Conformations and Barriers to Inversion of Seven-membered Cyclic Oxamides and their Monothio- and Dithio-analogues: A Study by Dynamic Nuclear Magnetic Resonance Spectroscopy and Molecular Mechanics

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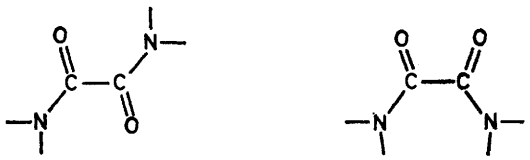
Conformations and barriers to inversion of *NN'*-dialkylperhydrodiazepine-2,3-dione and its monothio- and dithio-analogues have been studied by ^{1}H n.m.r. spectroscopy and by molecular mechanics calculations. Experiments as well as calculations indicate that the compounds studied adopt a twist-boat conformation (C_2 symmetry). The inversion of the ring system involves a passage through a C_s structure with a planar *s-cis*-(thio)oxamide unit. The free energy barriers increase in the order oxamide < monothio-oxamide < dithio-oxamide. The calculations indicate that the dominant part of the barrier is of steric origin; the electrostatic contribution is <20% of the total barrier height.

OXAMIDE and *N*-alkyl-substituted oxamides adopt a planar *s-trans*-conformation provided that the conformation of the *N*-substituted amide unit is *Z*.[1-5] If at least one of the amide units has an *E*-conformation, repulsive steric interactions in the planar *s-trans*-



s-trans *s-cis*

conformation between the *N*-substituent in one half of the molecule and the carbonyl group in the other are relieved by rotation around the central carbon–carbon bond. Thus, *NN'*-dimethyloxamide with both *N*-methyl-substituted amide units in the *Z*-conformation is planar *s-trans*,[3] while *NNN'N'*-tetramethyloxamide is twisted by 71.4° according to *X*-ray diffraction studies.[2] Replacement of one or both oxygens with sulphur increases the twist; *NNN'N'*-tetramethylmonothio-oxamide and *NN*-dimethyldithio-oxamide are 87.4 and 93.1° twisted, respectively, reflecting the relative steric size of oxygen and sulphur.[2]

The planar *s-cis*-conformation of oxamides and their monothio- and dithio-analogues may be expected to be disfavoured due to strong steric repulsions between the *E*-substituents on nitrogen and to repulsive electrostatic interactions between the two (thio)carbonyl groups. To our knowledge, no observations of the *s-cis*-conformation in acyclic oxamide derivatives have been reported.

The twisted conformation of tetra-alkyl-substituted oxamides and their thio-derivatives makes it possible to study the barrier to rotation through a planar transition state by the dynamic n.m.r. technique and thus obtain a quantitative estimate of the relative steric and electrostatic effects of oxygen and sulphur. Carter and Sandström [6] studied the barrier to rotation around the central carbon–carbon bond in tetrabenzyloxamide and its monothio- and dithio-analogues. They found the rotational barrier ($\Delta G^{\ddagger}$) to be very sensitive to replacement of oxygen with sulphur, the free energy barriers increasing in the order oxamide (9.7 kcal mol^{-1}), monothio-oxamide (17.6 kcal mol^{-1}), and dithio-oxamide (>24 kcal mol^{-1}). The barriers were interpreted in terms of steric interactions in a planar *s-trans*-transition state between the oxygen or sulphur atom in one half of the molecule and the benzylic methylene group in the other half. This interpretation was supported by empirical calculations of steric interactions.

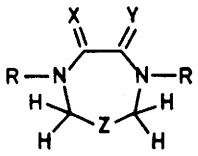
Twisted oxamides are chiral molecules and recently Mannschreck and Talvitie separated the enantiomers of *NNN'N'*-tetramethyldithio-oxamide.[7] They found the barrier to racemization for this molecule to be 25.6 kcal mol^{-1} ($\Delta G^{\ddagger}_{334}$).

The rotational barriers for oxamides obtained so far provide an estimate of steric interactions in a planar *s-trans*-conformation. The purpose of the present work was to investigate the corresponding barrier to passage through a planar *s-cis*-conformation in order to obtain an estimate of the electrostatic and steric interactions in this conformation.

We have investigated a series of seven-membered cyclic oxamides and their monothio- and dithio-analogues by studying their temperature-dependent ^{1}H n.m.r. spectra. In cyclic oxamides of appropriate ring size the oxamide unit is forced to adopt a twisted *s-cis*-conformation, and the inversion of the ring system should involve the passage of the carbonyl or thiocarbonyl groups in a planar or close to planar *s-cis*-conformation.

The seven-membered ring system was chosen since models indicate that it is large enough to keep the geometry of the oxamide unit largely unperturbed in the preferred ring conformation, but still small enough to only have a limited number of possible conformations, thus facilitating the interpretation of the n.m.r. spectra. The experimental results will be compared to those obtained for the corresponding acyclic compounds. To aid in the interpretation of the n.m.r. spectra and the observed inversion barriers, minimum energy conformations and conformational energies were calculated by

the molecular mechanics method. Calculations on six-membered cyclic oxamides indicate that the inversion barriers in such compounds are too low to make a dynamic n.m.r. study feasible.



