g; 77%): mp 113–115°; uv max (isooctane) 284 mμ (ε 21,000); ir ($CHCl_3$) 1695 (ester C=O), 1576 (C=C), and 2190 cm^{-1} (C≡N). *Anal.* Calcd for $C_9H_{12}N_2O_2$: C, 59.98; H, 6.71; N, 15.55. Found: C, 60.23; H, 7.00; N, 15.63.

1-Benzyl-2(cyanocarbomethoxymethylene)pyrrolidine (6). 1-Benzyl-2-pyrrolidone dimethyl acetal was prepared by heating 1-benzylpyrrolidone (35 g; 0.2 mol) and dimethyl sulfate (25.2 g) in an oil bath at 90–100° for 2 hr. To the above reaction mixture a methanolic solution of NaOMe (4.6 g of Na in 70 ml of MeOH) was added during 15 min, with ice-cooling and stirring. The mixture was left overnight at room temperature, the salt was filtered, and the filtrate was concentrated *in vacuo*. The resulting oil was fractionated by vacuum distillation, (13 g), bp 84° (0.01 mm).

Methyl cyanoacetate (3.80 g; 0.038 mol) and 1-benzyl-2-pyrrolidone dimethyl acetal (9.27 g; 0.042 mol) were mixed. The reaction mixture solidified immediately (exothermic), and the solid was crystallized from ethyl acetate–hexane (8.25 g; 85%): mp 126–128; uv max (isooctane) 286 mμ (ε 23,800); ir ($CHCl_3$) 1692 (ester C=O), 1553 (C=C), and 2181 cm^{-1} (C≡N). *Anal.* Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.42; H, 6.19; N, 10.92.

1-Phenyl-2-(cyanocarbomethoxymethylene)pyrrolidine (8). 1-Phenyl-2-pyrrolidone diethyl acetal was prepared by reacting 1-phenylpyrrolidone with triethyl oxoniumfluoroborate according to the general procedure given in ref 14, 62% yield, bp 113–114° (0.15 mm).

Methyl cyanoacetate (4.95 g; 0.050 mol) and 1-phenyl-2-pyrrolidone diethyl acetal (12.9 g; 0.055 mol) were mixed and left for 50 hr at room temperature. A solid was obtained by addition of hexane, crystallized from ethyl acetate (6.15 g; 51%): mp 164–65°, uv max (isooctane) 292 mμ (ε 15,900), shoulder 237 mμ (ε 3800); ir ($CHCl_3$) 1697 (ester C=O), 1547 (C=C), and 2198 cm^{-1} (C≡N). *Anal.* Calcd for $C_{14}H_{14}N_2O_2$: C, 69.40; H, 5.83; N, 11.56. Found: C, 69.62; H, 5.78; N, 11.43.

Studies on Oxime Hydrochlorides. IV. Nuclear Magnetic Resonance Studies of the Stereochemistry of 2-Substituted Cyclohexanone Oximes and Their Hydrochlorides. Conformation Change Caused by Protonation and Hydrogen Bonding

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Abstract: The configuration and conformation of 2-substituted cyclohexanone oximes and their hydrochlorides are investigated by means of ir and nmr spectroscopy. They include the compounds with substituents, OMe (I), OEt (II), Cl (III), Me (IV), OH (V), $OCOCH_3$ (VI), OCOPh (VII), piperidinyl (VIII), and morpholinyl (IX). The *E* isomer is predominant in compounds IV, V, VIII, and IX, whereas less than 20% of the *Z* isomer appears in the rest. In all the compounds except IV and V, the substituent is axially oriented. The substituent of V is held in the equatorial position in nonpolar solvents by the intramolecular hydrogen bond formed between the nitrogen atom of the hydroxyimino group and the hydroxyl substituent. No other type of intramolecular hydrogen bond is observed. The presence of the hydrogen bond is confirmed by the low wave-number shift in OH-stretching frequency under extremely dilute conditions. In V, the substituent shows an axial preference in polar solvents. A variation of the conformation and configuration is observed in some hydrochlorides. In the hydrochloride of IV the substituent turns to the axial position and, at the same time, the *Z* isomer appears because of the conversion from the *E* isomer. The substituents are partly equatorial in the hydrochloride of I, II, and III in the *E* isomer, while no appreciable change is observed in the *Z* isomer. This conformation change is interpreted in terms of electrostatic attraction between the lone-pair electrons of the substituent and the positive charge on the nitrogen atom due to the formation of the hydrochloride. The downfield shift of methyl signals is discussed in terms of the excess dipole moment of the nitrogen atom.

A number of conformational studies of 2-substituted cyclohexanones have been reported.[1-12] Allinger and his coworkers[1,2] showed that conformational energies of 2-alkyl compounds are about 2 kcal/mol in favor of the equatorial position. Studies of the conformation equilibria of 2-halocyclohexanones by infrared,[3,4] ultraviolet,[5,6] dipole moment,[7,8] optical dispersion,[9,10] and nmr measurements[11,12] have revealed that the substituents are axially oriented in nonpolar solvents and that the population of the equatorial substituent increases in polar media.

However, except for Chow's work,[13] no attention has been paid to the stereochemistry of 2-substituted cyclohexanone oximes. If the molecular backbone is in the chair form, there are four possible isomeric forms of 2-substituted cyclohexanone oxime (Figure 1). Destabilizing factors such as steric or electrostatic repulsions between the substituent and hydroxyl groups should be

(1) N. L. Allinger and H. M. Blatter, *J. Amer. Chem. Soc.*, 83, 994 (1961).
(2) N. L. Allinger, H. M. Blatter, L. A. Freiberg, and F. M. Karkowski, *ibid.*, 88, 2999 (1966).
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(6) N. L. Allinger, J. Allinger, L. A. Freiberg, R. T. Czaja, and N. A. Lebel, *ibid.*, 82, 5876 (1960).
(7) N. L. Allinger, J. Allinger, L. W. Chow, and G. L. Wang, *J. Org. Chem.*, 32, 552 (1967).
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(11) E. W. Garbisch, *J. Amer. Chem. Soc.*, 86, 1780 (1964).
(12) Y. H. Pan and J. B. Stothers, *Can. J. Chem.*, 45, 2943 (1967).
(13) Y. L. Chow, *ibid.*, 43, 2711 (1965).

