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A Nuclear Magnetic Resonance Study of the Structure and Mutarotation of Sugar Osazones in Dimethyl Sulfoxide Solution[1]

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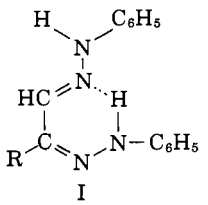
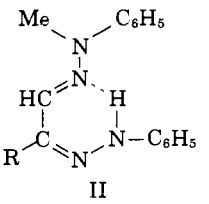
Study of the nuclear magnetic resonance spectra of sugar osazones and appropriate model compounds in dimethyl sulfoxide leads to the conclusion that sugar osazones possess chelate structure I. Mutarotation of sugar osazones is shown to be the result of equilibration of the osazone with an isomer. The nuclear magnetic resonance spectrum of the isomer shows that it still possesses an aldimine C–H but that it no longer possesses a chelate ring. The mutarotation process involves rupture of the chelate ring and concomitant geometric isomerization about the C_2–N bond.

Evidence has been presented that sugar phenylosazones contain a chelate ring both in solution and in the crystal.[2-5] Mester[3,6] has favored the chelate structure I on the basis of similarities in properties of glucose phenylosazone (I, R = $C_4H_9O_4$) and glucose 1-methyl-



I



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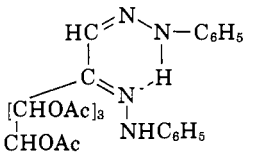
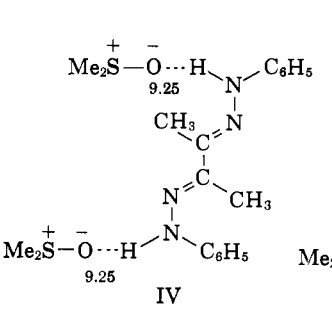


III

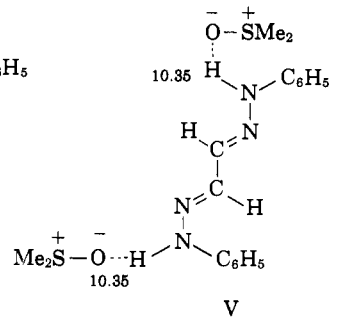
phenyl-2-phenylosazone (II, R = $C_4H_9O_4$). Wolfrom, Fraenkel, Lineback, and Komitsky[4] have favored chelate structure III for tetraacetylglucose phenylosazone on the basis of nuclear magnetic resonance studies in deuteriochloroform. Crystalline xylose *p*-bromophenylosazone shows an arrangement of carbons and nitrogens analogous to I in a two-dimensional X-ray analysis.[5]

We have examined the structure and mutarotation of sugar osazones in dimethyl sulfoxide solution. Dimethyl sulfoxide is a particularly useful solvent for such studies because of the solubility of sugar osazones in this solvent and the reduced rate of exchange of protons bound to heteroatoms.[7,8] This reduced rate of exchange permits observation of spin-spin splitting of hydroxyl protons (which facilitates assignments) and produces sharp N-H resonance lines.[7,8]

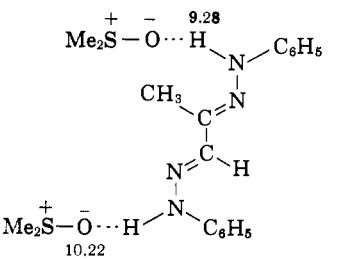
Structure of Sugar Osazones.—Examination of the n.m.r. spectra (Table I) of certain model compounds is necessary before turning to the sugar osazones. Biacetyl bisphenylhydrazone (IV) in dimethyl sulfoxide shows a single sharp resonance at δ 9.25.[9] The pres-



IV



V



VI

ence of a single N-H resonance implies that a single geometric isomer is present (three are possible; *syn-syn*, *syn-anti*, and *anti-anti*). The single geometric isomer cannot be the *syn-anti* form since only one N-H resonance line is observed. It is unlikely that the *syn-syn* form is present since this form would be steri-

TABLE I

NUCLEAR MAGNETIC RESONANCE SPECTRA OF MODEL BISPHENYLHYDRAZONES[a]

Compound	Solvent	Chelate N–H	Solvent bonded N–H	Aldimine C–H
Glyoxal bisphenylhydrazone	DMSO		10.35	7.68
Biacetyl bisphenylhydrazone	DMSO		9.25	
Pyruvaldehyde bisphenylhydrazone	DMSO		10.22 9.28	7.65
1,2-Cyclopentanedione bisphenylhydrazone	DMSO	12.12	9.45	
	$CDCl_3$	11.92	Under aromatic C–H	
1,2-Cyclohexanedione bisphenylhydrazone	DMSO	13.07	9.47	
	$CDCl_3$	12.92	Under aromatic C–H	
Phenylglyoxal bisphenylhydrazone	DMSO	12.75	10.90	8.25
	$CDCl_3$	12.60	Under aromatic C–H	7.68

[a] All resonance positions are given as p.p.m. downfield from internal tetramethylsilane (δ-scale).