(I) R = $CH(CH_3)_2$, X = Y = O, Z = CH_2
(II) R = $PhCH_2$, X = Y = O, Z = CH_2
(III) R = $PhCH_2$, X = Y = O, Z = $C(CH_3)_2$
(IV) R = $CH(CH_3)_2$, X = O, Y = S, Z = CH_2
(V) R = $PhCH_2$, X = O, Y = S, Z = CH_2
(VI) R = $CH(CH_3)_2$, X = Y = S, Z = CH_2
(VII) R = $PhCH_2$, X = Y = S, Z = CH_2
(VIII) R = $PhCH_2$, X = Y = S, Z = $C(CH_3)_2$

EXPERIMENTAL AND COMPUTATIONAL

Materials.—The preparation of the compounds studied in this work has been described previously.[8]

N.M.R. Measurements.—All spectra were recorded on a JEOL model JNM-MH-100 n.m.r. spectrometer, equipped with a standard variable temperature attachment (VT 3-C). The samples were 0.4—0.5M solutions in $CHCl_2F$ or $CDCl_3$ for low- and in isoquinoline for high-temperature measurements. Tetramethylsilane (TMS) or hexamethyldisiloxane (HMSO) was added to the solvents to provide the internal lock signal. The temperatures were measured as described elsewhere.[9]

The rate constants were evaluated by visual fitting of experimental to calculated spectra. The theoretical spectra of the isopropyl methyls were obtained by superposition of two spectra for uncoupled two-site cases using the McConnell equation for the two-site exchange.[10] The effect of coupling was taken into account by suitable amplitude factors. The determination of the effective transverse relaxation time (T_2) was performed as described in ref. 11.

For one of the compounds (I) a total bandshape analysis was performed. For the remaining compounds rate constants and free energies of activation were determined at 4—5 different temperatures around the coalescense temperature.

Molecular Mechanics Calculation.—These were performed using the MM1 program developed by Allinger and Wertz employing their 1973 force-field for the hydrocarbon parts of the molecules.[12] The (thio)-oxamide unit was treated as a composite of two (thio)amide units, using the parameter set for amides and thioamides previously employed in calculations on conformational energies and rotational barriers for this class of compounds.[9,13,14] The remaining parameters necessary for the calculations, mainly parameters for the connection of the two thioamide units, were estimated for the purpose of this investigation, with guidance from the corresponding values in a force-field for α-diketones.[15] Good experimental energy and geometry data for (thio)-oxamides are at present too scarce to make a complete optimization of the (thio)-oxamide force-field meaningful. Furthermore, for more general calculations on this class of molecules the π-electron energy should be explicitly taken into account. The force-field parameters used for the (thio)-oxamide units are given in Table 1.

TABLE 1

Force-field parameters

van der Waals constants

$E_v = -2.25\epsilon(r^*/r)^6 + 8.28 \times 10^5\epsilon \exp(-r/0.0736r^*)$

Atom	r^*/Å	ϵ/kcal mol^{-1}
N	1.700	0.039
O	1.650	0.046
S	2.000	0.184

Stretching constants

$E_s = 71.94\ k_s(l - l_0)^2[1 + C_s(l - l_0)]$ $C_s = -2.00$

Bond	l_0/Å	k_s/mdyn Å^{-1}
C=O	1.215	10.80
C=S	1.626	5.14
$C(sp^2)$–N	1.367	5.00
$C(sp^3)$–N	1.449	3.40
$C(sp^2)$–$C(sp^2)$	1.500	6.00
$C(sp^2)$–$C(sp^2)$ (phenyl)	1.394	8.07

Bending constants

$E_b = 0.021\ 914 k_b(\theta - \theta_0)^2[1 + C_t(\theta - \theta_0)]$ $C_t = -0.006$

Angle	θ_0/°	k_b/mdyn Å rad^{-2}
N–C=O	124.0	0.50
N–C=S	125.0	0.50
$C(sp^2)$–C=O	121.0	0.50
$C(sp^2)$–C=S	122.3	0.40
$C(sp^2)$–$C(sp^2)$–N	112.7	0.40
$C(sp^2)$–$C(sp^3)$–N	109.5	0.42
$C(sp^3)$–N–$C(sp^2)$	121.0	0.70
$C(sp^3)$–N–$C(sp^3)$	115.0	0.50
H–C–N	109.5	0.42
$C(sp^3)$–$C(sp^3)$–N	109.5	0.42
Out-of-plane N(sp^2)	0.0	0.05
Out-of-plane C(CO,CS)	0.0	0.80