Table I. 2-Methylene Signals of 4-*t*-Butylcyclohexanone Oxime and Its Hydrochloride

	Equatorial			Axial			δ_{ae}[a]	
	syn	*anti*	Δ[b]	*syn*	*anti*	Δ[b]	*syn*	*anti*
4-*t*-Butylcyclohexanone oxime	−3.38	−2.47	0.91	−1.67[c]	−2.08	−0.41	1.71	0.39
	(−3.39)[d]	(−2.48)[d]	(0.91)[d]	(−1.71)[d]	(−2.05)	(−0.34)[d]	(1.68)[d]	(0.43)[d]
Its hydrochloride	−3.43		0	−2.36		0	1.07	
Downfield shift[e]	−0.05	−0.96		−0.69	−0.28			

[a] $\delta_{axial} - \delta_{equatorial}$. [b] $\delta_{anti} - \delta_{syn}$. [c] Determined by the decoupling method. [d] Results by Trager and Huitric.[17] [e] Downfield shift with respect to the signals of the parent oximes.

taken into account in addition to an intramolecular attraction such as a hydrogen bond.

In this work we investigate the molecular configuration and conformation of nine 2-substituted cyclohexanone oximes by careful nmr measurements. It is found that many of the 2-substituted cyclohexanone oximes (more than 85%) are of the *E* isomer type with respect to the hydroxyimino group and the rest (less than 15%) are of the *Z* isomer type. Even the *Z* isomer is not capable of forming an intramolecular hydrogen bond, since all the substituents except the methyl group occupy the axial position. This is the case when the steric or electrostatic repulsion between the substituents and hydroxyimino group overcomes the attraction of the intramolecular hydrogen bond. In the case of 2-hydroxylcyclohexanone oxime, on the other hand, the equatorial conformer is stabilized by the OH–N intramolecular hydrogen bond in solvents of weaker polarity such as chloroform and carbon tetrachloride. In polar solvents the *E*-eq form is inverted into the *E*-ax form, since the intermolecular hydrogen bond between the solute and solvent overcomes the intramolecular hydrogen bond. Conformation change also results from protonation of the nitrogen atom in the hydroxyimino group. The equatorial methyl substituent becomes axial and a portion of the axial methoxyl, ethoxyl, and chlorine substituents reverts to the equatorial position in oxime hydrochlorides, in which a proton is donated to the nitrogen atom. These phenomena are of interest in view of the electrostatic repulsion which determines the molecular conformation, predominantly repulsion changes to attraction between the lone pair electrons of the substituent and the positive charge on the nitrogen atom in the hydrochlorides. The downfield shift of methyl signals in various hydrochlorides is also discussed.

Experimental Section

2-Methylcyclohexanoe oxime and its hydrochloride were supplied by the courtesy of Drs. Wakamatsu and Sando of the Nagoya Laboratory of the Toyo Rayon Company. The other 2-substituted cyclohexanone oximes were synthesized by substitution reactions of 2-chlorocyclohexanone oxime hydrochloride.[14] 4-*t*-Butylcyclohexanone oxime was prepared by the usual method.[15] Hydrochlorides were obtained by the method previously described.[16]

Nmr spectra were recorded by a Varian HA-100 and A-60 spectrometer using TMS as an internal standard. Double and triple irradiation were performed by a frequency sweep mode with the HA-100 spectrometer. Frequency calibration was made by the direct reading of a frequency counter or by the usual side-band method. Commercial deuterated solvents such as chloroform, methanol, acetone, and DMSO were used without purification.

Measurements of infrared spectra were carried out with a Perkin-Elmer 125 spectrometer equipped with a 3.5-cm cell in 0.0005 mol/l. carbon tetrachloride solution.

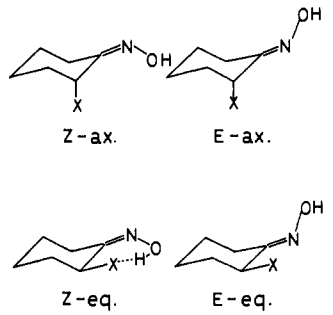

Figure 1. Four kinds of isomeric forms of 2-substituted cyclohexanone oximes.

Results and Discussion

Trager and Huitric[17,18] studied the nmr spectrum of 4-*t*-butylcyclohexanone-3-(axial)-5,5-d_3 oxime, and obtained peaks due to 2-equatorial and 2-axial proton pairs. The double irradiation method employed by us supports their results. The assignment of *syn* and *anti* protons for those peaks is given in Table I, according to our previous studies.[19,20] The values Δ and δ_{ae} are available for the configuration and conformation studies of 2-substituted cyclohexanone oximes.

The nomenclature of protons in 2-substituted cyclohexanone oximes is illustrated in Figure 2. The words *syn* and *anti* protons are used to describe the disposition of the proton in the same or opposite side of the hydroxyl group, respectively.[21] The assignment of the peaks of 2-substituted cyclohexanone oximes is straightforward, and was made by taking into account the results with 4-*t*-butylcyclohexanone oxime, and by using double or triple irradiation techniques. The results are listed in Table II. To clarify the discussion, the configuration and conformation of these compounds are considered separately, although there is a close relation between them.

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(16) H. Saitô, K. Nukada, and M. Ohno, *Tetrahedron Lett.*, 2124 (1964).

(17) W. F. Trager and A. C. Huitric, *ibid.*, 825 (1966).

(18) W. F. Trager and A. C. Huitric, *J. Pharm. Sci.*, 1111 (1967).

(19) H. Saitô, K. Nukada, I. Terasawa, and M. Ohno, Abstracts, 19th Annual Meeting of the Chemical Society of Japan, Tokyo, 1966, 1W 221.

(20) H. Saitô and K. Nukada, *Can. J. Chem.*, 46, 2989 (1968).

