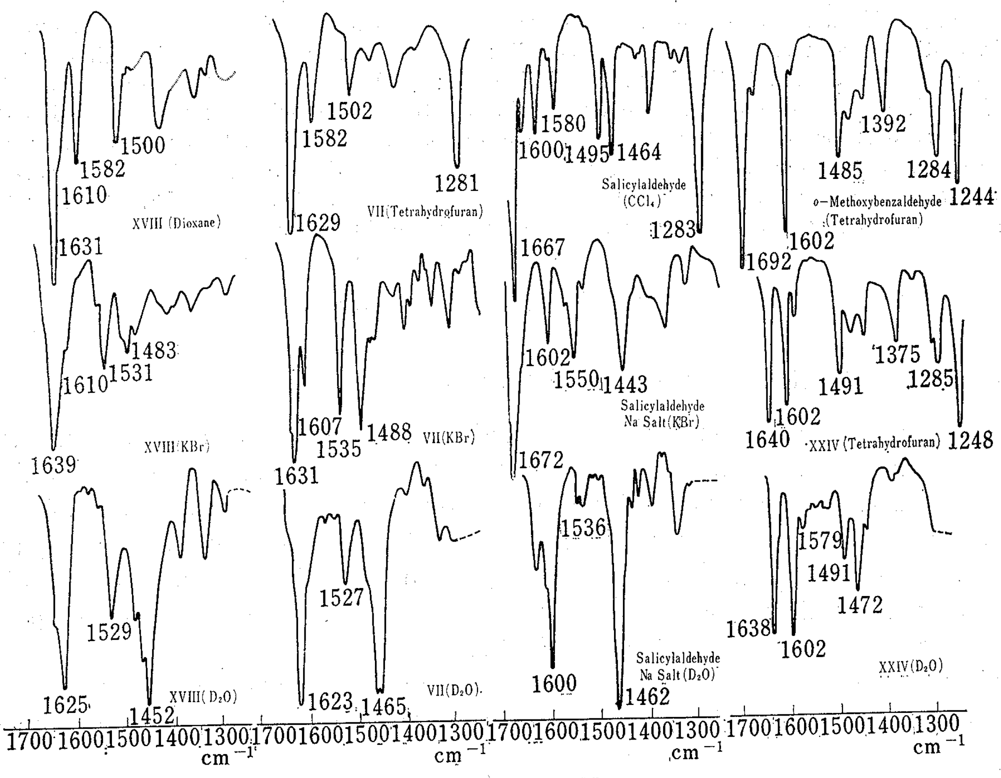

Fig. 1. Infrared Absorption Spectra of Methyl N-Salicylidene-3-amino-3-deoxy-*α*-D-mannopyranoside (XVIII), N-Salicylidene-2-amino-2-hydroxymethyl-1,3-propanediol (VII), Salicylaldehyde, *o*-Methoxybenzylidene-2-aminoethanol (XXIV), N-3-Methoxysalicylidene-2-aminoethanol (XXV) and 3-Methoxysalicylaldehyde

very similar to those of N-salicylidene-alkylamines in cyclohexane (Table III). The characteristic bands at 255 and 315 mμ were assigned to the π-π^* transitions of the phenolimine species, analogously to the bands of salicylaldehyde11) (256 and 325 mμ) which is in the intramolecular hydrogen-bonded form,16) and *o*-methoxybenzylidene derivatives11) (XXIV, 251 and 308 mμ) which existed in the phenolimine form. The characteristic infrared bands at 1630 ($\nu_{C=H}$), 1610, 1580, 1500 ($\nu_{C=C}$) and 1280 cm^{-1} (δ_{OH})[*3] in Fig. 1, coincided with the reported bands for the N-salicylidene-2-aminopropane in the phenolimine form,7) could be found as such in the spectra of salicylaldehyde with the exception of the band located at the highest wave-number. No extra band assignable to the oxazoline and carbinolamine species was detected.

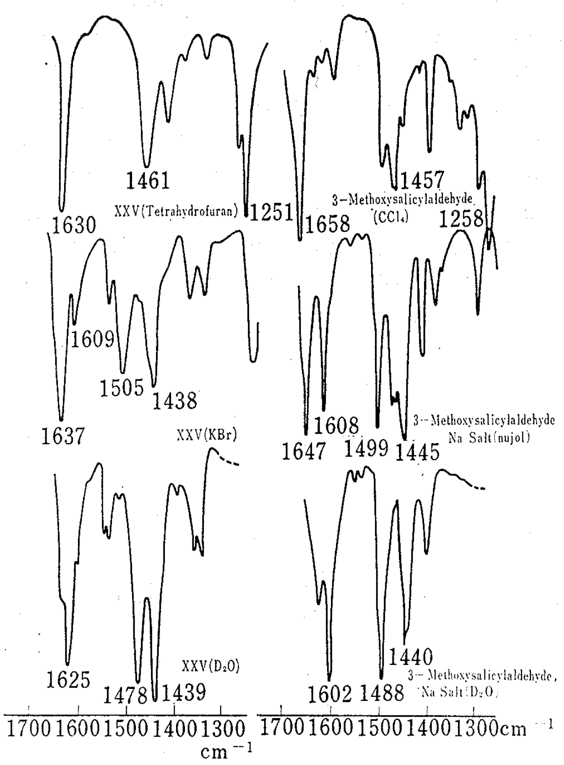

Fig. 1. (continued)

The electronic spectra of several members of N-salicylidene-amino-sugars and -amino-alcohols in water and in solid state exhibited only two absorption bands at *ca.* 280 and 400 mμ attributable to the ketoamine species. The bathochromic shifts of the two bands were comparable to the red-shift in salicylaldehyde sodium salt (266 and 378 mμ in water). In parallel with the electronic spectra, the characteristic bands in the infrared spectra measured in solid and in deuterium oxide corresponded well with those of salicylaldehyde anion in the 1700∼1240 cm^{-1} region (Fig. 1), except for the bands assigned to $\nu_{C=O}$ and $\nu_{C=N}$.[*4] The clearest manifestation of this was a strong band at 1462 cm^{-1} and a medium band at 1550 cm^{-1} in the aldehyde anion spectrum in deuterium oxide, whose positions and intensities were very close to those of the characteristic bands in the ketoamine (1460 and 1530 cm^{-1}). Obviously, such a remarkable alteration in changing the medium from dioxane to deuterium oxide (or solid) could not account for by the solvated phenolimine structure (III) proposed by Charette, *et al.*5) The infrared spectrum of *o*-methoxybenzylidene compound (XXIV) which should be similar to III in the electron density distribution of the conjugated system, remained essentially unaltered in going from tetrahydrofuran to deuterium oxide, and was quite different from the spectra of the ketoamine. In this respect, it was interesting to see that the ketoamine spectra resembled to the spectra of the metal chelates of the Schiff base in a sense of the disappearance of the bands at 1580, 1500 and 1280 cm^{-1}, typical for the phenolimine, and of the appearance of new bands around 1540 and 1470 cm^{-1}.7)

[*3] This band disappeared in the deuterated Schiff base in carbon tetrachloride, supporting the assignment.