Stretch-bend constants

$E_{sb} = 2.511\ 24\ k_{sb}(\theta - \theta_0)[(l_1 - l_0) + (l_2 - l_0)]$

Atoms	k_{sb}/mdyn rad^{-1}
X–F–Y F = first row atom	0.120
X–F–H F = first row atom	0.040
X–S–Y S = second row atom	0.160

X, Y = F or S

Torsional constants

$E_t = V_1/2\ (1 + \cos\omega) + V_2/2\ (1 - \cos2\omega) + V_3/2\ (1 + \cos3\omega)$

Angle	V_2/kcal mol^{-1}	V_3/kcal mol^{-1}
X–$C(sp^2)$–$C(sp^2)$–Y (X,Y = O,S,N)	1.5	
X–$C(sp^2)$–N–$C(sp^3)$ [X = S,$C(sp^2)$]	6.0	
O=C–N–C	4.0	
X–$C(sp^3)$–$C(sp^3)$–N [X = H,$C(sp^3)$]		0.53
X–$C(sp^3)$–N–Y (X = C,H; Y = C)		1.0
$C(sp^2)$–$C(sp^2)$–$C(sp^3)$–N		0.0
X–C–C–Y (phenyl, X = C,H)	10.017	

Bond moments

Bond	μ/D
C=O	2.91
C=S	3.23
$C(sp^2)$–N	−1.16

Fractional atomic charges

Unit	$C(sp^2)$	O/S	N	(N)–$C(sp^2)$
Amide	+0.29	−0.32	−0.15	+0.09 [a]
Thioamide	+0.15	−0.37	−0.03	+0.125 [a]

[a] Averaged net charges of the methyl groups in tetramethyloxamide and tetramethyldithio-oxamide.

Electrostatic interactions were calculated by two methods using (i) the dipole interaction model, employing point dipoles placed at the midpoints of the bonds [16] and (ii) the charge interaction model with atomic charges obtained from

CNDO/2 calculations on tetramethyloxamide and its dithio-analogue.[17] Bond moments and fractional atomic charges are given in Table 1. In all calculations of the electrostatic interactions an effective dielectric constant of unity was employed.

The energies of the molecules were minimized with respect to all degrees of freedom using the dipole interaction model to calculate the electrostatic interactions. Symmetry constraints were included where applicable. Charge interaction energies were dealt with separately and added to the results of the energy minimizations with the dipole interaction energies subtracted out.

RESULTS

At ambient temperature the ^{1}H n.m.r. spectra of the cyclic oxamides (I)—(III) show a doublet for the isopropyl methyls in (I) and a sharp singlet for the benzylic methylene protons (II) and (III). The signals broaden at lower temperatures and split at *ca.* 209 K into two isopropyl methyl doublets of equal intensities in the spectrum of (I), and at 213 and 248 K into an AB pattern for the benzylic protons in (II) and (III), respectively. In (III) the ring methylene protons show up as a singlet at probe temperature and as an AB quartet at low temperatures (<238 K). The signal from the geminal methyl groups in (III) is a sharp singlet at all temperatures investigated (down to 210 K). The AB shift for the benzylic protons in (III), 152.7 Hz, is much larger than the corresponding shift in (II), 33.2 Hz, indicating different conformational preferences of the benzyl groups in (II) and (III).

The ambient temperature spectra of the dithio-oxamides (VI)—(VIII) display two doublets (1 : 1) for the isopropyl methyls in (VI) and AB patterns for the benzylic methylene protons in (VII) and (VIII) and for the ring methylene group in (VIII). All signals broaden at higher temperatures and above 435 K they coalesce into one doublet for the isopropyl methyls in (VI) and above 448 K into singlets for the methylene groups in (VII) and (VIII). The coalescence for the benzylic methylene signals in (VIII) lies above the upper temperature limit of the spectrometer (473 K). In (VIII) as in (III) the singlet due to the geminal ring methyl groups does not change with temperature. The relative size of the AB shifts in (VII) and (VIII) show the same pattern as in (II) and (III). In (VII) the benzylic AB shift is 20.6 Hz, while in (VIII) the corresponding shift is 194.6 Hz. The temperature dependence of the ^{1}H n.m.r. spectra of the oxamides and of the analogous dithio-oxamides is thus very similar, but the temperature interval in which the spectral changes occur is displaced by >200° to higher temperatures on going from oxamides to dithio-oxamides. Due to lower molecular symmetry, the spectra of the monothio-oxamides (IV) and (V) are more complex than those of the corresponding dithio-oxamides. Four somewhat overlapped doublets of equal intensities for the isopropyl methyls in (IV) are observed at low temperatures. These signals coalesce at 299 K into two doublets. The downfield one is assigned to the thioamide half of the molecule from a comparison with the corresponding signals in the spectra of (I) and (VI). In (V) the benzylic protons give rise to two well separated AB spectra below probe temperature. The downfield one is assigned to the thioamide unit. The AB shifts in the spectra of this compound are significantly temperature-dependent. At 254 K the shifts are 33.4 and 26.8 Hz, respectively and at 300 K they have decreased to 26.8 and 16.3 Hz, respectively. The two AB quartets coalesce into two singlets at *ca.* 305 K.