(21) It should be noted that this is an extension of the definition usually used as an indication of *syn* and *anti* isomers with respect to methine proton. The new definition *Z* and *E* is employed to indicate the isomeric form: J. E. Blackwood, C. L. Gladys, K. L. Loening, A. E. Petrarca, and J. E. Rush, *J. Amer. Chem. Soc.*, 90, 509 (1968).

Table II. Nmr Spectra of 2-Substituted Cyclohexanone Oxime ($CDCl_3$ Solution Unless Otherwise Noted)

		Chemical shift, ppm, TMS standard					Spin coupling constants				Existence ratio, %	
		H_{2eq}		$H_{6,syn}$			$J_{2,3}$					
Substituent		*syn*	*anti*	eq	ax[a]	δ_{ae}	*syn*	*anti*	$J_{5,6}$[c]	$J_{6,6}$[d]	*Z*	*E*
I	OMe	−4.83	−3.70	−3.03	−1.92	1.11	5.3	5.3	6.8	14.2	14	86
II	OEt	−4.96	−3.86	−3.06	−2.03	1.03	5.2	5.3	6.5	14.0	14	86
III	Cl	−5.58	−4.65	−3.07	−2.23	0.84	5.2	5.2	7.1	14.5	22	78
IV	CH_3		−2.31[e]	−3.09	−1.80	1.29		19	6.1	13.1	0	100
Va	OH[f]		−4.01	−2.77	−2.15	0.62		6.9	8.0	14.0	0	100
Vb	OH[g]		−4.15[h]	−2.55	−2.55	0		9.1			0	100
Vc	OH		−4.17[h]	−3.00	−2.03	0.97		13.4	8.2	13.9	0	100
VIa	$OOCCH_3$[f]		−5.13[h]	−2.64	−2.23	0.41		7.5	10.1	14.5	0[i]	100
VIb	$OOCCH_3$[g]		−5.28[h]	−2.87	−2.31	0.56		7.3	9.5	14.4	0[i]	100
VIc	$OOCCH_3$	−6.32	−5.35[h]	−2.61	−2.61	0	6.4	10.1			5	95
VIIa	OOCPh[f]	−6.39	−5.43[h]	−2.72	−2.38	0.34	6.9	7.8	9.0	14.1	10	90
VIIb	OOCPh[g]	−6.51	−5.55	−3.05	−2.31	0.74	6.9	6.9	9.0	14.5	10	90
VIII	Piperidinyl		−2.70	−2.99	−2.07	0.92		7.0	5.6	13.3	0	100
IX	Morpholinyl		−2.75	−3.02	−2.15	0.88		6.2	6.0	13.2	0	100

[a] Determined by the decoupling method. [b] $J_{2eq,3ax} + J_{2eq,3eq}$. [c] $J_{6eq,5ax} + J_{6eq,5eq}$. [d] Geminal spin coupling constant. [e] Axial proton. [f] DMSO-d_6 solution. [g] Methanol-d_4 solution. [h] Equilibrium between the equatorial and axial position. See Tables IV and V. [i] No *Z* isomer appears in DMSO-d_6 and methanol-d_4 solution due to the conversion from *Z*, which exists in $CDCl_3$ solution, to *E* isomer.

Configuration of 2-Substituted Cyclohexanone Oximes. A pair of *syn* and *anti* H_2 is observed in I, II, III, VI, and VII. They are determined by studies of oxime hydrochlorides[22] and by the observation of simultaneous

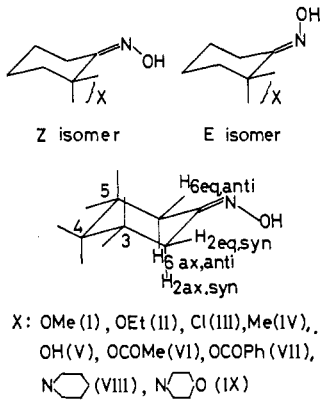


Figure 2. Nomenclature of protons in 2-substituted cyclohexanone oximes.

sharpening of peaks with the irradiation of adjacent H_3.[23] As described in the following section, H_2 is fixed in the equatorial position (I, II, and III) or it is predominantly in the equatorial position even in the presence of ring inversion (VI and VII). The higher and lower field peaks are assigned to the *anti* and *syn* proton, respectively, by comparison with the chemical shift of the equatorial peaks of 4-*t*-butylcyclohexanone oxime (Table I). The separations between *syn* and *anti* H_2 signals are listed in Table III, and they are in good agreement with that of 4-*t*-butylcyclohexanone oxime. The amount of *Z* and *E* isomers determined by comparison of the integrated peak intensities between *syn* and *anti* H_2 is listed in the last column of Table II.

The chemical shifts of H_{6eq}[24] and the difference δ_{ae} are also useful for determination of the configuration no only in I, II, and III but in IV, V, VIII, and IX. In the latter compounds *syn* and *anti* pairs in H_2 signals are absent. The $H_{6eq,syn}$[25] peaks of I, II, and III, the intensi-

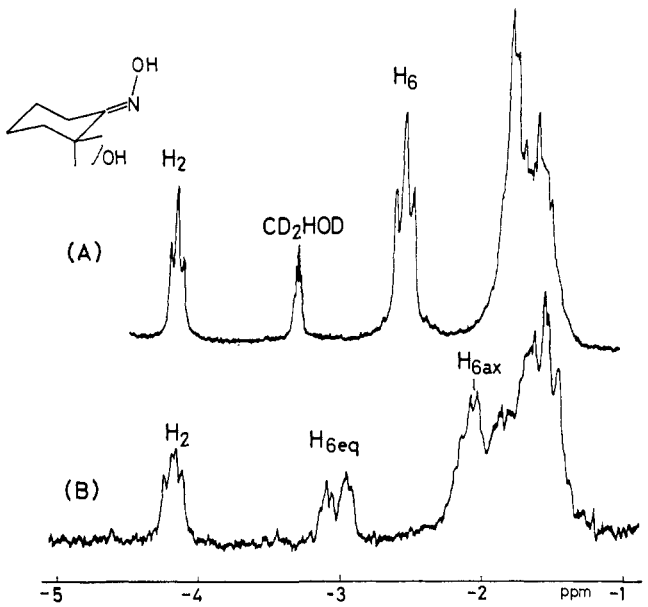


Figure 3. Nmr spectra of 2-hydroxycyclohexanone oxime (V) in various solvents. (A) Methanol-d_4 solution. (Rapid ring inversion.) (B) Deuteriochloroform solution (intermediate ring inversion). See text.