[*4] Though the motions of all the atoms involved in such a highly mesomerized system were strongly coupled, the major component responsible for the 1630 cm^{-1} band in the ketoamine was assigned to $\nu_{C=N}$. This was based on the fact that the corresponding band was not recognized in the aldehyde anion spectra, and that this band appeared slightly at a higher wave-unmber in crystal (*ca.* 1635 cm^{-1}) and at a lower wave-number (*ca.* 1624 cm^{-1}) in deuterium oxide than the $\nu_{C=N}$ (1630 cm^{-1}) of the phenolimine form, similar to the movement of the $\nu_{C=O}$ of the aldehyde anion (1672 cm^{-1} in crystal and 1600 cm^{-1} in solution) (Fig. 1). The most probable origin of the 1460 cm^{-1} band was ν_{C-O}. The high position of ν_{C-O} was in accord with the anticipated high contribution of the double bond character of this link.

16) D. Heinert, A. E. Martell: J. Am. Chem. Soc., 81, 3933 (1959).

The spectral resemblance between the aldehyde anion and the ketoamine was further demonstrated in the 3-methoxysalicylidene, 3,5-dibromosalicylidene and 2-hydroxynaphthylidene series. In all the compounds examined, the conversion of the neutral aldehydes and the phenolimines into the aldehyde anions and the ketoamines caused similar bathochromic shifts of the electronic absorption bands (Table III) and parallel change in the infrared spectra (Fig. 1). Thus, the analogous electron density distribution in the conjugated systems of the aldehyde anion and the ketoamine was demonstrated.

The same conclusion was derived from the analysis of the NMR spectra of the aromatic protons illustrated in Fig. 2. Of the two signal pairs in the spectra of

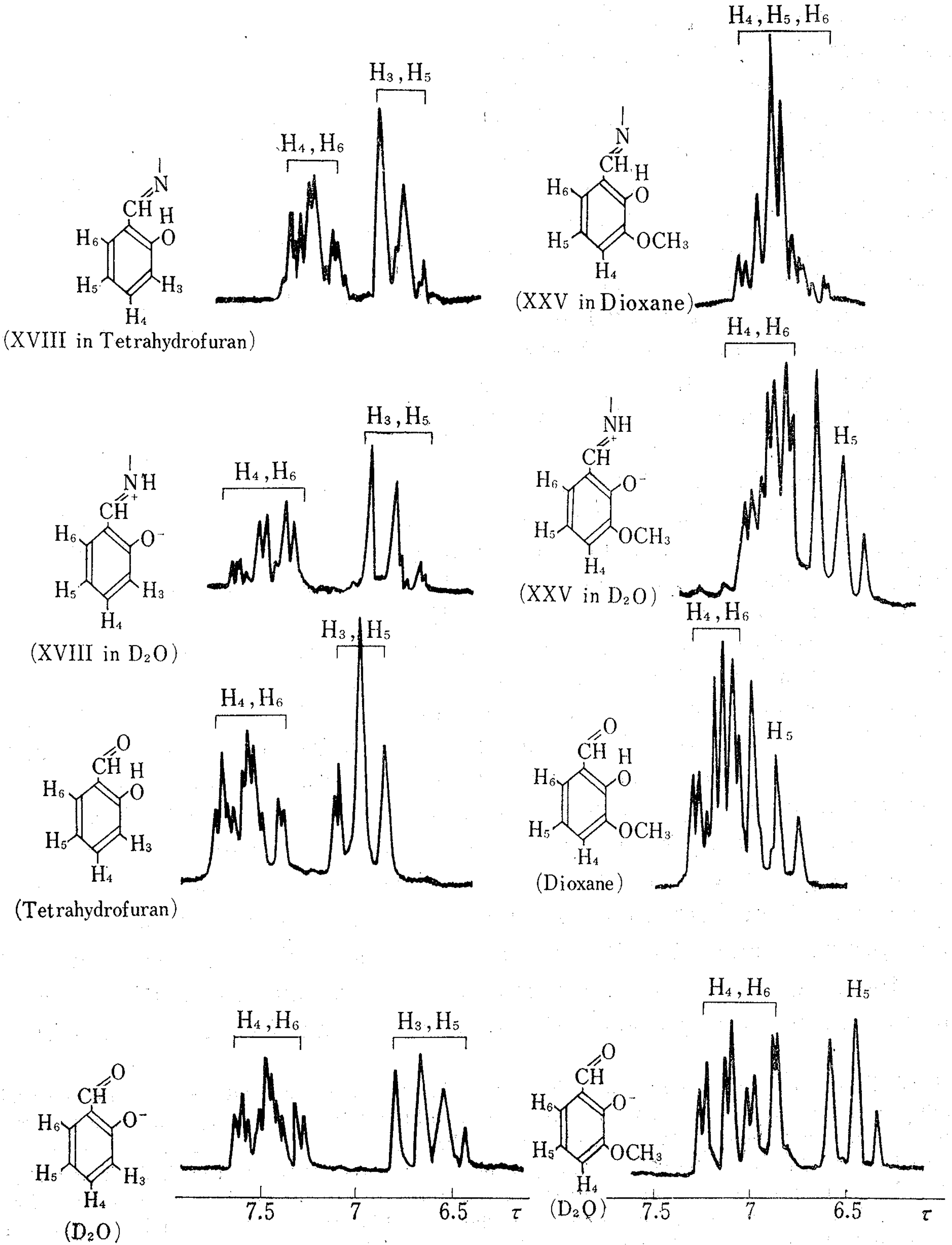

Fig. 2. NMR Spectra of Aromatic Protons in Methyl N-Salicylidene-3-amino-3-deoxy-α-D-mannopyranoside (XVIII), Salicylaldehyde, N-3-Methoxysalicylidene-2-aminoethanol (XXV) and 3-Methoxysalicylaldehyde

salicylaldehyde and its Schiff base in the phenolimine form, the lower pair was assigned to H_4 and H_6, since they were the para and ortho protons against the electron-withdrawing azomethine or aldehyde groups,[17] and then the remaining higher pair was assigned to H_3 and H_5. The high-field shift of the H_3 and H_5 against the H_4 and H_6 was consistently observed in the derivatives of salicylaldehyde (3-methoxysalicylaldehyde, 4-hydroxysalicylaldehyde, 3,5-dibromosalicylaldehyde, 2-hydroxynaphthylaldehyde and their Schiff bases). When the phenolic hydrogen was dissociated, the chemical shift difference in the two sets of signal pair would be expected to be much enhanced by the contribution of the quinoid structure (C). This occurred indeed in the spectra of the aldehyde anions and the ketoamine species in deuterium oxide and dimethylsulfoxide above 10^{-2} mole. The analogous signal separation was demonstrated also in the 3-methoxysalicylidene series (Fig. 2).