TABLE 2

^{1}H N.m.r. data for compounds (I)—(VIII) at ambient temperature

Compound	Solvent	δ [a] (multiplicity,[b] number of protons)
(I)	$CHCl_2F$	1.14 (d, 12), 1.83 (m, 2), 3.29 (m, 4), 4.77 (m, 2)
(II)	$CDCl_3$	1.29 (m, 2), 3.26 (m, 4), 4.59 (s, 4), 7.27 (s, 10)
(III)	$CDCl_3$	0.80 (s, 6), 3.01 (s, 4), 4.72 (s, 4), 7.27 (s, 10)
(IV)	$CDCl_3$	1.13 (m, 12), 1.92 (m, 2), 3.26 (m, 2) 3.55 (m, 2), 4.82 (m, 1), 5.67 (m, 1)
(V)	$CDCl_3$	1.29 (m, 2), 3.13 (m, 2), 3.40 (m, 2), 4.60 (m, 2), 5.20 (m, 2)
(VI)	Isoquinoline [c]	0.86 (m, 12), 1.55 (m, 2), 3.17 (m, 4), 5.67 (m, 2)
(VII)	*o*-Dichlorobenzene	1.08 (m, 2), 3.12 (m, 4), 4.98 (q, 4)
(VIII)	Isoquinoline [c]	0.58 (s, 6), 3.10 (q, 4), 5.20 (q, 4)

[a] P.p.m. from TMS unless otherwise stated. [b] s = singlet, d = doublet, m = multiplet. [c] At 373 K with HMSO as reference.

Chemical shifts and coupling constants for compounds (I)—(VIII) are given in Tables 2 and 3. Rate constants

TABLE 3

N.m.r. data at slow exchange

Compound	Signals studied	Solvent	T/K	$\Delta\nu$/Hz	J_{CH_3-CH}/Hz	J_{AB}/Hz
(I)	$CH(CH_3)_2$	$CHCl_2F$	204.2	5.9	6.8	
					6.8	
(II)	$PhCH_2$	$CDCl_3$	198.9	33.2		13.7
(III)	$PhCH_2$	$CDCl_3$	215.1	152.7		15.0
	$C(CH_3)_2CH_2$			39.5		15.5
(IV)	$CH(CH_3)_2$ [a]	$CDCl_3$	285.4	6.5	6.7	
					6.7	
	$CH(CH_3)_2$ [b]			7.5	7.1	
					7.1	
(V)	$PhCH_2$ [a]	$CDCl_3$	253.5	33.4		14.3
	$PhCH_2$ [b]			26.8		14.2
(VI)	$CH(CH_3)_2$	Isoquinoline	429.2	7.2	6.7	
					6.7	
(VII)	$PhCH_2$	Isoquinoline [c]	375.0	20.6		14.4
(VIII)	$PhCH_2$	Isoquinoline [c]	409.4	194.6		14.2
	$C(CH_3)_2CH_2$			41.9		14.4

[a] Amide unit. [b] Thioamide unit. [c] HMSO as reference.

TABLE 4

Free energy barriers to inversion for compounds (I)—(VIII)

Compound	$\Delta G^{\ddagger}$ [a]/kcal mol^{-1}	T/K
(I)	11.1 [b]	208.8
(II)	10.7	202.9
(III)	12.0	215.1
(IV)	17.2	298.6
(V)	15.7	284.4
(VI)	24.1	447.6
(VII)	23.3	431.5
(VIII)	23.2	409.4

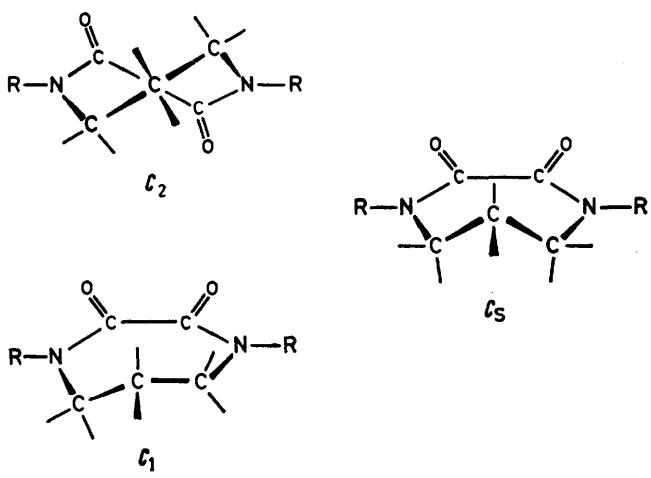
[a] Estimated error ± 0.1 kcal mol^{-1}. [b] $\Delta H^{\ddagger}$ 10.0 $\pm$ 0.1 kcal mol^{-1}, $\Delta S^{\ddagger}$ -5.2 ± 0.7 cal mol^{-1} K^{-1}, only random errors calculated from the standard deviations in the Eyring plot are included.

were evaluated from the temperature-dependent bandshapes as described in the Experimental part. The corresponding free energy barriers are given in Table 4.