ties of which are equal to that of $H_{6eq,anti}$, are observed in the range of −3.03 to −3.07 ppm. The separations between signals $H_{6ax,syn}$, and $H_{6eq,syn}$, δ_{ae}, are from 0.84 to 1.11 ppm. It corresponds with δ_{ae} of the *syn* side (1.71 ppm) of 4-*t*-butylcyclohexanone oxime (Table I), if one takes into account the fact that the axial H_6 peaks of 2-substituted cyclohexanone oximes should shift downfield considerably more than the equatorial peaks, because

(22) In oxime hydrochlorides, in which a proton is donated to the nitrogen atom, the separation between *syn* and *anti* H_2 decreases considerably, ref 22a; (a) H. Saitô and K. Nukada, *J. Mol. Spectrosc.*, 18, 1 (1965).

(23) There is no appreciable difference in chemical shift between *β syn* and *anti* position: H. Saitô and K. Nukada, *ibid.*, 18, 355 (1965).

(24) Suffixes eq and ax stand for the equatorial and the axial, respectively. Double suffixes such as $H_{6eq,syn}$ are used to indicate the equatorial proton at 6 position and *syn* side with respect to the hydroxyimino group.

(25) In the case of H_6 proton the notation of *syn* and *anti* is used in the opposite sense indicating the geometrical isomer. For example, H_6 proton of the *E* (*anti*) isomer is indicated as *syn* position with respect to the hydroxyimino group.

Table III. The Separation of *syn* and *anti*-H_2 Signals, ppm[a]

	X	Axial	Equatorial
	H[b]	−0.41 (−0.34)[c]	0.91 (0.91)[c]
I	OMe		1.13
II	OEt		1.10
III	Cl		0.93
VIc	$OOCCH_3$		0.97[d]
VIIa	OOCPh[e]		0.96[d]
VIIb			0.96[d]

[a] Deuteriochloroform solution. [b] 4-*t*-Butylcyclohexanone oxime. [c] Values by Huitric, *et al.*[17] [d] Equilibrium state for *anti*-H_2. See also Table V. [e] VIIa, DMSO-d_6 solution; VIIb, methanol-d_4 solution.

of the magnetic anisotropy effect of the substituents.[26] The H_{6eq} and δ_{ae} of IV, V, VIII, and IX are very close to those of I, II, and III. The configuration of IV, V, VIII, and IX is thus of the *E* form. The conclusion for VIII and IX is consistent with the recent revision of Chow, *et al.*, employing thin-layer chromatography.[27] H_{6eq} and δ_{ae} of V, VI, and VII vary with the nature of solvents, which can be interpreted in terms of the conformational change as described later.

The Conformation of 2-Substituted Cyclohexanone Oximes. We can analyze the pattern of the H_2 multiplet as the X portion of an ABX system. The sum of the vicinal coupling constants, $J_{2,3} = |J_{AX} + J_{BX}|$ varies as

$$J_{2,3} = J_{ax} = 17\text{–}18 \text{ Hz} \quad \text{(axial proton)} \qquad (1)$$

$$J_{2,3} = J_{eq} = 5.5\text{–}6.5 \text{ Hz} \quad \text{(equatorial proton)} \qquad (2)$$

depending on whether H_2 is fixed in the axial (eq 1) or in the equatorial position (eq 2), respectively. We have employed the *cis*- and *trans*-2-halo-4-*t*-butylcyclohexanones[12] as models for the coupling constants in eq 1 and 2 because of their similarity with the present oximes in the presence of the trigonal carbon next to H_2.[28] When the molecule undergoes rapid ring inversion, the observed $J_{2,3}$ becomes the weighted average of the values, J_{ax} and J_{eq}

$$J_{2,3} = pJ_{ax} + (1 - p)J_{eq} \qquad (3)$$

where p is a fraction of the conformation in which H_2 is in the axial position.

(A) Fixed Conformation (I–IV, VIII, and IX). As no temperature variation of the value, $J_{2,3}$, was observed in the range from −60° to 150° in I–IV, VIII, and IX, the ring inversion is not present in this group. The values of $J_{2,3}$ in the *Z* and *E* isomers of I, II, and III, and those of the *E* isomer of VIII and IX range from 5.2 to 7.0 Hz as shown in Table II. These values are very close to that of eq 2 and it is concluded that H_2 is fixed in the equatorial position in I–III, VIII, and IX. Slightly larger values in VIII and IX are probably caused by ring deformation owing to steric hindrance with the bulky substituents. The configuration and conformation of these compounds are therefore of the *E*-ax and *Z*-ax type as summarized in Table IV.

Table IV. Summary of Configuration and Conformation of 2-Substituted Cyclohexanone Oximes and Their Hydrochlorides[a]

	E configuration	*Z* configuration[d]
I	*E*-ax	*Z*-ax
II	*E*-ax	*Z*-ax
III	*E*-ax	*Z*-ax
IV	*E*-eq	
V	*b*	
VI	*b*	*Z*-ax[c]
VII	*b*	*Z*-ax
VIII	*E*-ax	
IX	*E*-ax	
I-HCl	*b*	*Z*-ax
II-HCl	*b*	*Z*-ax
III-HCl	*b*	*Z*-ax
IV-HCl	*E*-ax	*Z*-ax

[a] The conformation energy of *E*-ax and *Z*-ax is estimated to be larger than 2.7 kcal/mol assuming that 1% of error is included by the measurement of 100% stable isomer. According to a similar consideration, the conformation energy is smaller than −2.7 kcal/mol for the *E*-eq form with respect to the *E*-ax form. [b] Equilibrium state between *E*-ax and *E*-eq conformations; see Table V. [c] Value in $CDCl_3$ solution. [d] In the case of *Z* isomer, no conformation change due to the solvent effect and protonation is observed.