Tautomerization of (2-hydroxynaphthylidene)benzylamine (XXIX) and -methylamine in deuteriochloroform was studied by Dudek[18] and the presence of the ketoamine species was shown by the observed spin-spin splitting of the aldehydic proton with NH. The similar splitting of the CH=NH proton signals were observed for the 3,5-dibromosalicylidene derivative (XXVIII, 11.0 c.p.s.) in dimethylsulfoxide as well as the 2-hydroxynaphthylidene derivatives (XXIX, 9.0 c.p.s.; XXX, 12.0 c.p.s.; XXXI, 12.0 c.p.s.). These results provided the complementary evidence for the structure of the ketoamine.

Additional evidence for the ketoamine structure came from the solution equilibrium studies described below.

Effect of Solvent on Solution Equilibrium

The relative amount of the two tautomers (apparent equilibrium position, K_T) in solution was calculated from the equation,

TABLE IV. Effect of Solvent on Solution Equilibrium (K_T) and λ_{max} of the Longest Wave-length Band of the Ketoamine in Salicylidene Schiff Bases (II, V, XVIII), 3-Methoxysalicylidene Schiff Base (XXV), 3,5-Dibromosalicylidene Schiff Base (XXVII) and 2-Hydroxynaphthylidene Schiff Base (XXIX)* at $10^{-4}M$ (22~23°)

Solvent	E_T	K_T (λ_{max} mμ)					
		II	V	XVIII	XXV[a]	XXVII[b]	XXIX[c]
H_2O	63.1	2.9 (396)	4.8 (391)	2.6 (399)	7.3 (414)	>10 (418)	>10 (412)
Formamide	56.6	0.92 (402)	1.0 (402)	0.67 (406)	2.3 (421)	5.2 (425)	>10 (420)
MeOH	55.5	0.28 (402)	0.46 (402)	0.64 (405)	0.79 (420)	1.8 (422)	>10 (418)
DMSO	45.0	0.03 (420)	0.03 (414)	0.11 (415)	0.18 (428)	1.6 (429)	3.2 (423)
Dimethylformamide	43.8	0.02 (410)	0.02 (410)	0.08 (410)	0.09 (426)	1.1 (428)	2.6 (424)
$CHCl_3$	39.1	0.03 (414)	0.04 (415)	0.06 (411)	0.07 (430)	0.19 (438)	2.0 (424)
Dioxane	36.0	0.01	0.01	0.03 (412)	0.02	0.15 (435)	0.85 (424)
CCl_4	32.5	0.01	0.01	0.16[e,f]	0.01	0.03[e] (441)	0.25 (427)
Cyclohexane	30.9	<0.01	<0.01	0.24[e]		0.03[e]	0.09 (427)

* For numbering of the compounds, see Table I.

a) Calculated on the basis of $\varepsilon_{880}=2500$ (phenolimine) and $\varepsilon_{420}=4500$ (ketoamine).

b) Calculated on the basis of $\varepsilon_{840}=4000$ (phenolimine) and $\varepsilon_{420}=7500$ (ketoamine).

c) Calculated on the basis of $\varepsilon_{860}=7000$ (phenolimine) and $\varepsilon_{420}=10500$ (ketoamine).

d) Contained 10% MeOH.

e) Contained 10% $CHCl_3$.

f) K_T values at $2\times10^{-5}M$ and $10^{-5}M$ were 0.12 and 0.04, respectively.

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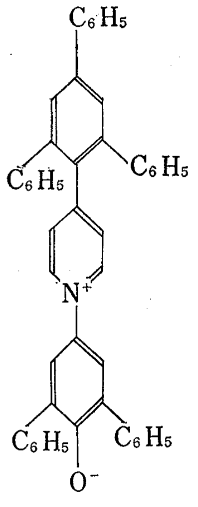
17) J.B. Stothers: "Elucidation of Structures by Physical and Chemical Methods," Part I, 209 (1963). Interscience Publishers, New York.

18) G.O. Dudek: J. Am. Chem. Soc., **85**, 694 (1963).

$$K_{\mathrm{T}}=\frac{[\text{ketoamine}]}{[\text{phenolimine}]}=\frac{\varepsilon_{315}}{\varepsilon_{405}}\times\frac{A_{405}}{A_{315}}=0.69\times\frac{A_{405}}{A_{315}}$$

where ε_{315}, ε_{405} were molar absorption coefficients at the maximum wave-lengths around 315 and 405 mμ, and A_{315}, A_{405} were observed absorbances at the maximum wave-lengths. In the case of high K_{T} value, wing-correction[19] was computed for the A_{315} value.



E

Chemical Structure II.

The K_{T} values of six members of Schiff bases in various solvents were summarized in Table Ⅳ, which revealed the primary dependence of the equilibrium position upon the polarity of solvent. This was especially true for the 3,5-dibromosalicylidene and 2-hydroxynaphthylidene Schiff bases, where the monotonic relationship was observed between the K_{T} values and the E_{T} values which was a measure for the polarity of solvent determined from the magnitude of the wave-length shift of pyridinium N-phenolbetaine (E).[20] Interestingly, the longest wave-length bands of the ketoamine species showed similar blue shift (with increasing polarity of the solvent) as did the phenolbetaine (E) that has an analogous resonance system.

The K_{T} values in the salicylidene Schiff bases, however, depended not only on the polarity but also on the hydrogen-bonding ability of solvents.[4,5] This was seen, for example, by the marked drop of the K_{T} in aprotic dimethylsulfoxide and dimethylformamide compared with that in a protic chloroform in going from the 3,5-dibromosalicylidene derivatives to the salicylidene derivatives. The K_{T} values of the 3-methoxysalicylidene derivatives were intermediate between the two series of the Schiff bases.