For (III) and (VIII) two different proton groups, the benzylic methylene protons and the ring methylene protons, could be studied. The two sets of rate constants thus obtained were identical within error limits at all temperatures where a comparison could be made, indicating that they correspond to the same dynamic process.

DISCUSSION

Conformations of (I)—(VIII).—From the ^{1}H n.m.r. spectra described above it can be concluded that the four isopropyl methyls in (I) and (VI), and the four benzylic methylene protons in (II), (III), (VII), and (VIII) are pairwise equivalent or enantiotopic in the lowest energy conformation of the molecules. This is only consistent with conformations having a C_2 axis (possibly pseudo-rotationally averaged) or a mirror plane through the ring system and bisecting the (thio)carbonyl–(thio)carbonyl bond. The conformational freedom of the cyclic oxamides is restricted by the rigidity of the (thio)amide units, and thus only conformations with planar or close to planar thioamide units may be considered as candidates for the low energy conformations. This restriction makes the ring system in the compounds studied in this work similar to the cyclohepta-1,3-diene ring system, for which calculations indicate that the molecule has three low energy conformations with C_2 (twist-boat), C_s, or C_1 symmetry.[18] The three conformations have essentially identical energies and are separated by very small energy barriers. The corresponding conformations apply to cyclic oxamides. Other formally possible conformations like twist-chair, chair, and boat all require considerable twisting around the amide C–N bond(s) and may therefore be excluded.

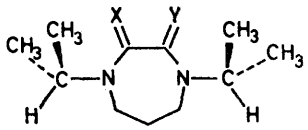


Unfortunately, the ring methylene resonances in (I), (II), and (IV)—(VII) are not sufficiently resolved at low temperatures to allow an unambiguous analysis of this part of the spectra and to deduce the preferred conformation from these spectral data. However, the spectra of (III) and (VIII), showing a sharp singlet for the geminal methyl groups attached to the ring at all temperatures investigated, are only consistent with the C_2 (twist-boat) conformation. Strictly, these experimental data only allow the C_s and the C_1 conformations to be excluded for (III) and (VIII), but molecular mechanics calculations clearly indicate that the C_2 conformation is very strongly preferred for all compounds studied in this work. The energy for the C_s conformation is calculated to be 9—20 kcal mol^{-1} higher than that for the C_2 twist-boat. The C_1 conformer lies *ca.* 2 kcal mol^{-1} below the C_s conformer but still 7—18 kcal mol^{-1} above the C_2 twist-boat. More important, unrestricted energy minimizations show that the C_s and C_1 conformers are not local minima on the potential energy surface for the cyclic oxamides. As will be discussed below, the C_s conformation may in fact be regarded as a good model for the transition-state geometry for the degenerate inversion process C_2 twist-boat $\rightleftharpoons$ C_2 twist-boat.

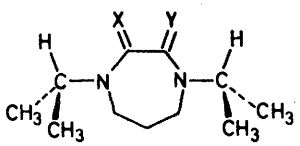
The X=C–C=Y (X = O, S; Y = O,S) dihedral angle for compounds (I)—(VIII) is calculated to be 61—65°, with the higher values for the sulphur compounds, showing in comparison with acyclic analogues (see Introduction) that the seven-membered ring system prohibits the relative steric size of oxygen and sulphur to be reflected in twisting around the central carbon–carbon bond. The calculated dihedral angles are close to the value found in an *X*-ray study for the twisting around the N–N bond in seven-membered cyclic azines (66.8°) which also adopt a C_2 twist-boat conformation.[19]

N-*Alkyl Conformations*.—As shown in Table 2 the resonances for the isopropyl methine protons appear at δ 4.77 for (I), at δ 4.82 and 5.67 for (IV), and at 5.67 for (VI). The resonance position of the methine protons in *N-Z*-isopropyl groups in amides and thioamides has been shown to be very sensitive to the conformation of the isopropyl group. For amides the *Z*-isopropyl group conformation, in which the methine proton is in or close to the amide plane and pointing towards the carbonyl group, exhibits a methine proton resonance at δ 4.8—5.0, which is significantly downfield to the resonances for methine protons in other positions. For thioamides the corresponding value is δ 5.5—6.3.[9] The methine proton resonances in (I), (IV) and (VI) thus indicate that this proton eclipses (or nearly so) the amide C–N bond in the preferred conformation [conformer (B)]. This preference is apparently quite strong, since the observed shifts

are close to the shifts found for the corresponding 'frozen' *N*-isopropyl conformer in amides and thioamides. Molecular mechanics calculations of the relative energies of conformations (A) and (B) support this conclusion. Conformer (B) is calculated to be lower in energy by 0.32, 0.80, and 1.43 kcal mol^{-1} for (I), (IV), and (VI), respectively.