The value $J_{2,3}$ of IV, as deduced by double irradiation of the methyl signal, is about 19 Hz in a quadruplet. Thus, the substituent occupies exclusively the equatorial position and the most stable form of IV is the *E*-eq form.[29]

(B) Variation of Conformation with Solvent (V–VII). Since the spectral patterns of V, VI, and VII change considerably with the solvent, the conformation of these compounds must vary with solvents.[30] The *E* isomer of Va, the *Z* isomers of VIc, and both *E* and *Z* isomers of VIIb are all axial conformers, because they give the smallest values of $J_{2,3}$ (6.4–6.9 Hz) within Va–Vc, VIa–VIc, and VIIa–VIIb, respectively (Tables II, IV, and V). The above $J_{2,3}$ values are in good agreement with that of eq 2.

A rapid ring inversion occurs in the *E* isomers of Vb and VIc, since δ_{ae} of $H_{6,syn}$ is zero as shown in Table II. This is also shown by the increased $J_{2,3}$ values as compared with those of the fixed conformation mentioned above.

A ring inversion with an intermediate rate occurs in the *E* isomer of Vc, VIa, VIb, and VIIa, where the $J_{2,3}$ values increase compared with those of the fixed conformation, while the axial and equatorial H_6 do not coalesce into a single peak ($\delta_{ae} \neq 0$). This contradiction is due to the rate of inversion k lying between the two terms[31]

$$\pi/\sqrt{2} \cdot \delta_{ae}(H_2) < k < \pi/\sqrt{2} \cdot \delta_{ae}(H_6) \qquad (4)$$

In the case of Vc, for instance, δ_{ae} (H_6) is 97 Hz, while δ_{ae} (H_2) is estimated to be less than 20 Hz as shown later. The equilibrium between the axial and equator-

(26) The anisotropy effect is decreased according to R^{-3} or R^{-2}, where R is the distance between the functional group which produces the effect and the proton in question.

(27) Y. L. Chow and C. H. Colón, *J. Org. Chem.*, 33, 2598 (1968).

(28) The values employed in this paper are somewhat larger compared with those of cyclohexane derivatives; J_{ax} = 10–12 Hz, J_{eq} = 4–6 Hz, with J_{aa} = 8–9 Hz, $J_{ae} \approx J_{ee} \approx$ 2–3 Hz (J. N. Shoolery, "Nmr and Epr Spectroscopy," Pergamon Press, New York, N. Y., p 114). However, the proximity of trigonal carbon appears to have some effect on the magnitude of the vicinal coupling adjacent with it, as shown in 2-halo-4-*t*-butylcyclohexanone (ref 12) and some cyclic ketones.

(29) After completion of this manuscript, an article by Paulsen, Todt, and Ripperger (H. Paulsen, K. Todt, and H. Ripperger, *Chem. Ber.*, 101, 3365 (1968)) was published describing the structure of IV, which is in agreement with our result.

(30) *Z* isomer of VI is not observed in solvents such as DMSO-d_6, acetone-d_6 and methanol-d_4, while it is observed in $CDCl_3$ solution. This is an example in which the conversion between the *Z* and *E* isomers occurs depending on the nature of solvents.

(31) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p 233.

Table V. Conformation Equilibrium in Various Solvents[a], 23°

	Solvent	Equatorial substituent, *E*-eq, %	Equilibrium constant, *K*	Conformation[b] free energy, kcal/mol
V	DMSO-d_6 (Va)	0 *E*-ax		>2.7[c] (1.7–1.8)[d]
	Acetone-d_6	(10–21)[c]	(0.23–0.26)[d]	(0.82–0.90)[d]
	MeOH-d_4 (Vb)	20–22	0.26–0.28	0.76–0.80
		(22—24)[c]	(0.28–0.31)[d]	(0.72–0.79)[d]
	$CDCl_3$ (Vc)	59–64	1.64–1.56	−0.26–0.29
VI	MeOH-d_4 (VIb)	8–9	0.088–0.098	1.4
	DMSO-d_6 (VIa)	9–10	0.100–0.110	1.3–1.4
	$CDCl_3$ (VIc)	32–35	0.439–0.515	0.39–0.42
VII	MeOH (VIIb)	0 *E*-ax		>2.7[c]
	DMSO-d_6 (VIIa)	8–9	0.088–0.098	1.4
I-HCl[e]	$CDCl_3$	37–40	0.617–0.635	0.27–0.28
II-HCl[e]	$CDCl_3$	17–19	0.210–0.229	0.87–0.92
III-HCl[e]	$CDCl_3$	20–22	0.257–0.275	0.76–0.80

[a] The axial coupling constant J_{ax} = 17–18 Hz is assumed throughout the compounds listed in this table. The equatorial coupling J_{eq} is utilized with the following values: V, 6.9 Hz in DMSO-d_6 solution; VI, 6.4 Hz of the *Z* isomer in $CDCl_3$ solution; VII, 6.9 Hz in MeOH-d_4 solution; I-HCl, 5.3 Hz; II-HCl, 5.3 Hz; and III-HCl, 5.5 Hz. [b] The conformation energy is computed with respect to *E*-ax conformation throughout this paper. [c] The 1% error in 100% stable isomer is assumed. [d] Values at 38°. [e] *E* isomer. In case of the *Z* isomer, see Table IV.

Table VI. Variation of H_2 Signal and Spin Coupling Constant with Temperature of V

Temp, °C	DMSO-d_6 solution: Spin coupling constant, Hz	DMSO-d_6 solution: H_2 signal, ppm	MeOH-d_4 solution: Spin coupling constant, Hz	MeOH-d_4 solution: H_2 signal, ppm	Acetone-d_4 solution: Spin coupling constants, Hz	Acetone-d_4 solution: H_2 signal, ppm
81	9.0	−4.05				
65	8.5	−4.07				
47	7.9	−4.07				
38	7.5	−4.05	9.3	−4.17	9.0	−4.13
7	7.1		9.0	−4.17	8.8	
−8	7.0	−4.05	8.2	−4.18		
−28			7.5	−4.19		
−44			7.2	−4.21	8.0	−4.19
−57			7.0	−4.23	8.0	−4.22

ial substituents, for both rapid and intermediate inversions, is calculated as given in Table V.