TABLE V. Effect of Concentration on Apparent Equilibrium Position (K_{T}) and Absorption Bands of Methyl N-Salicylidene-3-amino-3-deoxy-α-D-mannopyranoside (XVIII) and N-Salicylidenecyclohexylamine (V) in Chloroform and Methanol (22～23°)

Concentration	K_{T} in $CHCl_3$ ($\lambda_{\max}$ mμ)		K_{T} in MeOH ($\lambda_{\max}$ mμ)	
	XVIII	V	XVIII	V
$10^{-4}M$	0.06(411)	0.04(415)	0.59(405)	0.42(402)
$2\times10^{-4}M$	0.06(408)			
$4\times10^{-4}M$	0.10(406)			
$10^{-3}M$	0.20(407) (0.4)[a]	0.04(416)	0.59(405)	0.42(402)
$2.5\times10^{-3}M$	0.35(406) (0.8)[a]			
$5\times10^{-3}M$	0.50(404) (1.2)[a]	0.04(418)		
$10^{-2}M$	0.57(404) (1.9)[a]	0.06(419)	0.61(405)	0.43(402)

a) The ratio of apparent absorbannce at 3390 cm^{-1} to absorbance at 3596 cm^{-1} in the infrared spectra.

The profound effect of hydrogen bonding on the solution equilibrium was further shown by the concentration dependence of the apparent K_{T} value of methyl N-salicylidene-3-amino-3-deoxy-α-D-mannopyranoside (XVIII) in chloroform (Table V). As the concentration of the solute increased in the range of $10^{-4}\sim10^{-2}$ mole, the K_{T} value of

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19) Y. Shimura, R. Tsuchida: Bull. Chem. Soc. Japan, **28**, 572 (1955).
20) K. Dimroth, C. Reichardt, T. Siepmann, F. Bohlmann: Ann., **661**, 1 (1963).

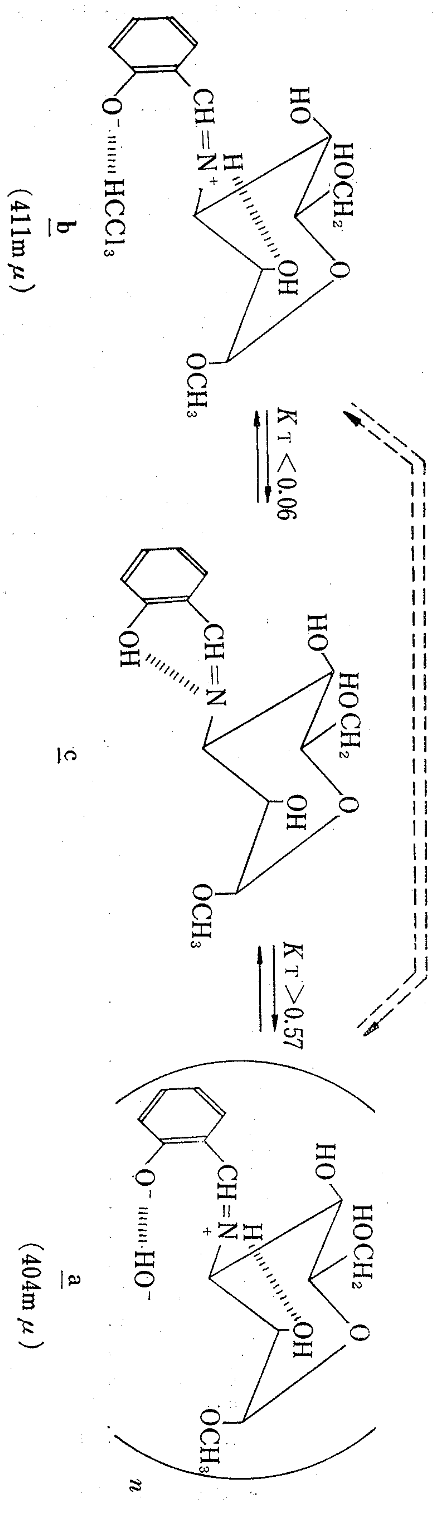

Fig. 3. Tautomeric Equilibrium and Schematic Representation of Hydrogen Bonding in Methyl N-Salicylidene-3-amino-3-deoxy-α-D-mannopyranoside (XVIII) in Chloroform

XVIII increased markedly with the simultaneous hypsochromic shift of the 411 mμ band. Since the K_T of N-salicylidenecyclohexylamine (V) measured for a comparison was nearly constant in this concentration range, the concentration dependence in XVIII could be best interpreted in terms of the competitive hydrogen bonding among the associated solute (a), the solvated solute (b) and the intramolecularly bonded solute (c) (Fig. 3). In fact, the associated molecule of XVIII in chloroform increased rapidly in the range of $10^{-3} \sim 10^{-2}$ mole, as evidenced by the intensity increase of a broad hydroxyl band at 3390 cm^{-1} compared with a sharp band at 3596 cm^{-1} assignable to a free or solvated hydroxyl group (Table V). In the solution below 10^{-4} mole, competition occurred mainly between b and c, where the equilibrium was favorable to c ($K_T \leq 0.06$). As the concentration of the solute increased, the equilibrium shifted more towards a ($K_T > 0.57$), whose hydrogen bonding of the OH-O^- type was undoubtedly stronger than that of solvation (CCl_3H-O^-)[21] and competed well with the intramolecular hydrogen bonding (OH-N) of c. A logical site for molecular association or solvation in a and b was the anionic oxygen, since the cationic nitrogen was involved in the intramolecular hydrogen bonding with the C-2-*cis*-hydroxyl group (See p. 1551). Similarly, the unusual K_T increase at 10^{-4} mole in going from chloroform to carbon tetrachloride and cyclohexane (Table IV) was attributable to the molecular association of the solute, since the apparent K_T value in carbon tetrachloride decreased by further dilution. Infrared spectroscopy of XVIII in carbon tetrachloride indicated that the intermolecular hydrogen bonding existed even at the concentration of 10^{-4} mole ($A_{3390}/A_{3600} = 0.2$), which became dominant at 10^{-3} mole ($A_{3390}/A_{3600} = 2.6$). Thus, the molecular association in carbon tetrachloride occurred in more dilute solution than in chloroform, implying the existence of the competitive hydrogen bonding between a and b. As would be expected, the K_T values and λ_{max} in V and XVIII in methanol were almost constant in the range of $10^{-4} \sim 10^{-2}$ mole, indicating little association of the solute. These results suggested that, in solvents with sufficiently strong hydrogen bonding ability, the more polar ketoamine species would be stabilized by solvation. The solvation effect to the phenolimine species may be much less, because the two polar groups in the phenolimine were involved in the strong intramolecular hydrogen bonding.

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[21] G.C. Pimentel, A.L. McClellan: "The Hydrogen Bond," 224 (1960). W.H. Freeman and Company, San Francisco.