(1) Portions of this work were described: Abstracts, 145th National Meeting of the American Chemical Society, New York, N. Y., Sept., 1963, p. 36Q.

(2) The chelate structure for osazones was first suggested by L. F. Fieser and M. Fieser, "Organic Chemistry," 2nd Ed., D. C. Heath and Co., Boston, Mass., 1950, pp. 369–372.

(3) L. Mester, *J. Am. Chem. Soc.*, **77**, 4301 (1955); L. Mester and A. Major, *ibid.*, **77**, 4305 (1955).

(4) M. L. Wolfrom, G. Fraenkel, D. R. Lineback, and F. Komitsky, Jr., *J. Org. Chem.*, **29**, 457 (1964).

(5) K. Bjamer, S. Dahm, S. Furberg, and C. S. Petersen, *Acta Chem. Scand.*, **17**, 559 (1963).

(6) L. Mester and A. Major, *J. Am. Chem. Soc.*, **79**, 3232 (1957).

(7) O. L. Chapman and R. W. King, *ibid.*, **86**, 1256 (1964).

(8) D. E. McGreer and M. M. Mocek, *J. Chem. Educ.*, **40**, 358 (1963).

(9) All resonances are expressed as p.p.m. downfield from internal tetramethylsilane [δ scale].

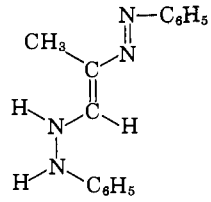
TABLE II

NUCLEAR MAGNETIC RESONANCE SPECTRA OF SUGAR PHENYLOSAZONES[a]

Phenylosazone	Solvent	Chelate N-H	Hydrogen bonded N-H	Aldimine C-H	Low-field OH (multiplicity)
Glyceraldehyde	DMSO	12.10	10.68	7.85	5.17 (t)
	$CDCl_3$	11.98	Under aromatic C-H	7.67	
Glyceraldehyde-3-acetate	DMSO	12.00	10.80	7.78	
Erythrose	DMSO	12.20	10.67	7.78	5.27 (d)
Arabinose	DMSO	12.23	10.66	7.80	5.23 (d)
Glucose	DMSO	12.23	10.68	7.92	5.19 (d)
Glucose 1-methylphenyl-2-	DMSO	12.12		7.67	5.03 (d)

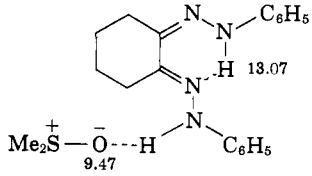
[a] All resonance positions are given as p.p.m. downfield from internal tetramethylsilane (δ-scale).

cally unfavorable; *i.e.*, rotation about the C_2-C_3 bond would be hindered. The *anti-anti* form IV is certainly the most favorable form sterically. Exchange is not averaging the N-H peaks of two or more isomers since the *syn* and *anti* forms of acetaldehyde phenylhydrazone show separate resonance lines, and the sugar osazones (*vide infra*) show discrete N-H resonances under the same conditions. Glyoxal bisphenylhydrazone (V) also shows a single N-H resonance at somewhat lower field (δ 10.35). The bisphenylhydrazone VI of pyruvaldehyde shows, as expected, two N-H resonances at 9.28 (C-2 phenylhydrazone N-H) and 10.22 p.p.m. (C-1 phenylhydrazone N-H). In each case the bisphenylhydrazone (IV, V, and VI) exists as a single geometric isomer in dimethyl sulfoxide solution. Tautomers of IV, V, and VI are excluded from consideration by the observation that there is no detectable spin-spin coupling between the nonequivalent N-H protons or in the CH_3—C=CH system of VII.

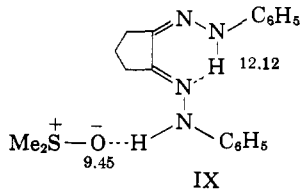


VII

The bisphenylhydrazones of cyclohexane-1,2-dione (VIII) and cyclopentane-1,2-dione (IX) in contrast to



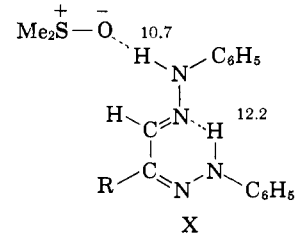
VIII



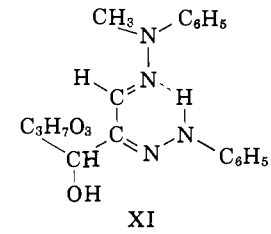
IX

biacetyl bisphenylhydrazone show two sharp, singlet N-H resonances. One resonance (δ 9.47, VIII; 9.45, IX) is in the region characteristic of biacetyl bisphenylhydrazone type N-H resonances; the other (δ 13.07, VIII; 12.12, IX) appears at much lower field and must be associated with a chelate ring. Evidence that the low-field N-H resonance is due to an intramolecular hydrogen bond is available from the n.m.r. spectra of VIII and IX in deuteriochloroform. In deuteriochloroform the low-field N-H resonances are retained (δ 12.92, VIII; 11.92, IX) but the higher field N-H resonances shift upfield by approximately 2.4 p.p.m. (under the aromatic protons). This clearly demonstrates that VIII and IX have one intramolecular hydrogen bond and one hydrogen bond to solvent. The low-field position of the chelate N-H is analogous to the low-field position of the enolic hydroxyl proton in acyclic β-diketones.[10]