We can interpret the solvent effect in terms of an intramolecular hydrogen bond and/or an electrostatic interaction between the substituent and hydroxyimino group, the latter being discussed in detail in the next section. The intramolecular hydrogen bond between OH and N, illustrated in Figure 4,[31a] is formed in the *E*-eq form of V in solvents with weaker polarity such as chloroform and carbon tetrachloride. It is confirmed by a shift of the OH-stretching frequency to a lower region measured in extremely dilute carbon tetrachloride solution (0.0005 mol/l.). The low wave-number shift ($\Delta\nu$ = 70 cm^{-1}) lies between that of ethylene glycol[32] ($\Delta\nu$ = 32 cm^{-1}) and 2-hydroxylcyclohexanone[33] ($\Delta\nu$ = 127 cm^{-1}), both of which form five-membered intramolecular hydrogen bonds just as in the present case. In polar solvents the intermolecular hydrogen bond between the solute and solvent molecules makes a major contribution to the molecular conformation, and the hydroxyl group prefers to take the axial position. Such a solvent effect on V is interpreted as due to competition between the intra- and intermolecular hydrogen bond.

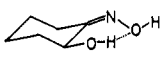


Figure 4. OH–N intramolecular hydrogen bond of 2-hydroxycyclohexanone oxime in nonpolar solvent (Vc).

(C) Varied Conformation with Temperature (V). The conformation of V is also considerably influenced by temperature (Table VI). At elevated temperatures the intermolecular hydrogen bond is broken and the OH group tends to occupy the equatorial position where it is capable of forming an intramolecular hydrogen bond. The upfield shift of 0.06 and 0.09 ppm for H_2 at the elevated temperature in methanol-d_4 and acetone-d_6 solutions, respectively, indicates that the axial H_2 resonates at a higher field than the equatorial, contrary to the case of 2-halocyclohexanones.[34]

We estimate the chemical shift of H_2 at the axial position δ_{ax} by eq 5, where the observed chemical shift δ, δ_{eq} at −60° and the population, *p*, computed from the variation of the coupling constant data (Table VI) are employed.

$$\delta = p\delta_{ax} + (1 - p)\delta_{eq} \quad (5)$$

δ_{ax} is −3.98 ppm in methanol-d_4 solution. Thus we obtain a $\delta_{ae} = \delta_{ax} - \delta_{eq}$ of 0.24 ppm. In the same way,

(31a) Note Added in Proof. The intramolecular hydrogen bond shown in Figure 4 is incorrect. The correct drawing should be the type of the *E*-eq form in Figure 1, where x indicates OH group.

(32) L. P. Kuhn, *J. Amer. Chem. Soc.*, 74, 2492 (1952).

(33) M. Ōki, H. Iwamura, J. Aihara, and H. Iida, *Bull. Chem. Soc. Jap.*, 41, 176 (1968).

(34) (a) E. W. Garbisch, *J. Amer. Chem. Soc.*, 86, 1780 (1964); (b) N. Nichon, M. A. Castle, R. Harada, C. E. Berkoff, and R. O. Williams, *ibid.*, 85, 2185 (1963); (c) K. M. Wellman and F. G. Bordwell, *Tetrahedron Lett.*, 1703 (1963).

Table VII. Nmr Spectra of 2-Substituted Cyclohexanone Oxime Hydrochlorides

	X		Chemical shift, ppm, TMS standard				Spin coupling constants, Hz		
			H_2	H_6 eq	H_6 ax	δ_{ae}	$J_{2,3}$	$J_{6,5}$	$J_{6,6}$
I-HCl	OMe	E[b]	−4.58[d]	−2.91	−2.91	0	10.0	11.2	
		Z	−4.77				5.3		
II-HCl	OEt	E[b]	−4.66[d]	−2.93	−2.78	0.15	7.5		14.5
		Z	−4.83				5.3		
III-HCl	Cl	E[b]	−5.61[d]	−3.34	−2.61[a]	0.73	8	8	15.0
		Z	−5.74				5.5		
IV-HCl	CH_3	E[c]	−3.39[e]	−3.03	−2.47[a]	0.56	6.5	6.3	14.0
		Z	−3.53[e]	−3.24	−2.45[a]	0.79	6.5	6.3	14.0

[a] Determined by the decoupling method. [b] The ratio of the *Z* to *E* isomer is the same as in the parent oxime. [c] [*Z*]:[*E*] = 44:56%. Parent oxime, [*E*] = 100%. [d] Equilibrium between the axial and equatorial conformer. See Tables IV and V. [e] Equatorial proton.

δ_{ae} is calculated to be 0 ppm in DMSO-d_6. The difference of δ_{ae} between them seems to result partly from the solvent effect on the chemical shift. In either case δ_{ae} of H_2 is smaller than that of H_6 (Table II) and this explains the phenomena concerning the rate of inversion described in the previous section.

Configuration and Conformation of Oxime Hydrochlorides (I-HCl–IV-HCl). As we can see in Table I, the extent of the downfield shift of the H_2 signal in oxime hydrochlorides can be used for the assignment of peaks if the molecule is in a fixed conformation. The chemical shifts and coupling constants of the hydrochlorides of I–IV (I-HCl–IV-HCl) are listed in Table VII. The configuration of the oxime hydrochlorides does not change except in IV-HCl, in which the *Z* isomer appears owing to the *Z*–*E* conversion catalyzed by a trace of acid. Ring inversion of the *E* isomer occurs in I-HCl and II-HCl, since an increase in $J_{2,3}$, which originates from the increased contribution of the equatorial substituent, is observed in contrast to the case of the parent oximes (Table II and VII). A considerable increase of $J_{2,3}$ is also observed in the *E* isomer of III-HCl, although the rate of inversion is smaller than $\pi\sqrt{2}\delta_{ae}$ of H_6 in this case (intermediate ring inversion). The influence of protonation on the coupling constant is negligible because the protonation site is far from the interacting pair of H_2 and H_3. An estimation of the relative population of the equatorial substituent of the *E* isomer of I-HCl, II-HCl, and III-HCl is shown in Table V. In the *Z* isomer of I-HCl, II-HCl, and III-HCl no variation of $J_{2,3}$ is observed, probably because the conformational change is hampered by the steric repulsion between the oxygen atom of the hydroxyimino group and the equatorially oriented substituent.