Effect of Substituent on Solution Equilibrium in Methanol

Table VI. Acid Dissociation Constants (p*K*a′) of *o*-Hydroxyaromatic Aldehydes in 50% Methanol and Anhydrous Methanol at 23°

Compound	p*K*a′	
	50% MeOH	MeOH
Salicylaldehyde	8.97	>13
3-Methoxysalicylaldehyde	8.81	>13
3,5-Dibromosalicylaldehyde	6.48	10.70
2-Hydroxynaphthylaldehyde	8.11	12.72

Table VII. Substituent Effects of Amino-components on Apparent Equilibrium Position (K_T) of Salicylidene Schiff Bases in Methanol, Water, Solid and Potassium Bromide Medium and p*K*a Values of Parent Amines in Methanol (22~23°)

N-Salicylidene derivative*	K_T		K_T'		p*K*a′ of Parent Amines (MeOH)
	MeOH	H_2O a)	KBr b)	Solid c)	
Aniline	0.02 6)				5.80
I	0.14	2.1		0.0	10.27
II	0.28	2.9	0.39	0.5 d)	11.03
III	0.31	4.0		0.2 d)	11.40
IV	0.43	4.5		0.0 d)	11.83
V	0.46	4.8	0.03	0.0 d)	11.83
VI	0.52	2.4	2.5	>5	10.93
VII	1.06	4.6	8.1	>5	10.57
VIII	0.09	0.60		0.8	
IX	0.02	—		0.05 e)	
X	0.03	—		0.1 e)	
XI	0.20	0.50		2.4	10.23
XII	0.23	0.58		1.6 e)	
XIII	0.18	0.43		1.2 e)	
XIV	0.38	1.1		0.1 e)	9.96
XV	0.03	0.24	0.11 e)	0.0	
XVI	0.07	0.47	0.25 e)	0.2 e)	10.17
XVII	0.06	0.43	0.21 e)	0.2 e)	10.07
XVIII	0.64	2.6		>5(4.3) e)	10.31
XIX	0.31	2.4	0.15 e)	0.0	10.81
XX	0.23	2.3		0.0	
XXI	0.18	0.69		0.0	
XXII	0.16	0.92		0.0	
XXIII	0.41	2.0		0.9	

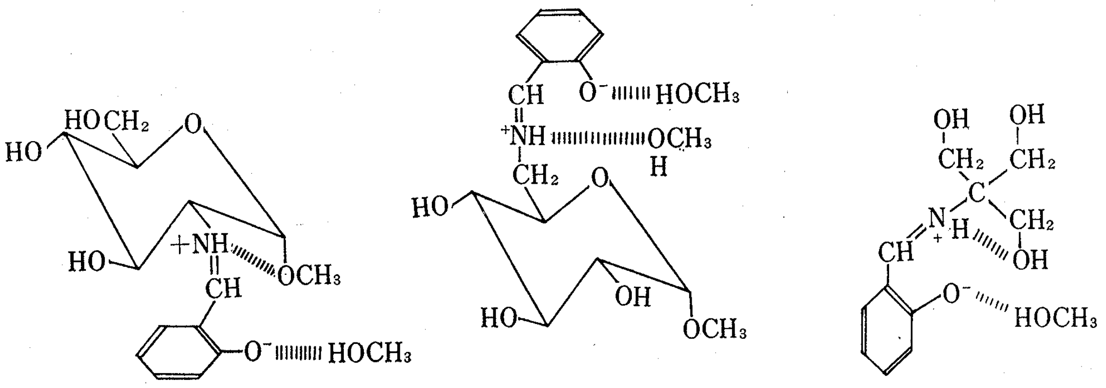
* For numbering of the compounds, see Table I.
a) Contained 10% MeOH. *b*) Estimated from the electronic spectra.
c) Estimated from the infrared spectra. *d*) Liquid. *e*) Amorphous state.

The effect of the benzene nuclear substitution on the K_T values was seen in Table IV, in which the K_T values increased in the following order: salicylidene <3-methoxysalicylidene <3,5-dibromosalicylidene <2-hydroxynaphthylidene series. Except for the naphthalene derivative, this order coincided with the sequence of the p*K*a of the parent aldehyde phenols given in Table VI, suggesting that the ease of ionization of a phenolic hydrogen shifted the equilibrium in favor of the ketoamine. Since 3,5-dibromosalicylaldehyde was present in part as a phenolate anion in water and methanol, the dissociation of a phenol in the corresponding Schiff base would also be expected. This was confirmed by the measurement of the pKa of the Schiff bases as shown later.

The substituent effect of the amino-component on the K_T values were summarized in Table VII. In this case also, a correlation was possible between the K_T of the compounds I～IV and the pKa of the parent acyclic amines: the K_T values increased with the increasing electron-donating ability of the substituents.[*5] The low K_T values in IX, X and N-salicylideneaniline were probably the reflection of the weak basicities of the parent amines.

Another important factor that was comparable in effect with the basicity was the steric requirement of the substituents in the vicinity of a chromophore. This was clearly seen by comparing the K_T values of methyl N-salicylidene-3-amino-3-deoxy-α-D-mannopyranoside (XVIII) and the corresponding glucopyranoside (XVI) and another pair of methyl N-salicylidene-2-amino-2-deoxy-α-D-glucopyranoside (XIV) and its β-D-isomer (XV). In both cases, the larger K_T values were exhibited by the compounds having the *cis*-axial hydroxyl (or methoxyl) group (XVIII, XIV), rather than the *trans*-equatorial substituents (XVI, XV), against the equatorial azomethine group. In this connection it was noted that the K_T value of XVIII (0.64) was larger than that of V (0.46) (a model of deoxy-compound), while the K_T values in XVI (0.07) and XV (0.03) were much smaller than V. Similarly, the N-salicylidene derivatives of acyclic polyhydroxylamines (2-amino-2-deoxy-D-glucitol (VI) (0.52) and 2-amino-2-hydroxymethyl-1,3-propanediol (VII) (1.06)) displayed larger K_T values than that of N-salicylideneethylamine (IV) (0.43), though the Schiff bases of monohydroxylamines (2-aminoethanol (II) (0.28) and 3-amino-*n*-propanol (III) (0.31)) exhibited smaller K_T values. Obviously, a hydroxyl (methoxyl) group had opposite effect on the equilibrium position depending upon the relative configuration. In this case, the basicity of the parent amines was a minor factor (see Table VII).

