Conformations and conformational changes of 3-isobutyl- and 3-neopentyl-rhodanines. A case of steric attraction studied by X-ray crystallography, NOE effects and force-field calculations

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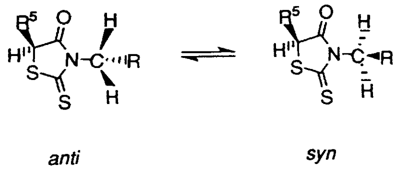
An X-ray crystallographic study of 3-neopentyl-5-phenylrhodanine [3-neopentyl-5-phenyl-2-thioxo-2,3-dihydro-1,3-thiazol-4(5*H*)-one **4**] shows that the crystal is composed of the *syn* form, previously supposed to be less stable than the *anti* form. MM2(91) calculations also predict the *syn* form to be the most stable one due to an attractive steric effect, mainly between two methyl groups of the *tert*-butyl group and the nearest carbon and hydrogen atoms in the benzene ring. MM2 calculations of the barriers to rotation the 3-isobutylrhodanines **1** and **3** and on the 3-neopentyl analogues **2** and **4** reproduce the experimental barriers quite well and indicate that the preferred path of rotation of the 3-substituent is with the isopropyl or *tert*-butyl group passing the carbonyl rather than passing the thiocarbonyl group.

A substantial NOE enhancement was observed between *tert*-butyl and phenyl protons, but this was not strong enough to exclude the possibility that it was caused by a minor form present in *ca.* 30%.

Suitably chosen alkyl or aryl groups attached to the nitrogen atom in 2-thioxo-2,3-dihydro-1,3-thiazol-4(5*H*)-ones (rhodanines) take up preferred orientations between the flanking oxo and thioxo groups and hindered rotation between two forms has been observed by NMR[1,2] and polarimetric[3] techniques. The 3-isobutyl (**1**, **3**) and 3-neopentyl compounds (**2**, **4**) were shown to have two perpendicular[4] conformations, with the isopropyl and *tert*-butyl group *anti* or *syn* to the substituent in position 5 (Scheme 1).



1 R^5 = Me, R = Pr^i
2 R^5 = Me, R = Bu^t
3 R^5 = Ph, R = Pr^i
4 R^5 = Ph, R = Bu^t

Scheme 1

For 5-unsubstituted compounds the two conformers are enantiomers but for **1** and **2** with R^5 = Me and for **3** and **4** with R^5 = Ph the two forms are diastereoisomers. The free energy differences and free energy barriers between the *anti* and *syn* forms are shown in Table 1.

In the previous study,[1] the *anti* form was proposed to be the most stable one for steric reasons, and the higher *syn* ⟶ *anti* barrier for **4** than for **2** was ascribed to repulsive steric interactions in the transition state involving the phenyl ring.

However, an alternative explanation for the higher barrier for **4** could be that the phenyl and *tert*-butyl groups approach one another in the *syn* form to a distance, which leads to an attractive steric interaction. This hypothesis is supported by the observation that the minor − major energy difference is rather similar in magnitude to the difference in rotational barrier between **2** and **4**. This difference could be ascribed to a stabilization of the *syn* form of **4** caused by the attractive steric effect.

Table 1 $\Delta G^\circ_{\text{major-minor}}$ and $\Delta G^\ddagger_{\text{major}\rightarrow\text{minor}}$ values (kJ mol^{-1}) for compounds **1**–**4**[a]

Compound	$\Delta G^\circ_{\text{major-minor}}$	$\Delta G^\ddagger_{\text{major}\rightarrow\text{minor}}$
1	*ca.* 0	30 ± 2
2	*ca.* 0	39 ± 1
3	−0.4	30 ± 2
4	−2.1	42 ± 1

[a] From ref. 1.

In most force-fields the attractive contribution stems from the London dispersion forces between non-bonded atoms, and the contribution from a pair of atoms *i* and *j* is in general given by a term in $(r_{ij})^{-6}$. The number of known cases where attractive steric effects have a dominant influence on the conformation of a flexible molecule is rather limited. A classical example is 2,4-dimethyl-1,3,5-trineopentylbenzene,[5–7] for which the all-*syn* form is *ca.* 4 kJ mol^{-1} more stable than the 1,3-*syn*-5-*anti* form. 1,5-Di-*tert*-butylcyclooctatetraene has been shown to prefer the valence tautomer, which has the *tert*-butyl groups in closest proximity.[8–10] A more general study of 1,6-dialkylcyclooctatetraenes has been reported by Anderson and Kirsch.[11] Berg and Pettersson[12] found that *N*,*N*′-di(RCH_2)-imidazoline-2-thiones and *N*,*N*′-di(RCH_2)-thiobarbiturates prefer the *syn* form even for R as small as Pr^i and CF_3. In all these cases, the observed effects were satisfactorily reproduced by force-field calculations.