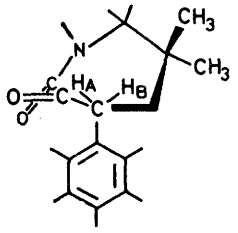
(A)



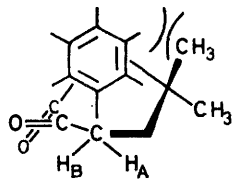
(B)

The conformation of the benzyl groups in (II), (III), (V), (VII), and (VIII) may also be inferred from the chemical-shift data for these compounds. As mentioned above, $\Delta\nu_{AB}$ is much larger for (III) and (VIII), with geminal methyl groups attached to the ring, than for (II) and (VII). The large $\Delta\nu_{AB}$ in (III) and (VIII) indicates that one of the benzylic methylene protons is pointing towards the (thio)carbonyl group. The size of the observed $\Delta\nu_{AB}$ is similar to those found for the *Z*-methylene protons in amides and thioamides substituted on nitrogen with primary alkyl groups, which have been found to adopt an antiparallel perpendicular arrangement.[13]

In the *N*-benzyl compounds studied in this work, the benzyl groups may have two non-equivalent approximately perpendicular conformations, (C) and (D) (see below). Fast interchange (on the n.m.r. time-scale) between these conformations tends to reduce the $\Delta\nu_{AB}$.



(C)



(D)

However, in (III) and (VIII) the geminal methyl groups may interfere with the phenyl group in conformation (D), leaving this conformation essentially unpopulated with a large (unaveraged) AB shift as the result.

This interpretation is supported by molecular mechanics calculations which indicate that for (II) and (VII) two stable conformers corresponding to (C) and (D) are present, while for (III) and (VIII) no local minimum corresponding to conformation (D) is obtained. The X=C–N–C–C(phenyl) dihedral angles are calculated to be less than 90°, varying between 62 and 66°, but the potential surface around the minimum is very shallow.

Barriers to Inversion.—The free energy barriers to inversion for compounds (I)—(VIII) increase in the order oxamide < monothio-oxamide < dithio-oxamide (Table 4). The *N*-isopropyl compounds have slightly higher barriers than those of the *N*-benzyl-substituted ones, reflecting small differences in steric interactions between the *N*-substituent and the ring system. The barriers for compounds (II), (V), and (VII) are quite similar to those found by Carter and Sandström for the related acyclic tetrabenzyloxamide (9.7 kcal mol^{-1}), its monothio- (17.9 kcal mol^{-1}), and dithio-(>24 kcal mol^{-1}) analogues.[6] Mannschreck *et al.*[7] found the rotational barrier for tetramethyldithio-oxamide to be 25.6 kcal mol^{-1}, and the barrier for tetrabenzyldithio-oxamide should be close to this value. The barriers for these acyclic compounds were interpreted as mainly reflecting differences in steric interactions in a planar *s-trans*-transition state between sulphur and oxygen in one-half of the molecule and the *E* methylene group in the other. Simple empirical calculations of steric strain not including minimization of energy with respect to geometry, indicated that the energies for the *s-cis*-conformations are extraordinarily high. The barriers to inversion in (I)—(VIII) should reflect steric and electrostatic interactions in a planar or close to planar *s-cis*-conformation of the (thio)-oxamide unit. The similarity of the barriers in the acyclic and the corresponding cyclic compounds is therefore quite unexpected.

In the acyclic as well as the cyclic series of oxamide derivatives, the influence on the barrier of the replacement of oxygen with sulphur is very significant. Comparing the free energy barriers for compounds (II), (V), and (VII), replacement of one oxygen with sulphur increase the barrier by 5.0 kcal mol^{-1}. Replacement of both oxygens in (II) with sulphur gives an increase by 12.6 kcal mol^{-1}. The corresponding barrier increases for tetrabenzyloxamide and its thio-derivatives are even larger, 7.9 and >14.3 kcal mol^{-1}, respectively. If the barrier found for tetramethyldithio-oxamide is taken to represent the undetermined barrier for tetrabenzyldithio-oxamide, the latter value becomes 15.9 kcal mol^{-1}. These comparisons show that the height of the barrier through an *s-trans*-transition state is significantly more sensitive to sulphur–oxygen exchange than is the barrier through an *s-cis*-transition state.

In order to analyse the data presented above further, and to obtain an estimate of the relative importance of the steric and electrostatic contributions to the inversion barriers of (I)—(VIII), conformational energies were calculated by the molecular mechanics method as described in the Experimental and Computational section. The C_s structure described above was used as a transition state model. It was shown to be a local maximum on the potential energy surface by calculating the energy changes for small stepwise increases of the (thio)carbonyl–(thio)carbonyl dihedral angle. A possible transition-state alternative, having all ring carbon atoms in one plane, was calculated to be >20 kcal mol^{-1} higher in energy. Other formally possible transition-state structures all involve large twists around the thioamide bond(s) with concomitant very high energies. Calculated inversion barriers using two methods for calculating the electrostatic interactions are summarized in Table 5.