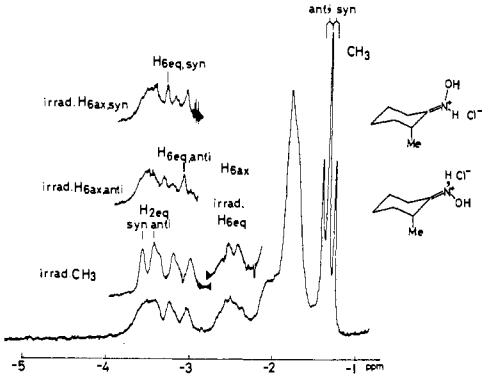


Figure 5. Nmr spectrum of 2-methylcyclohexanone oxime hydrochloride (IV-HCl).

In IV-HCl, the methyl signal appears as a triplet (Figure 5), while a doublet appears in the *E* isomer of the parent oxime. This arises from the overlap of two doublets, one of which is attributed to the *Z* isomer newly apparent by the *Z*–*E* conversion. By successive decoupling, the four peaks due to $H_{2eq,anti}$ and $H_{6eq,syn}$ (*E* isomer), and $H_{2eq,syn}$ and $H_{6eq,anti}$ (*Z* isomer) are observed. We can assign these peaks by considering the case of I-HCl and II-HCl, in which the *anti* peak of the equatorial H_2 resonates at a higher field than the corresponding *syn* peak.[35] The methyl signals at higher and lower fields are assigned to *syn* and *anti* positions, respectively, contrary to the case of the methylene protons of oxime hydrochlorides. A slight preference for the *E* isomer is apparent from the intensity ratio of the *syn* to *anti* methyl signal. Interference between the equatorial methyl and hydroxyimino group would occur in the *Z* isomer of the oxime hydrochloride. On the other hand, an alternative steric repulsion between the proton bonded to the nitrogen atom and the equatorial methyl group would exist in the hydrochloride of the *E* isomer. In both cases a conformational change is inevitable and the methyl substituent is forced to convert to the axial position (see Figure 6). In fact $J_{2,3}$ (6.5 Hz) for both *Z* and *E* isomers indicates that the substituent is in the axial position, whereas it is 19 Hz in the parent oxime.

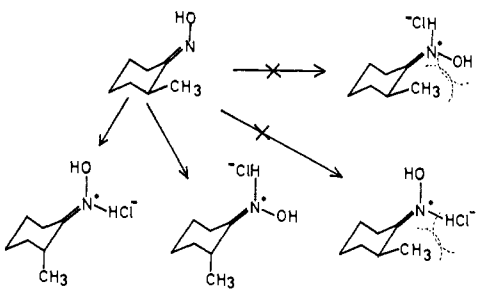
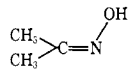
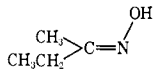
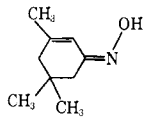
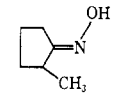
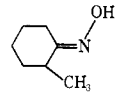
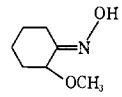
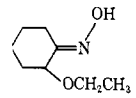


Figure 6. Conformation change of 2-methylcyclohexanone oxime caused by protonation to the nitrogen atom.

Differences of the chemical shift between *syn* and *anti* H_2 signals are very slight (0.13 to 0.19 ppm) among the hydrochlorides of I–IV listed in Table VII and are in good agreement with the case of cyclohexanone oxime

(35) The intensity ratio of *syn* to *anti* H_2 protons is not changed in going from oximes to their hydrochlorides, the assignment of the latter being performed in the preceding section.

Table VIII. Comparison of Methyl Signals between Oximes and Their Hydrochlorides

	Oxime		Oxime hydrochloride		Downfield shift		
	syn	*anti*	*syn*	*anti*	*syn*	*anti*	Footnote
	−1.84	−1.84	−2.19	−2.28	0.35	0.44	*a*
	α −1.81 β −1.04	−1.81 −1.04	−2.44 −1.29	−2.56 −1.27	0.63 0.25	0.75 0.23	*a* *a*
	−1.81	−1.79	−2.21	−2.00	0.41	0.21	*a*
	−1.81	−1.14	−1.35	−1.43	0.17	0.29	*b*
		−1.10	−1.28	−1.36		0.26	*b*
	−3.22	−3.18	−3.38	−3.46	0.16	0.28	*b*
	−1.16	−1.14	−1.20	−1.23	0.04	0.09	*b*

[a] Reference 22a and further investigations. [b] This paper.

in a fixed state and with that of 4-*t*-butylcyclohexanone oxime, as shown in Figure 7.

Electrostatic and Steric Interaction between the Substituent and the Hydroxyimino Group. The conformation energy ($\Delta F = F_{equatorial} - F_{axial}$) is composed of

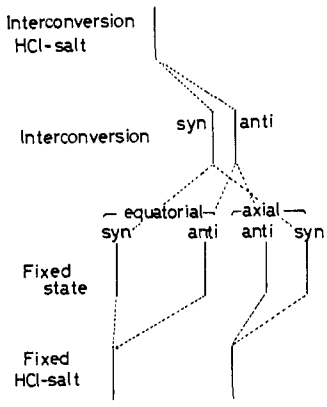


Figure 7. Comparison of 2-methylene signals between six-membered oxime and its hydrochloride. Fixed states correspond with 4-*t*-butylcyclohexanone oxime and its hydrochloride. States of interconversion are obtained from the result of cyclohexanone oxime and its hydrochloride (ref 22).

two factors, the electrostatic ΔF_e and steric ΔF_s. From inspection of Figure 8 (A), it seems that the electrostatic interaction between the lone pairs of the nitrogen atom and those of the substituent favors the axial substituent, *i.e.*, $\Delta F_e > 0$, while the steric repulsion among the substituent, H_4 and H_6 destabilizes the axial substituent, *i.e.*, $\Delta F_s < 0$. The conformation energy of the compounds studied in this paper is positive except for IV and V in deuteriochloroform solution[36,37] (Tables IV and V). Therefore the electrostatic repulsion is the major factor in determining the molecular conformation in I–III and VI–IX.