With the background provided by these model compounds we are now in a position to examine the n.m.r. spectra of the sugar osazones. The data are summarized in Table II and typical spectra are shown in Fig. 1A and 2A. The following general observations are pertinent. Each sugar phenylosazone in dimethyl sulfoxide shows a low-field N-H resonance (δ 12.2 ± 0.1) characteristic of a chelate N-H, a higher-field, solvent-bonded N-H (10.7 ± 0.1) in a position characteristic of an aldehyde phenylhydrazone type N-H [*cf.* glyoxal bisphenylhydrazone, 10.35] and one hydroxyl proton at lower field (5.2 ± 0.2) than the other hydroxyl protons. This low-field hydroxyl proton is a triplet in the glyceraldehyde phenylosazone spectrum and a doublet in the other phenylosazone spectra. The low-field hydroxyl proton thus must be at C-3. These observations lead to structure X for the sugar phenylosazones in dimethyl sulfoxide.

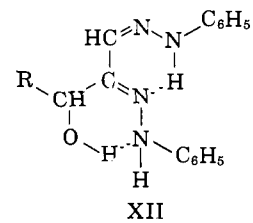


X



XI

The n.m.r. spectrum of glucose 1-methylphenyl-2-phenylosazone (XI) is exactly analogous to that of the other osazones showing only a chelate N-H (δ 12.12) and a low-field hydroxyl proton (δ 5.03). The low-field position of the C-3 hydroxyl proton must be attributed to electronic deshielding by the adjacent C=N rather than to an intramolecular hydrogen bond in the alternate type of chelate (XII) since XI which cannot form two hydrogen bond rings (as in XII) still shows the low-field hydroxyl proton.



XII

The n.m.r. spectrum of glyceraldehyde phenylosazone in deuteriochloroform retains the low-field N-H (δ

(10) L. M. Jackman, "Nuclear Magnetic Resonance Spectroscopy," Pergamon Press, New York, N. Y., 1959, pp. 70–71.

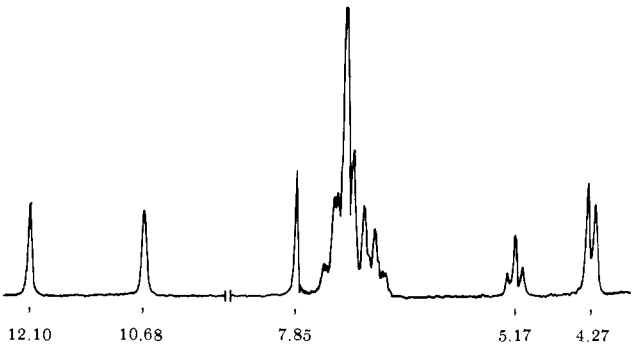


Fig. 1A.—Glyceraldehyde phenylosazone in dimethyl sulfoxide. Resonance positions are given as p.p.m. (δ-scale) relative to internal tetramethylsilane.

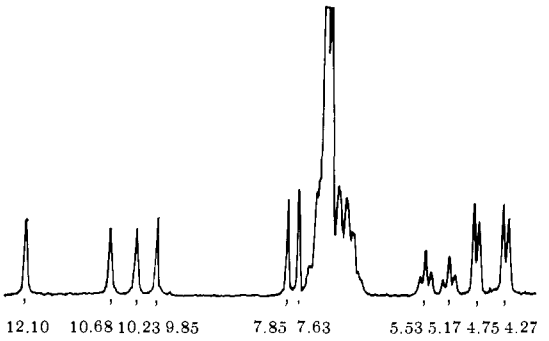
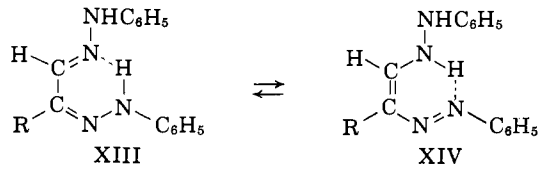


Fig. 1B.—Equilibrium mixture of glyceraldehyde phenylosazone and its isomer in dimethyl sulfoxide. Resonance positions are given as p.p.m. (δ-scale) relative to internal tetramethylsilane.

11.98) but shows an upfield shift (2.5 p.p.m.) in the solvent bonded N-H clearly demonstrating that the low-field N-H proton is part of an intramolecular hydrogen bond. The other phenylosazones are too insoluble in deuteriochloroform to give satisfactory n.m.r. spectra.