For the interpretation of these results, it was postulated that the solvation or intramolecular hydrogen bonding to the cationic nitrogen of the ketoamine, together with the simultaneous hydrogen bonding to the anionic oxygen as shown in Fig. 4,



XIV XIX VII

Fig. 4. Schematic Representation of Hydrogen Bonding in the Ketoamine in N-Salicylidene Derivatives of Methyl 2-Amino-2-deoxy-α-D-glucopyranoside (XIV), Methyl 6-Amino-6-deoxy-α-D-glucopyranoside (XIX) and 2-Amino-2-hydroxymethyl-1,3-propanediol (VII) in Methanol

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[*5] In view of the fact that increases of the basicity of an amine and acidity of a phenol shifted the equilibrium towards the ketoamine side, the conversion of the phenolimine into the ketoamine may be regarded as the intramolecular prototropy in the ground state as a result of maximization of the intramolecular hydrogen bonding strength. The occurrence of such prototropy in the excited state was implied for some salicylates (A. Weller: Z. Electrochem., **60**, 1144 (1956)).

played a major role in determining the equilibrium position. The profound effect of intramolecular hydrogen bonding was inferred from the fact that the K_T values increased only when the hydroxyl (methoxyl) groups carried by the amino-components were located close to the azomethine chromophore as seen in Ⅵ, Ⅶ, Ⅺ (α-anomer), Ⅻ (α-anomer), XIV, XVIII and XXIII. The idea of dimolar solvation was already proposed by Charette, *et al.*,5) though they considered the solvation to the phenolimine species. According to the above postulate, the extremely low K_T values in XV, XVI and XVII could be readily interpreted in terms of the steric shielding of solvation, as the solvation to the cationic nitrogen was susceptible to steric interaction.

Table Ⅷ. Values for Apparent Enthalpy (ΔH) on Tautomerization of Some N-Salicylidene Schiff Bases in Methanol at 20°

Compounds[a)]	ΔH kcal. M^{-1}	Compounds[a)]	ΔH kcal. M^{-1}
Ⅶ	−1.7	XIX	−0.5
XVIII	−0.9	V	−0.5
Ⅵ	−0.8	XVI	0.6
XIV	−0.8	XV	1.0

a) For numbering of the compounds, see Table I.

Table Ⅷ gave the found values for the apparent enthalpy (ΔH) associated with the tautomerization of some N-salicylidene derivatives in methanol. The ΔH values were obtained from a linear relation between log K_T and the reciprocal of absolute temperature over a range of 5~25°. Above 30°, the linearity became unsatisfactory. It may be seen from Table Ⅷ that the ΔH were in roughly parallel with the K_T values, and that the ΔH of the Schiff bases for which the intramolecular hydrogen bonding was expected (Ⅵ, Ⅶ, XIV, XVIII) were a little larger than the ΔH of V and XIX, for which the solvation was expected. If the steric shielding of solvation to the cationic nitrogen was operative in XV, its ΔH value (1.0 kcal/mole) would be approximate to the enthalpy difference between the intramolecularly bonded phenolimine and the monomolecular-solvated ketoamine species.

Acid-base Equilibria of Two Tautomers in Methanol

Acid-base equilibria of the phenolimine and ketoamine species were shown in Plate I. A preliminary problem to settle first before any discussion on the equilibrium constant was the exact assignment of the electronic bands for the cation (a) and the anion (d). Heinert and Martell22) assigned, for the characteristic bands of the

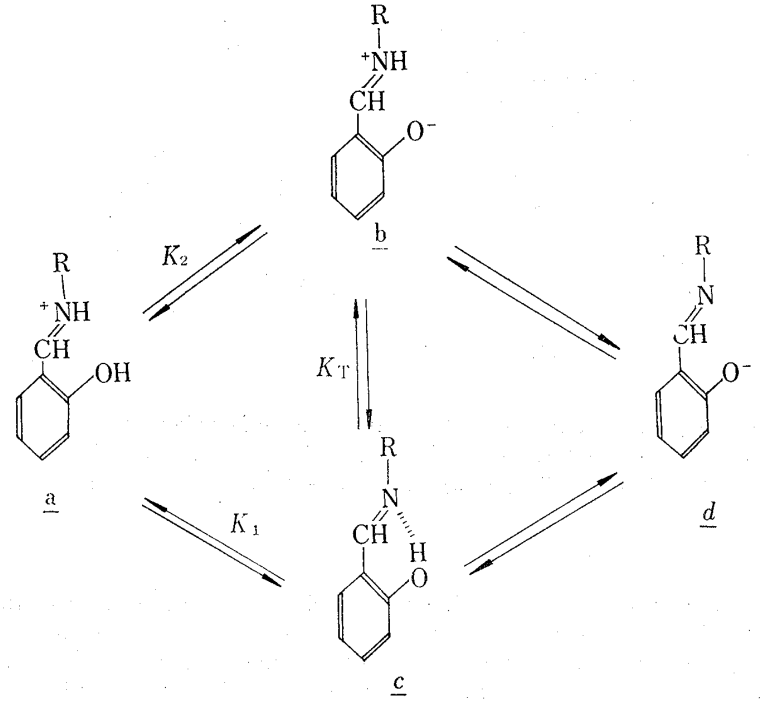

Plate I.

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[22] D. Heinert, A. E. Martell: J. Am. Chem. Soc., 85, 188 (1963).

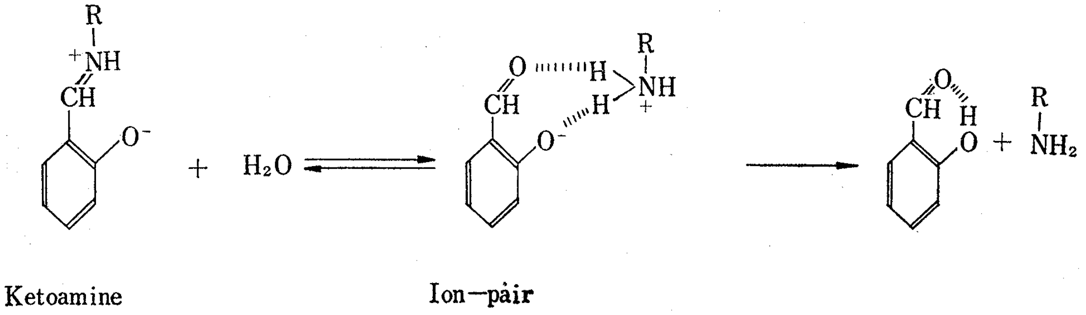

Plate II.

cation of N-salicylidene-valine potassium salt, 261 mμ ($\varepsilon \times 10^{-4}=1.38$) and 321 mμ (0.46), and for the anion 263 mμ (0.71) and 377 mμ (0.66). Whereas, Charette, *et al.*[5] reported 278 mμ (1.90) and 350 mμ (0.60) for the cation of N-salicylidene-2-aminopropane and 250 mμ (0.80) and 350 mμ (0.50) for the anion. The discrepancy was apparently anomalous, since the substituent effect on the electronic transition of the chromophore should be not so large as reported. The results obtained in the present investigation (Table III) fully agreed with the data reported by Charette, *et al.* In support of the above assignment, the λ_{max} and ε values of the N-salicylidene cation resembled closely to those of the cation of *o*-methoxybenzylidene-Schiff base (Table III).