The free energies of activation were determined at significantly different temperatures, spanning a large temperature interval (*ca.* 200°). In order to make quantitative comparisons with calculated values meaningful, activation enthalpies were evaluated from the free activation energies in Table 4 and the activation entropy found for (I). The similarity of compounds (I)—(VIII) justifies this procedure. The activation enthalpies are given in Table 5.

TABLE 5

Calculated inversion barriers and experimental $\Delta H^{\ddagger}$ for (I)—(VIII)

Compound		Calc. barrier (kcal mol^{-1})	Electrostatic part of the barrier (kcal mol^{-1})	Exp. $\Delta H^{\ddagger}$ (kcal mol^{-1})
(I)	DI [a]	13.7		10.0
	CH [b]	10.3	0.7	
(II)	DI	11.5		9.6
	CH	8.8	1.2	
(III)	DI	12.2		10.9
	CH	9.7	1.1	
(IV)	DI	15.7		15.6
	CH	13.4	1.1	
(V)	DI	13.6		14.2
	CH	12.2	1.9	
(VI)	DI	21.6		21.8
	CH	19.9	1.6	
(VII)	DI	19.2		21.1
	CH	19.4	3.3	
(VIII)	DI	19.6		21.1
	CH	18.9	2.3	

[a] DI = dipole interaction model. [b] CH = charge interaction model.

The agreement between the experimental and calculated barriers is very satisfactory, considering the approximations involved in the calculations. It should be noted that the calculated values refer to isolated molecules in the gas phase. Consequently we do not wish to place too much emphasis on the agreement between the absolute heights of experimental and calculated values. However, the calculated numbers clearly provide a basis for the interpretation and analysis of the experimental data. As may be expected, the calculations using the charge interaction model to calculate the electrostatic interactions reproduce the experimental trends better than do the calculations employing the dipole approximation. In the following, we will therefore mainly discuss the results from the former calculations.

The electrostatic contributions (charge interaction energies) to the calculated barriers are given in Table 5. These contributions constitute only a minor part (8—17%) of the total heights of the barriers. Steric interactions, notably angle bending in the (thio)-oxamide unit and non-bonded van der Waals repulsions between the (thio)carbonyl groups, are predominant. The C(sp^2)–C(sp^2)–N bond angle increases by *ca.* 13° and the O=C–N angle decreases by *ca.* 9° on going from the initial state to the transition state.

The experimental and calculated influences on the inversion barriers of the replacement of oxygen with sulphur in the three series (I)–(IV)–(VI), (II)–(V)–(VII), and (III)–(VIII) are summarized in Table 6.

TABLE 6

Calculated and experimental influences of replacement of oxygen with sulphur on the inversion barriers for (I)—(VIII)

Compound	$\Delta\Delta H^{\ddagger}_{exp.}$/ kcal mol^{-1}	$\Delta\Delta E$ calc./ kcal mol^{-1}	Electrostatic part of $\Delta\Delta E$/ kcal mol^{-1}
(I)	0	0	0
(IV)	5.6	3.1	0.4
(VI)	11.8	9.6	0.9
(II)	0	0	0
(V)	4.6	3.4	0.6
(VII)	11.5	10.6	2.0
(III)	0	0	0
(VIII)	10.2	9.2	1.2

The numbers are given relative to the oxamide parent compound. The electrostatic parts of the relative barriers are also included in Table 6. The agreement between the experimental and calculated values is quite good, but the calculated influence of the oxygen–sulphur exchange on the barriers is somewhat underestimated. The steric component is clearly dominant and even if the entire difference between calculated and experimental values were taken to be due to deficiences in the electrostatic model, the steric contributions would still be the larger ones.

It may thus be concluded that the dominant part of the inversion barriers is of steric origin, as well as the larger part of the effects on the barriers of replacing one or both oxygens with sulphur. The steric contributions reflect the larger steric size of the sulphur atom compared to the oxygen.

Returning to the acyclic tetrabenzyloxamide and its thio-analogues, the steric contribution to the increase of the rotational barrier on replacement of oxygen, assuming a planar *s-trans*-transition state, was calculated. Electrostatic contributions should play a minor role in this case. Tetramethyloxamide and its thio-derivatives were used as models in the calculations. The calculated values for replacement of one or two oxygens are 6.5 and 15.5 kcal mol^{-1}, respectively. The experimental values ($\Delta\Delta G^{\ddagger}$) are 7.9 and 15.9 kcal mol^{-1}, respectively. Steric interactions thus completely account for the sensitivity of the inversion barrier through an *s-trans*-transition state to the exchange of oxygen by sulphur, supporting the conclusions drawn by Carter and Sandström.[6] Inspection of the details of the calculations suggests that the observed differences in the barrier increments due to the sulphur–oxygen exchange for the *s-cis*-transitions state in (I)–(VIII) and the *s-trans*-transition state in the acyclic tetra-alkyloxamides and its thio-analogues, are mainly due to different possibilities to relax steric strain in the two series of compounds.