Mutarotation of Sugar Phenylosazones.—The mutarotation of sugar phenylosazones, first reported in 1909,[11] has been the subject of much speculation. Many early suggestions concerning the nature of the mutarotation process have been refuted.[6,12] Two grossly different views of the mutarotation have appeared in the recent literature. The first, proposed by L. Mester,[6] suggests that mutarotation is the result of equilibration of XIII and XIV. The primary basis of



this proposal was the observation that the yield of formazan obtained from aliquot samples of a mutarotating solution of glucose phenylosazone decreased as the optical rotation decreased and leveled off when optical equilibrium was achieved. The second view of osazone mutarotation, proposed by Henseke,[12] is that mutarotation is caused by rupture of an —O···H—N— hydrogen bond as shown in XV and XVI.

It is now necessary to review the facts about mutarotation of osazones: (1) Only starting osazone is recovered on work-up of the solution after mutarotation.

(11) P. A. Levene and W. A. Jacobs, *Ber.*, **42**, 3247 (1909).
(12) G. Henseke and H. Kohler, *Ann.*, **614**, 105 (1958).

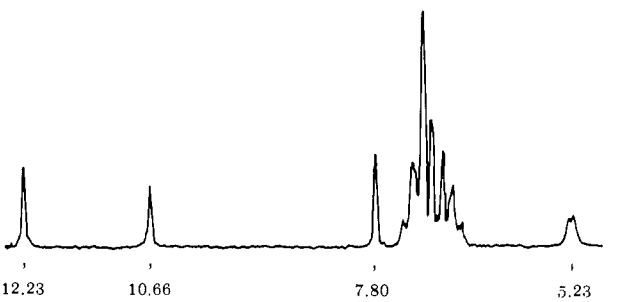


Fig. 2A.—Arabinose phenylosazone in dimethyl sulfoxide. Resonance positions are given as p.p.m. (δ-scale) relative to internal tetramethylsilane. The high-field resonances are partially obscured by solvent absorption and are not shown.

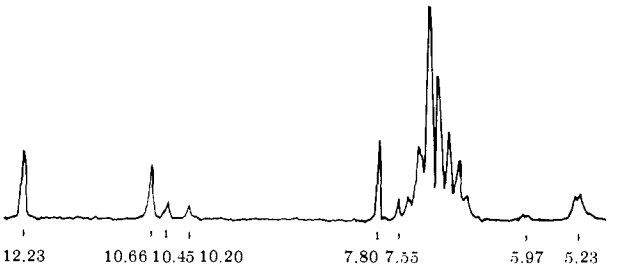
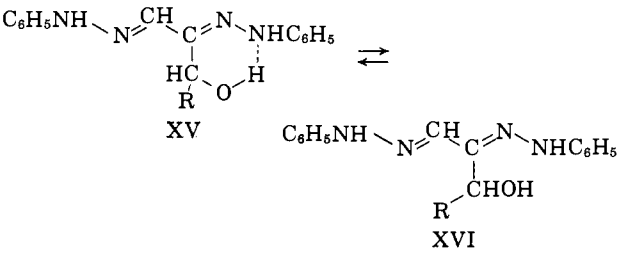
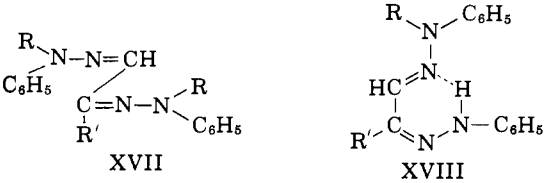


Fig. 2B.—Equilibrium mixture of arabinose phenylosazone and its mutarotated isomer in dimethyl sulfoxide. Resonance positions are given as p.p.m. (δ-scale) relative to internal tetramethylsilane. The high-field resonances are partially obscured by solvent absorption and are not shown.

There can thus be no dramatic chemical transformation of the osazone on mutarotation. (2) Mutarotation of the osazones is accompanied by a shift of the long wave length ultraviolet maximum to shorter wave lengths.[6,12]



(3) The yield of formazan from glucose phenylosazone falls off as mutarotation progresses.[6] (4) Alkyl phenylosazones (XVII, R = alkyl) do not mutarotate, but 1-alkylphenyl-2-phenylosazones (XVIII, R = alkyl) do mutarotate.[12]



(5) The mutarotation is base catalyzed (pyridine in ethanol). In dimethyl sulfoxide the osazones are sufficiently basic to mutarotate without added base.[13] (6) The pyridine-catalyzed mutarotation of a variety of osazones is complete in a few hours at room temperature. It is difficult to rationalize such a slow process on the basis of the Mester and Henseke proposals which involve in one case proton transfer between electronegative atoms and in the other rupture of a hydrogen bond.

(13) The uncatalyzed mutarotation in dimethyl sulfoxide is much slower than the mutarotation catalyzed by pyridine.