The solution equilibrium between the cation ($\underline{a}$) and the two tautomers ($\underline{b}$ and $\underline{c}$) in methanol was illustrated by the presence of the isosbestic points in the electronic spectrum. The measurement of the equilibrium constant, however, was more convenient to use the potentiometric titration rather than the spectral change, because of the unstabilty of the C=N bond in acidic and basic media and because of the lack of buffer of wide range of pH in methanol.

The measured dissociation constant, Ka', was given by

$$Ka' = \frac{[\mathrm{H}^+][\underline{b}+\underline{c}]}{[\underline{a}]} = K_1 + K_2.^{23)}$$

Then, the pKa of the two tautomers (pKa_1, phenolimine; pKa_2, ketoamine) could be obtained from Ka' and K_T using the following equations,

$$\mathrm{p}Ka_1 = \mathrm{p}Ka' + \log(1+K_T) \text{ and } \mathrm{p}Ka_2 = \mathrm{p}Ka' + \log(1+1/K_T).^{*6}$$

When the pKa_1 values of eleven members of N-salicylidene Schiff bases were plotted against the pKa of the parent amines, no definite relation was obtained. But, when plotted against the K_T values as shown in Fig. 5, two parallel lines were obtained. The parallel increases of the ketoamine content and the pKa_1 was to be expected, if the intramolecular hydrogen bonding involving the alcoholic hydroxyl group and solvation which increased the $-\Delta H$ of the ketoamine stabilized the cation ($\underline{a}$) as well.

[*6] Heinert and Martell[22] reported the pKa_1 and pKa_2 of N-salicylidene-valine potassium salt by the use of the spectral change. We could not apply this technique to the present case, because, addition of dilute acetic acid (up to $0.1M$) as described by them caused the increase of the K_T instead of producing the cation. Addition of $0.1 \sim 1.0M$ potassium hydroxide as reported caused complete hydrolysis of the C=N bond within 5~10 minutes at room temperature. In this connection, it should be noted that the γ_{max} and ε values reported for $\underline{a}$ and $\underline{d}$ were very close to those of the phenolimine and salicylaldehyde anion, respectively.

23) Reference 17, p. 357.

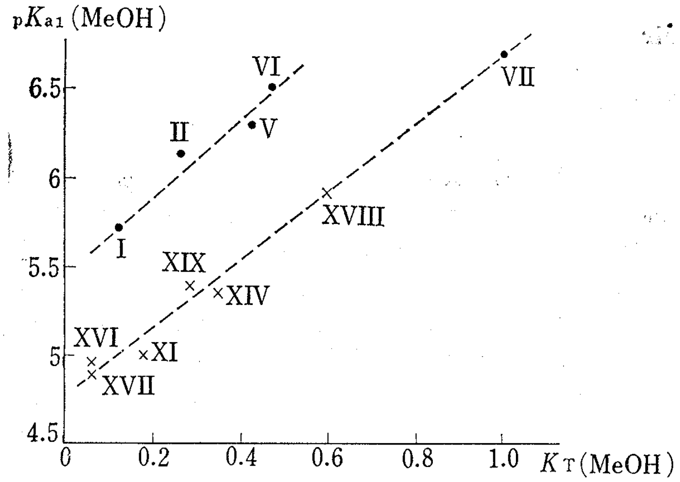

Fig. 5. Relationship between the pKa$_1$ of the Phenolimine Species in N-Salicylidene Schiff Bases and K_T Values in Methanol at 23°

●: Derivatives of alkylamines and acyclic amino-alcohols.
×: Derivatives of amino-sugars.
Numbers attached were compound No. listed in Table I.

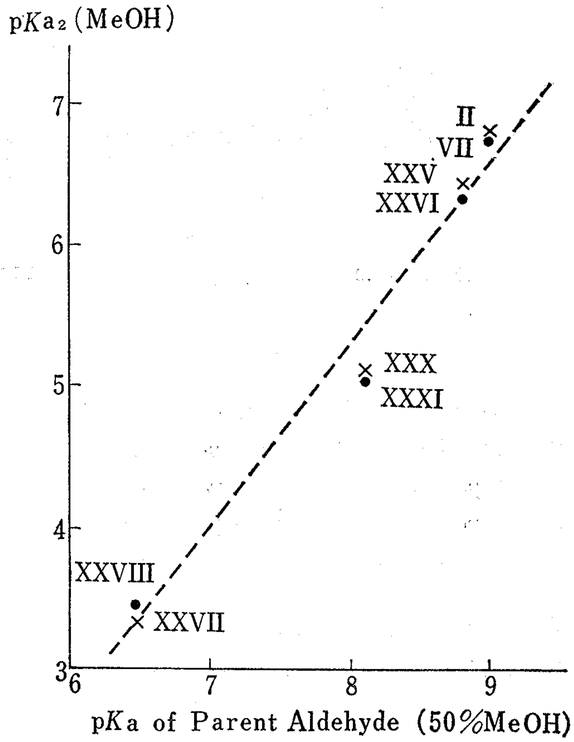

Fig. 6. Relationship between the pKa$_2$ of the Ketoamines in Methanol and the pKa of Parent Aldehydes in 50% Methanol at 23°

×: Derivatives of 2-aminoethanol.
●: Derivatives of 2-amino-2-hydroxymethyl-1,3-propanediol.
Numbers attached were compound No. listed in Table I.

Undoubtedly, these effects were weakened in c where the azomethine nitrogen linked up with the phenolic hydrogen.

Differed from the pKa$_1$, the pKa$_2$ were not related with the K_T, but in parallel with the pKa of the parent aldehydes as shown in Fig. 6. It was most likely therefore that the pKa$_2$ was related with the dissociation of the phenolic hydrogen, rather than the ammonium hydrogen. In this approximation, the structure around the cationic nitrogen atom in the conjugate acid (a) and the dipolar ketoamine (b) remained almost unchanged, and hence the effect of the amino-components on the pKa$_2$ would be small, as indeed found.

Solution Equilibrium in Aqueous Solution

The K_T values of various N-salicylidene derivatives in water were listed in Table VII. The tautomeric equilibrium in aqueous solution was more favorable to the ketoamine side than in methanol, but the Schiff bases for which the steric inhibition of solvation was suggested showed lower K_T than an unity, indicating the predominance of the phenolimine even in water. Of particular significance was the large K_T values of the Schiff bases for which the solvation to the cationic nitrogen was considered, as compared with the Schiff bases for which the intramolecular hydrogen bonding was assumed. According to the postulated theory, the remarkable increment of the K_T values was rationalized in terms of the large hydration energy which probably surpassed the energy of intramolecular hydrogen bonding.