In the *s-trans*-conformer, substitution of oxygen by the larger sulphur leads to larger non-bonded repulsive interactions with the *E*-methylene group in the opposite half of the molecule. These interactions may partly be relaxed by bending of the thioamide unit, but a mode of bending that decreases the non-bonded repulsions on one side of the molecule, increases it on the other side. In the (cyclic) *s-cis*-conformation, such bendings may be distributed among several degrees of freedom, thus increasing the efficiency of the relaxation.

The rotational barrier through an *s-cis*-transition state in the tetra-alkyl-substituted acyclic oxamides should be appreciably higher than those found for the corresponding cyclic compounds (I)—(VIII). The very large non-bonded repulsions between the *E*-methylene groups in the acyclic *s-cis*-conformer should increase the barriers compared to those for the cyclic molecules, where only a part of these interactions is present. Furthermore, the dihedral angle between the (thio)-carbonyl groups is less than optimal in the cyclic compounds, leading to a relative increase of the initial state energy.

On the basis of preliminary calculations on tetramethyloxamide and its monothio- and dithio-analogues, the rotational barriers through an *s-cis*-transition state in these molecules may be estimated to be *ca.* 20, 25, and 30 kcal mol^{-1}, respectively. More accurate calculations must await further development of the force-field employed in this work. In the *s-cis*-transition state of the acyclic oxamides considerable twisting of the thioamide C–N bonds occurs. Thus, in a force-field suitable for more general calculations, explicit consideration of changes in the π-electron energy is probably required.

The free energy barriers to inversion in the dithio-oxamides (VI)—(VIII) are high enough to make a separation of the enantiomers possible at room temperature. If such a separation can be successfully performed this would provide an opportunity to study the chiroptical properties of *cisoid* dithio-oxamides. Work along this line is in progress.

This work was supported by the Swedish Natural Science Council and by the Royal Physiographic Society of Lund. We are grateful to Professor A. Mannschreck, University of Regensburg, Germany for communicating his results to us prior to publication and to Professor J. Sandström and Dr. R. Carter for valuable discussions.

[1/338 *Received*, 27*th February*, 1981]

REFERENCES

[1] E. M. Ayerst and J. R. C. Duke, *Acta Crystallogr.*, 1954, **7**, 588.
[2] G. Adiwidjaja and J. Voss, *Chem. Ber.*, 1977, **110**, 1159.
[3] A. Christensen, H. J. Geise, and B. J. Van der Veken, *Bull. Soc. Chim. Belg.*, 1975, **84**, 1173.
[4] K. H. Klaska, O. Jarchow, W. Schäm, H. Widjaja, J. Voss, and H. W. Schmalle, *J. Chem. Res.* (*S*), 1980, 104.
[5] D. Rinne and U. Thewalt, *Z. Anorg. Allg. Chem.*, 1978, **443**, 185.
[6] R. E. Carter and J. Sandström, *J. Phys. Chem.*, 1972, **76**, 642.
[7] A. Talvitie and A. Mannschreck, in preparation.
[8] R. Isaksson, T. Liljefors, and J. Sandström, *J. Chem. Res.*, 1981; (*S*) 43; (*M*) 664.
[9] A. Lidén, C. Roussel, T. Liljefors, M. Chanon, R. E. Carter, J. Metzger, and J. Sandström, *J. Am. Chem. Soc.*, 1976, **98**, 2853.
[10] H. M. McConnell, *J. Chem. Phys.*, 1958, **28**, 430.
[11] A. Lidén and J. Sandström, *Tetrahedron*, 1971, **27**, 2893.
[12] D. H. Wertz and N. L. Allinger, *Tetrahedron*, 1974, **30**, 1579.
[13] U. Berg, M. Grimaud and J. Sandström, *Nouv. J. Chim.*, 1979, **3**, 175.
[14] S. Karlsson, T. Liljefors and J. Sandström, *Acta Chem. Scand., Ser. B*, 1977, **31**, 399.
[15] R. Isaksson and T. Liljefors, to be published.
[16] J.-M. Lehn and G. Ourisson, *Bull. Soc. Chim. Fr.*, 1963, 1113.
[17] R. Isaksson, unpublished work.
[18] N. L. Allinger and J. T. Sprague, *Tetrahedron*, 1973, **29**, 3811.
[19] E. Cuthbertson, R. K. Mackenzie, D. D. MacNicol, H. H. Mills, F. B. Wilson, K. M. Ghouse, and D. G. Williamson, *Spectrochim. Acta, Part A*, 1980, **36**, 333.