TABLE III

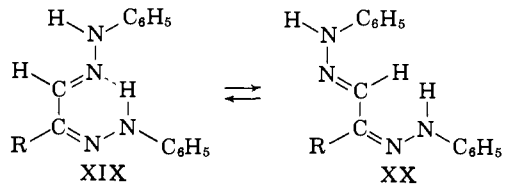
NUCLEAR MAGNETIC RESONANCE SPECTRA OF OSAZONE ISOMERS IN DIMETHYL SULFOXIDE[a]

Phenylosazone	Low field N-H	High field N-H	Aldimine C-H	Low field O-H
Glyceraldehyde	10.23	9.85	7.63	5.53
Glyceraldehyde-3-acetate	10.37	9.93	7.69	
Erythrose	10.53	10.22	Under aromatic CH	6.15
Arabinose	10.45	10.20	7.55	5.97
Glucose	10.65	10.13	7.57	5.87
Glucose 1-methyl-phenyl-2-	10.62		Under aromatic CH	6.18

[a] All resonance positions are given as p.p.m. downfield from internal tetramethylsilane (δ-scale).

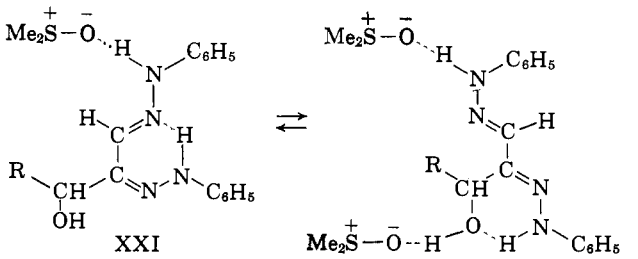
Treatment of a dimethyl sulfoxide solution of an osazone with a few drops of deuterium oxide exchanges both N-H protons in a few minutes, thereby establishing proton exchange as a much faster process than mutarotation.

During the course of mutarotation of osazones, several striking changes are observed in the n.m.r. spectra. The appearance of the new resonance lines correlates with the partial disappearance of the original lines and with the rate of change of optical rotation. When the optical rotation becomes constant, the n.m.r. spectrum no longer changes. It is thus possible to study the nature of the equilibration responsible for the mutarotation of the osazones by n.m.r. methods. The spectrum of a mutarotated solution of arabinose phenylosazone is shown in Fig. 2B. Glyceraldehyde phenylosazone which is optically inactive clearly undergoes a similar equilibration (Fig. 1B). The significant changes observed in the n.m.r. spectra of the osazones during isomerization are: (1) appearance of two new N-H resonances in the region characteristic of solvent-bonded N-H resonance lines, (2) a new aldimine C-H at slightly higher field, and (3) a downfield shift (0.4-1.0 p.p.m.) of the C-3 hydroxyl proton. In terms of structure these changes have the following significance: (1) the chelate ring has been opened; (2) the isomer has an aldimine C-H, *i.e.*, the isomer cannot be an analog of XIV; and (3) the C_3-hydroxyl group is now part of an intramolecular hydrogen bond. It seems unlikely that the mutarotation process can be as simple as rupture of the chelate N-H [XIX → XX].



XIX XX

Rotation about the C_1-C_2 bond in XX would place the molecule again in a conformation suitable for chelate formation as long as the geometric configurations about the carbon-nitrogen double bonds are retained. Furthermore, XX provides no explanation of the shift of the C_3-hydroxyl proton to lower field. We suggest that the process responsible for mutarotation involves opening of the chelate ring with concomitant geometric isomerization about the C_2-N bond [XXI ⇄ XXII].



XXI XXII

The n.m.r. spectrum of the isomer is in accord with formulation XXII. The solvent-bonded N-H is essentially in the same position while the second N-H, now part of an intramolecular hydrogen bond, is shifted to lower field than it would be if it were simply bonded to solvent.[14] The C_3-hydroxyl proton is shifted to lower field by formation of the O···H—N hydrogen bond. The equilibrium XXI ⇄ XXII is consistent with the recovery of a single isomer (XXI) on work-up[15] and with the shift of the ultraviolet maximum to lower wave length. The methylphenylosazones which cannot exist in the chelate form absorb at shorter wave length than the phenylosazones which exist in the chelate form.[12,18] The mutarotated solutions absorb at intermediate wave lengths as expected on the basis of equilibrium XXI ⇄ XXII. The elegant work of Mester and Major[6] on formazan formation in mutarotating solutions of glucose phenylosazone is difficult to account for on the basis of the equilibrium XXI ⇄ XXII. This problem will exist, however, for any formulation of the isomer which takes cognizance of the aldimine C-H required by the n.m.r. spectrum.[19] We prefer the physical evidence over the chemical evidence on this point. Alkylphenylosazones do not mutarotate, as expected, since they cannot exist in the chelate form.[20]

(14) The hydrogen bond is written as H—O···H—N rather than —O—H···NH— for the following reasons: (1) The C_6H_5NH—N=CH—CR=N—NH—C_6H_5 resonance is maintained in XXII but is lost if the nitrogen lone pair is used for intramolecular hydrogen bonding. (2) The N-H resonance of the isomer of the phenylosazone of glyceraldehyde 3-acetate is in essentially the same position (9.93) as that of the unacylated compound (9.85).