The predominant formation of the ketoamine in aqueous solution provided an interesting problem on the hydrolytic mechanism of the salicylidene Schiff base.[24] Actually, the following evidence suggested that the non-catalytic hydrolysis of the N-salicylidene derivatives proceeded *via* the solvated ketoamine species with the formation of an ion-pair in the intermediate step. 1) The measurement of the electronic spectra of II and III in function of time revealed the successive blue shifts of the characteristic bands of the ketoamine (278 and 396 mμ), with the well-defined isosbestic points (Fig. 7). This phenomenon was clearly recognized only in the concentrated solution above 10^{-3} mole. In the more dilute solution, the above change was obscured by the concomitant appearance of the absorption bands of salicylaldehyde produced by hydrolysis. The electronic spectrum (264 mμ (7300) and 380 mμ (4800)) of the 10^{-3} mole solution keeping for 30~60 minutes after dissolution were very close to the spectrum of salicylaldehyde sodium salt, except for the shortest wave-length region. 2) The possibility of the carbinolamine that was a common intermediate in the hydrolysis of a Schiff base,[25] was excluded, because the bands of the saturated compounds including the carbinolamine and oxazoline should appear at shorter wave-length region with lower absorption coefficient. For example, 2-(N-trihydroxymethyl)aminomethylphenol showed bands at 275 mμ (1600) in methanol and 240 mμ (6500) and 292 mμ (2600) in 0.1*N* sodium hydroxide-methanol. 3) NMR Spectra of II, III, VI and VII in deuterium oxide showed two signals assignable to the aldehydic protons, of which the main signal at about 8.45 p.p.m. was assigned to the CH=N proton. The minor signal (*ca.* 10% in intensity) appeared at lower field (10.05 p.p.m.) was very close to the CH=O proton signal (10.08 p.p.m.) of the parent aldehyde anion. 4) When a large amount of methanolic hydrogen chloride (or dioxane) was added to the aqueous solution, there appeared the spectra of the Schiff base cation (or the phenolimine) and salicylaldehyde, the relative intensities of which depended on the initial concentration of the Schiff base and the period after dissolution. 5) Mixing of an amino-component and salicylaldehyde in the concentration range of 10^{-3}~10^{-2} mole did not yield the spectrum mentioned above.

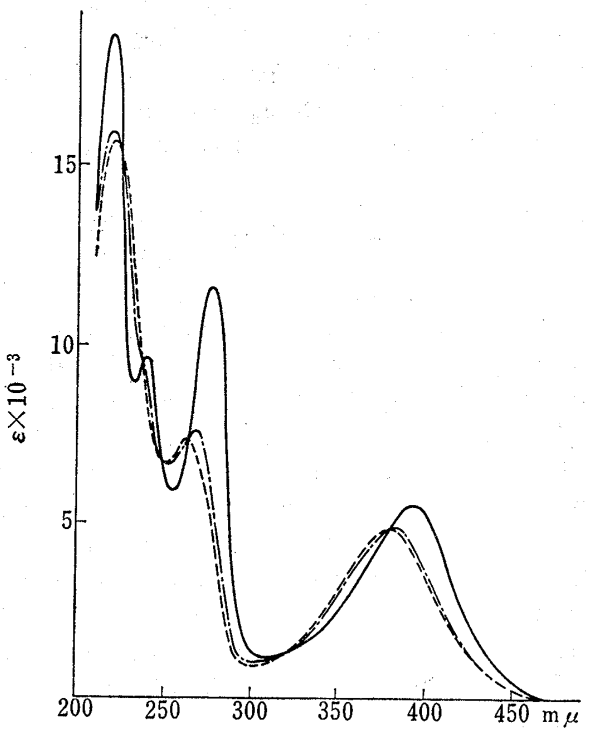

Fig. 7. Electronic Absorption Spectra of N-Salicylidene-2-aminoethanol (II) in Water at $10^{-3}M$

——— Within 2 minutes after dissolution.
------ 20 Minutes after dissolution.
– – – – 30 Minutes after dissolution.

Thus, the formation of an ion-pair gave the indirect evidence for the dissociation of the phenol in the ketoamine form.

Tautomeric Structure in Solid State

The relative amount (K_T') of the two tautomers in a solid state were estimated *via* two routes : 1) from the electronic spectra in potassium bromide medium using the same equation as employed in solution, 2) from the infrared spectra in potassium

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[24] R.L. Reeves : J. Org. Chem., **30**, 3129 (1965).
[25] Y. Ogata, A. Kawasaki, N. Okumura : Kagaku, **21**, 629 (1966).

bromide or nujol mull by the use of the characteristic band intensities of the phenolimine ($1581\pm4\,\mathrm{cm}^{-1}$, $\varepsilon=50\pm10$) and the ketoamine ($1530\pm5\,\mathrm{cm}^{-1}$, $\varepsilon=45\pm10$). As the half band width ($\Delta_{1/2}$) of the two bands varied with the measuring condition, the triangular area ($t=\varepsilon\times\Delta_{1/2}$) was used for the band intensity, rather than the apparent ε value.[7] Then, the relative amount of the two tautomers could be estimated by

$$K_T{}'=\frac{\varepsilon_{1581}}{\varepsilon_{1530}}\times\frac{A_{1530}\times\Delta_{1/2}}{A_{1581}\times\Delta_{1/2}}$$

The $K_T{}'$ values determined *via* the two ways were in fairly agreement as seen in Table VII. The $K_T{}'$ values in solid state were different in crystalline and amorphous states reflecting the different combination of the hydrogen bonding. Judged from the $K_T{}'$ values shown in Table VII, the salicylidene chromophore in XVIII was completely ketoamine in a crystalline state and 80% ketoamine in an amorphous state. The chromophore in XIX, on the contrary, was phenolimine in crystal and 13% ketoamine in an amorphous state. Of special interest was the structure of XXIII in a crystalline state. The observed $K_T{}'$ value, 0.9, suggested the different tautomeric structure for the two chromophores in the molecule. The assignment of the C-6 chromophore to the phenolimine and the C-3 chromophore to the ketoamine was derived from the $K_T{}'$ values of XVIII ($K_T{}'>5$) and XIX ($K_T{}'\fallingdotseq0$) in crystal. In this connection, it was noted that the chromophores in VI, VII, XI, XVIII and XXIII, for which the formation of the intramolecular hydrogen bonding involving the *cis*-alcoholic hydroxyl groups was suggested in solution, took preferably the ketoamine form in crystal, and that the chromophores in XIX, XX and XXII for which the solvation was expected were all the phenolimine in crystal. Similarly, little formation of the ketoamine was recognized in N-salicylidene-alkylamines which contained no alcoholic hydroxyl group in potassium bromide and in liquid state.

Thus, the formation of the ketoamine in a solid state (or liquid) was closely related with the formation of the intra- and intermolecular hydrogen bonding involving the alcoholic hydroxyl groups.

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[7] Similar expression has been used for the tautomer calculation in arylazonaphthols (K. J. Morgan: J. Chem. Soc., 1 (1961)).