In order to clarify the conformational situation for **4**, this compound has been subjected to an X-ray crystallographic study, to an NOE study by ^1H NMR, and to analysis by empirical force-field calculations using the MM2(91) force-field. The latter technique has also been employed to study conformational equilibria and barriers to rotation of the 3-substituents in all of compounds **1**–**4**.

Experimental

Material

The synthesis of compound **4** has already been described.[1]

Table 2 Crystal data and intensity collection for **4**

Empirical formula	$C_{14}H_{17}NOS_2$
Colour; habit	Yellow; chunk
Crystal size (mm)	0.48 × 0.25 × 0.22
Space group	$P2_1/c$; Monoclinic
Unit cell dimensions	a = 12.316(3) Å b = 5.781(1) Å; β = 91.18(2)° c = 20.120(6) Å
No. reflns. for indexing	15 (12.76° < 2θ < 30.57°)
Volume	1432.3(6) Å^3
Z	4
Formula weight	279.4
Density (calc.)	1.296 Mg m^{-3}
Absorption coefficient	0.345 mm^{-1}
F(000)	592
Diffractometer used	Siemens R3m/V
Radiation	Mo-Kα (λ = 0.710 73 Å)
Temperature	297 K
Monochromator	Highly oriented graphite crystal
2θ Range	2.5 to 48.0°
Scan type	$\theta/2\theta$
Scan speed	Variable; 2.93 to 14.65° min^{-1} in ω
Scan range (in ω)	0.96° plus Kα-separation
Background measurement	Stationary crystal and stationary counter at beginning and end of scan, each for 25.0% of total scan time
Standard reflections	3 measured every 50 reflections
Index ranges	$-14 \leqslant h \leqslant 14, 0 \leqslant k \leqslant 6, -22 \leqslant l \leqslant 22$
Reflections collected	5349 [3444 > 3.0$\sigma(I)$]
Independent reflections	2270 [1240 > 3.0$\sigma(I)$]
Hydrogen atoms	Located from difference map
Weighting scheme	$w^{-1} = \sigma^2(F) + 0.0004F^2$
Number of parameters refined	232
Final R indices (obs. data)	R = 0.0295, Rw = 0.0309
Goodness-of-fit	1.08
Largest and mean Δ/σ	0.001, 0.000
Data-to-parameter ratio	5.3:1
Largest difference peak	0.29 e Å^{-3}
Largest difference hole	−0.16 e Å^{-3}

X-Ray crystallography

Experimental single-crystal X-ray structure analysis. A yellow and chunky crystal of compound **4** was selected for indexing and intensity data collection. Axial oscillation photographs along the three axes were taken to check the symmetry properties and unit-cell parameters. Of the 5349 reflections collected, 1240 unique reflections were considered observed [I > 3.0$\sigma(I)$] after Lorentz polarization corrections. On the basis of the systematic absences the space group was determined to be $P2_1/c$. Direct methods were used to locate most of the non-hydrogen atoms in the structure with the remaining atoms being found from successive difference maps. The hydrogen atoms were located from a difference Fourier map calculated at the final stage of structure analysis. The final cycles of refinement, including the atomic coordinates and anisotropic thermal parameters for all non-hydrogen atoms and atomic coordinates and fixed isotropic thermal parameters for the hydrogen atoms, converged at R = 0.0295 and R_w = 0.0309. Corrections for secondary extinction and anomalous dispersion were applied, and neutral-atom scattering factors were used.[13] Structure solution and least-squares refinements were performed on a DEC VAX 4000/VLC workstation using the SHELXTL-Plus programs.[14] Crystal data and information about the intensity collection are found in Table 2. The atomic numbering follows from Fig. 1.