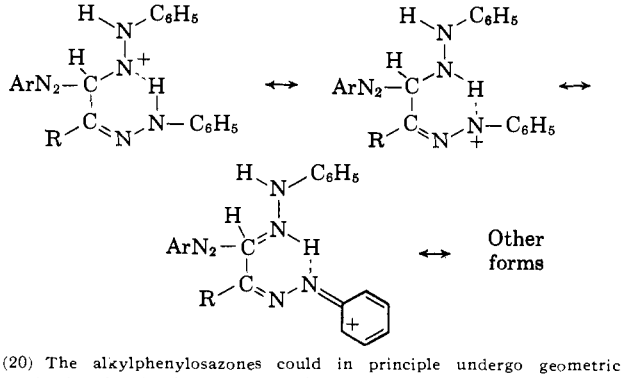
(15) In a study of the geometric isomerization of imines it was found that solutions of mixtures of geometric isomers frequently gave a single isomer on crystallization.[16] Similar behavior is shown by oximes.[17]

(16) D. Y. Curtin and J. W. Hausser, *J. Am. Chem. Soc.*, **83**, 3474 (1961).

(17) See references cited by J. Meisenheimer and W. Theilacker, "Stereochemie," Vol. 2, K. Freudenberg, Ed., Franz Deuticke, Leipzig, 1933, p. 1033.

(18) This shift is a result of the same factors which cause homoannular dienes to absorb at longer wave lengths than heteroannular dienes.

(19) The problem may be one of the relative rates of formazan formation for XXI and XXII. It is reasonable to anticipate that formazan formation will proceed more readily in XXI than XXII since the transition state for XXI is stabilized by additional resonance involving the second aromatic ring.



(20) The alkylphenylosazones could in principle undergo geometric isomerization, but in the absence of chelation there is no driving force for

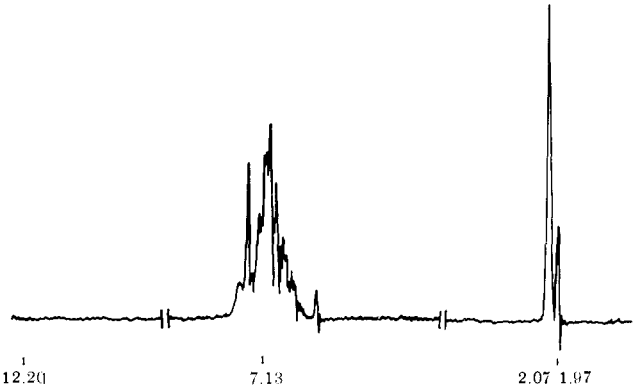


Fig. 3A.—Pyruvaldehyde bisphenylhydrazone immediately after dissolving in deuteriochloroform. Resonance positions are given as p.p.m. (δ-scale) relative to internal tetramethylsilane.

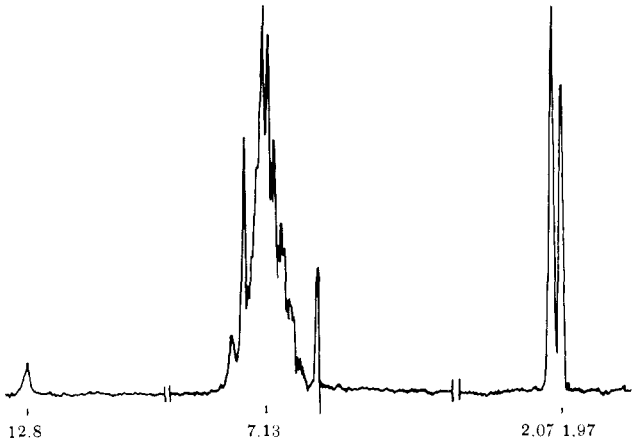
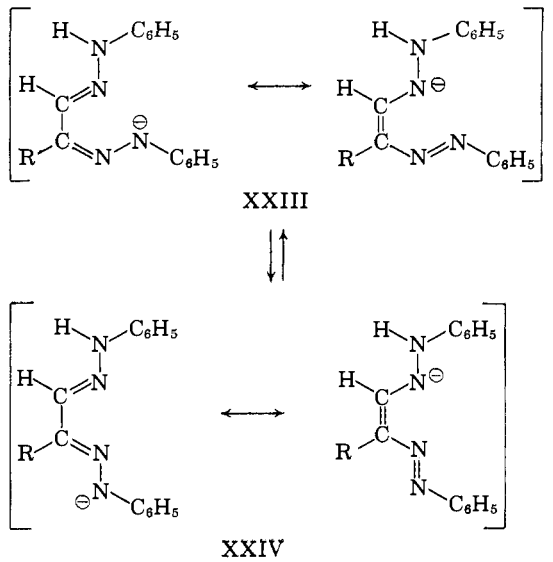


Fig. 3B.—Pyruvaldehyde bisphenylhydrazone after standing 2 days in deuteriochloroform at ambient temperature. Note appearance of low N–H resonance. Resonance positions are given as p.p.m. (δ-scale) relative to internal tetramethylsilane.