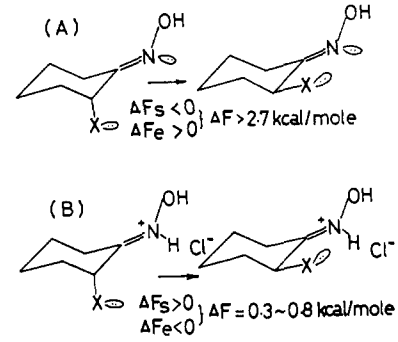
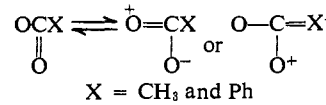


Figure 8. Electrostatic and steric interaction between the substituent and the hydroxyimino group in oximes (A) and their hydrochlorides (B).

In some cases, however, the original electrostatic repulsion is decreased by a partial positive charge appearing either on the substituent or on the hydroxyimino group. We interpret the fairly reduced conformation energy of VI and VII to be the result of such an effect (Table V). This structure is stabilized in a solvent such



X = CH_3 and Ph

(36) Conformation energy is also negative for IV and Vc. The discussion of the electrostatic term, however, is eliminated for IV, since there is no electronegative atom in this substituent. In Vc, a strong intramolecular hydrogen bond exists.

(37) See footnote *a* of Table IV and *c* of Table V.

as DMSO-d_6 or $CDCl_3$. In protic solvents such as methanol, the equatorial substituent is again destabilized by steric repulsion between the bonded solvent molecule and substituent.

In oxime hydrochlorides, in which the nitrogen atom is protonated, the positive charge on the nitrogen atom tends to stabilize the equatorial substituent, *i.e.*, $\Delta F_e < 0$. An additional steric effect, which causes $\Delta F_s > 0$, also arises from the interaction between the equatorial substituent and the proton attached to the nitrogen atom (Figure 8 (B)). The conformation energies of oxime hydrochlorides in *E* isomers are considerably reduced as compared with the parent oximes (Table V). The value of the latter compounds are estimated as 2.7 kcal/mol or larger because of the pronounced preference of the axial substituent.[37]

Assignments of Methyl Signals in Oxime Hydrochlorides. The chemical shift of the methyl signals of oximes and their hydrochlorides are listed in Table VIII together with those studied in the previous paper.[22a] From a comparison of peak intensity and the ratio of isomers studied previously, the methyl signals at higher and lower field are assigned to the *anti* and *syn* peaks, respectively. In their hydrochlorides, however, the *anti* methyl signals are shifted downfield with respect to the *syn* signals with some exceptions.[38] This is probably due to the electric field effect of the excess dipole moment produced by the formation of the hydrochloride. This interpretation has successfully explained the downfield shift due to hydrogen bond formation in aziridines[39] and also peak assignment in triazine.[40] The electric dipole moment on the nitrogen atom is directed along the N^+–H bond which replaces the former sp^2 lone-pair orbital (Figure 9), and methyl protons parallel with it suffer the largest deshielding effect by the electric field. The electric-field effect well explains all of the downfield shift of Table VIII except acetoxime and methyl ethyl ketoxime.

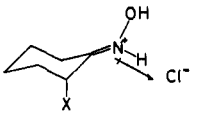


Figure 9. The electric-field effect caused by a protonation to the nitrogen atom. The arrow indicates the excess dipole moment.

Acknowledgment. We are grateful to Mr. Yuji Tanaka for his experimental assistance.

(38) The exceptions are β-methylene proton of isophorone oxime and methyl ethyl ketoxime.

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Acid–Base Behavior of Sulfoxides. Measurement of pK_a Values by Ultraviolet and Nuclear Magnetic Resonance Techniques

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Abstract: The protonation of several aliphatic and aromatic sulfoxides has been measured by nmr and uv techniques in aqueous sulfuric and perchloric acids. The sulfoxides do not follow the H_0 acidity function and the thermodynamic pK_a's have been calculated by the linear free energy relationship (l.f.e.r.) proposed by Bunnett and Olsen. The pK_a's range from −1.8 for DMSO to −2.9 for *p*-nitrophenylmethyl sulfoxide, and the ϕ values lie within the range 0.4–0.6. Such ϕ values are very similar to the ones reported for amides and indeed it seems that the H_A function satisfactorily represents the protonation behavior of sulfoxides. Structural effects on the basicity of the SO group are not very large; the Hammett ρ value for substituted phenyl methyl sulfoxides is +0.85. The evaluated thermodynamic pK_a's give good correlations with half-neutralization potentials (HNP) in acetic anhydride and with the shift of OH stretching frequencies in solutions of sulfoxides with phenol in CCl_4.

The behavior of sulfoxides as weak bases has been long recognized.[2] However there is much disagreement on the basic strength of even the most common sulfoxides.[3–8] Terjesen and Sandved[3] found by titration studies in nonaqueous media that the basicity of diethyl sulfoxide was between acetanilide and acetamide, whereas Nylen[4] found no measurable basicity of dimethyl and diethyl sulfoxide in aqueous solution (pK_a

(1) (a) Universita' di Milano, Milano, Italy 20133; (b) Universita' di Padova, Padova, Italy 35100; (c) Universita' di Modena, Modena, Italy 41100.

(2) E. Fromm, *Ann. Chem.*, 396, 75 (1913); C. Finzi, *Gazz. Chim. Ital.*, 46, 186 (1916).

(3) S. G. Terjesen and K. Sandved, *Kgl. Norske Videnskab. Selskabs Forh.*, 10, 117 (1937); *Kgl. Norske Videnskab. Selskabs Skrifter*, No. 7, 1 (1938). Data quoted in ref 4.

(4) P. Nylen, *Z. Anorg. Allgem. Chem.*, 246, 227 (1941).

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