The mutarotation of compounds such as XVIII (R = alkyl; R′ = asymmetric group), however, is easily accounted for on the basis of a XXI ⇄ XXII type equilibrium. The base catalysis of mutarotation poses no problems, and the rate of mutarotation is comparable to recently measured rates of geometric isomerization of imines[16] and oximes.[21]



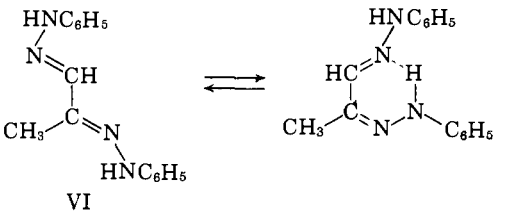
XXIII ⇅ XXIV

such isomerization. In fact, simple N,N-dimethylhydrazones and N-methyl-N-phenylhydrazones do not exist as geometric isomers [G. J. Karabatsos, R. A. Taller, and F. M. Vane, *Tetrahedron Letters*, 1081 (1964)].

(21) R. J. W. LeFevre and J. Northcott, *J. Chem. Soc.*, 2235 (1949).

Equilibration of XXI and XXII probably proceeds by way of the anion XXIII. In XXIII the barrier to rotation about the C_1–C_2 bond is increased since it assumes partial double bond character while the barrier to rotation about the C_2–N bond is reduced as it goes from a double bond to a partial double bond. Geometric isomerization about the C_2–N bond is thus more facile in XXIII than in the un-ionized osazone. This is in accord with the observed catalysis of mutarotation by added bases.

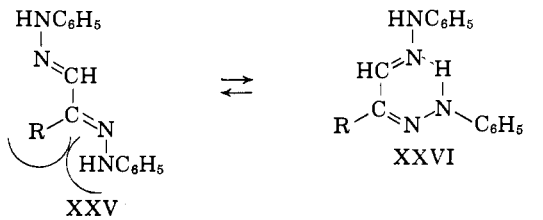
The equilibration of XXI and XXII suggests that under appropriate conditions simple bisphenylhydrazones should exist at least partially in the chelate form. Chelation should be favored in solvents in which N—H···solvent bonds are substantially weaker than N—H···O⁺—S⁺Me_2 bonds. The n.m.r. spectrum (Fig. 3A) of pyruvaldehyde bisphenylhydrazone immediately after dissolving in deuteriochloroform does not show a detectable resonance attributable to a chelate N–H (a small methyl resonance caused by the methyl group of the chelate form is, however, visible). After standing for 2 days the solution shows an n.m.r. spectrum (Fig. 3B) in which the chelate N–H (δ 12.8) is clearly visible. The equilibrium is being approached from the nonchelate form in this instance. Glyoxal bisphenylhydrazone



VI

also equilibrates with the chelate form (chelate N–H, 12.1) on standing in deuteriochloroform.

The equilibrium ratio of the chelate and nonchelate forms of the bisphenylhydrazones and of the osazones depends in part on the steric size of the group R in XXV and XXVI. When R = H or CH_3, the nonchelate



XXV XXVI

form XXV is the only form visible in the n.m.r. spectrum in dimethyl sulfoxide; as the size of R is increased the equilibrium shifts in favor of the chelate form (R = CH_2OH, 50% chelate; R = $CH(OH)CH_2OH$ or larger, *ca.* 80% chelate). The n.m.r. spectra of phenylglyoxal bisphenylhydrazone (XXVI, R = C_6H_5) in dimethyl sulfoxide and in deuteriochloroform show chelate NH resonances (DMSO, 12.75; $CDCl_3$, 12.60). Integration indicates that the chelate form is essentially the only form present in both solvents. This result shows clearly that the size of R is the important factor and not some unforseen intramolecular hydrogen bond. This effect of the bulk of R is in accord with expectation for geometric isomerization of the C_2–N bond. Chelate ring formation is possible only after the geometric isomerization and consequently increasing the bulk of R favors XXVI at equilibrium. It should be noted that there is no

reason to expect geometric isomerization about the C_1-N bond since the geometric configuration of this bond is already the most favorable, *i.e.*, the C_6H_5NH group is *syn* to the hydrogen atom at C-1.

Experimental

Proton resonance spectra were obtained with a Varian HR-60 spectrometer at 14,100 gauss. Dimethyl sulfoxide [Crown-Zellerbach Co.] was stored over Linde Molecular Sieve 4A and used without further purification.

The bisphenylhydrazones of biacetyl, cyclopentane-1,2-dione, and cyclohexane-1,2-dione and the phenylosazones of erythrose, arabinose, and glucose were prepared from the reaction of phenylhydrazine on the corresponding carbonyl compound. The observed melting points agreed with those reported in the literature. Glyoxal bisphenylhydrazone was obtained from the reaction of phenylhydrazine and formaldehyde[22] and glyceraldehyde phenylosazone from dihydroxyacetone and excess phenylhydrazine. Glucose 1-methylphenyl-2-phenylosazone was prepared by the displacement reaction of glucose methylphenylosazone and 1 equiv. of phenylhydrazine.[23]

Pyruvaldehyde Bisphenylhydrazone.—Acetol acetate (2 g.), phenylhydrazine (7 g.), acetic acid (4 ml.), and 80% aqueous ethanol (20 ml.) were warmed on a steam bath for 10 min. On cooling, pale yellow plates, m.p. 145–147°, slowly precipitated (lit.[24] 146–147°).

3-Acetylglyceraldehyde Phenylosazone.—Acetic anhydride (1 ml.) was added to a solution of 0.45 g. of glyceraldehyde phenylosazone in 7 ml. of pyridine and the mixture allowed to stand overnight at room temperature. Hydrolysis of the excess acetic anhydride with water followed by ether extraction and recrystallization from ether gave the acetate, m.p. 123–124°.

Anal. Calcd. for $C_{17}H_{18}N_4O_2$: C, 65.78; H, 5.85; N, 18.05. Found: C, 66.07; H, 6.14; N, 17.90.

Acknowledgment.—The authors wish to thank the Alfred P. Sloan Foundation for financial support of this investigation.

(22) H. von Pechmann, *Ber.*, **30**, 2459 (1897).

(23) L. L. Engel, *J. Am. Chem. Soc.*, **57**, 2419 (1935); G. Henseke and H. Hantschel, *Chem. Ber.*, **87**, 477 (1954).

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Extrathermodynamic Relationships in Schiff Base Formation

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The rates of reaction of substituted benzaldehydes with *n*-butylamine in dioxane at 25° and with *n*- and *t*-butylamine in methanol at 25 and 45° are reported. The data do not follow the simple Hammett equation, but are correlated approximately by the two-parameter equation $\log k/k_H = -1.335\sigma^\circ + 0.803\sigma^+$ (methanol, 25°). This relationship is probably the result of σ^+ dependence for the carbonyl-addition equilibrium and σ° or σ dependence for subsequent equilibria and for the rate-controlling step Enthalpy-enthropy plots are given for these series and for the series of alkylamines previously studied.

Several reasons have been advanced for the nonlinearity of Hammett plots of the rates of carbonyl-addition reactions. Some of these, if correct, should cause the curvature to be critically dependent on the solvent. Hemiacetal formation with an alcoholic solvent, for example, while it could in principle decrease the net rate of competing cyanohydrin formation,[2] obviously is not possible in a nonhydroxylic solvent. A shift in rate-controlling step with changing aromatic substituent has been proposed to account for nonlinear ρ–σ plots in condensation reactions[3] and Schiff base formation[4] and is definitely responsible in semicarbazone formation.[5] Such a shift would, like a change in mechanism[6] with substituent or even the diversion of the reaction through a different series of intermediates,[7] almost certainly be so solvent dependent as not to take place at all in a different type of solvent or, at the very least, to change markedly the type of curvature observed.

There is, on the other hand, a possible cause of abnormal depression of reactivity for electron-donating *para* substituents which would be more likely to persist from one solvent to another. Resonance of such substituents with the carbonyl group could give rise to a σ^+ dependence of one step of the reaction which, combined with a σ dependence for other steps, would yield a nonlinear Hammett plot with no change in rate-controlling step.

We have therefore measured the rates of reaction of a series of substituted benzaldehydes with *n*-butylamine both in methanol[4] and in dioxane. In order to study the superposition of structural effects in the amine[8] and the aldehyde, we have also determined the corresponding rates with *t*-butylamine in methanol at 25 and 45°.

Experimental

Materials.—Reagent-grade methanol (Mallinckrodt) was used without purification. Dioxane was refluxed over several portions of sodium hydroxide pellets. Concentrated hydrochloric acid was then added and the solution boiled in contact with air. After drying with sodium hydroxide and sodium wire, the dioxane, b.p. 101.1–101.2°, was distilled under nitrogen and used immediately. Liquid aldehydes were also freshly vacuum distilled under nitrogen. *p*-Nitrobenzaldehyde and *p*-dimethylaminobenzaldehyde were recrystallized from water, *p*-chlorobenzaldehyde from ethanol-water; this last aldehyde also sublimes well.

Procedure.—The kinetic runs were made as previously described.[4] When dioxane was the solvent the reaction was carried out under nitrogen and protected from light. The concentrations of both aldehyde and amine were generally 0.005–0.05 *M*. Each 1-ml. sample regardless of solvent was diluted with methanol to a concentration suitable for the Beckman Model DU spectrophotometer. Except in runs involving *m*- and *p*-nitrobenzaldehydes, hydrochloric acid was added to the diluent to convert the Schiff bases to their conjugate acids, $ArCH{=}N^+HR$, and unreacted aldehydes to acetals.

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