Empirical force-field calculations

The *syn* and *anti* structures of compounds **1–4** were constructed with the Macintosh molecular modelling program Mac Mimic[15] and the energies were minimized with the Allinger MM2(91) force-field.[16,17] The rotational barriers were calculated by driving the C(9)–N(1)–C(10)–C(11) dihedral angle from the *syn* to the *anti* form and *vice versa.* The non-standard force constants used for the N–C=O and N–C=S frameworks have been published earlier.[18,19]

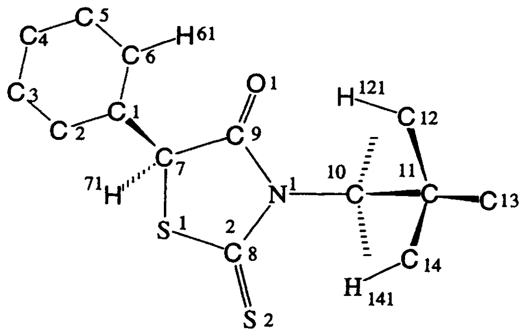


Fig. 1 Numbering of atoms in the *syn* form of (*S*)-**4**, to be used, *mutatis mutandis*, also for **1–3**

Table 3 Selected bond lengths (pm) and bond angles (°) for **4**

S(1)–C(7)	180.6(4)	S(1)–C(8)	174.6(3)
S(2)–C(8)	163.5(3)	O(1)–C(9)	120.4(5)
N(1)–C(8)	137.4(4)	N(1)–C(9)	140.1(4)
N(1)–C(10)	147.5(4)	C(7)–C(9)	151.5(4)
C(1)–C(7)	151.4(4)		
C(7)–S(1)–C(8)	93.5(1)	C(8)–N(1)–C(9)	116.3(2)
C(8)–N(1)–C(10)	123.1(2)	S(1)–C(7)–C(1)	115.3(2)
S(1)–C(7)–C(9)	106.3(2)	C(1)–C(7)–C(9)	112.6(2)
S(1)–C(8)–S(2)	121.3(2)	S(1)–C(8)–N(1)	111.4(2)
S(2)–C(8)–N(1)	127.3(2)	O(1)–C(9)–N(1)	123.6(3)
O(1)–C(9)–C(7)	124.3(3)	N(1)–C(9)–C(7)	112.1(3)
N(1)–C(10)–C(11)	116.3(3)		

NOE enhancements

These were studied as ^{1}H difference NOEs with a Bruker Model ARX 500 MHz NMR spectrometer, using the steady state-saturation method with [^{2}H]chloroform as solvent. For NOE-difference measurements the saturation irradiation was applied for 20 s and followed by a 90° excitation pulse before the aquisition time of 4 s.

Results and discussion

Crystal structure of 4

The crystal of **4** was found to consist of the *syn* form and the same form is therefore likely to dominate in solution. Two methyl groups from the *tert*-butyl group point in the direction of the phenyl group (Fig. 2). The projection of the latter group on the thiazole ring falls closer to S(1) than to C(9), the C(6)–C(1)–C(7)–C(9) dihedral angle (in the *S* enantiomer) being −75.8°. The C(6)–C(12) and C(6)–C(14) distances are 483 and 538 pm, and the shortest H ··· H distances Bu^t ··· Ph [H(61) ··· H(121) and H(61) ··· H(141)] are 307 and 330 pm, respectively. The geometry of the thioxothiazolone ring and the lengths of the bonds to the attached atoms agree well with those reported for 3-isopropyl-5-phenylrhodanine[20] and for 5-methylrhodanine.[21] Selected bond lengths and angles for **4** are found in Table 3.

Molecular mechanics calculations

The first calculations were performed with **4**, using the crystal structure as a starting geometry. The *syn* and *anti* forms were energy minimized, starting from several different geometries. The energy of the most stable *syn* form is calculated to be 2.6 kJ

Table 4 Calculated energies (kJ mol^{-1}) and typical dihedral angles for the lowest-energy *syn* and *anti* forms of **1**–**4** (*S* enantiomers)

Compound	Form	E_{ster}	$\Delta E°_{syn\text{-}anti}$ [a]	$\theta_1/°$ [b]	$\theta_2/°$ [c]	$\theta_3/°$ [d]
1	*anti*	9.18		−99.3	61.0	−176.2
	anti	9.72		−76.7	−60.9	176.1
	anti	13.32		−88.0	62.4	−62.9
	syn	8.54	−0.64	98.7	−60.3	176.8
	syn	9.36		76.0	60.4	−176.6
	syn	12.87		87.5	−62.9	62.4
2	*anti*	15.42		−88.4	60.9	−179.9
	syn	13.74	−1.67	88.2	−61.0	179.8
	syn	14.98		87.6	−61.8	179.1
3	*anti*	5.75		−99.1	60.7	−176.4
	anti	6.29		−76.9	−59.8	177.3
	anti	9.69		−88.6	62.3	−63.0
	syn	4.82	−0.94	75.3	−60.7	176.3
	syn	4.93		75.1	60.0	177.0
	syn	8.70		86.8	−63.8	61.6
4	*anti*	6.31		−87.6	61.3	−179.6
	anti	11.77		−88.0	61.9	−179.0
	syn	3.71	−2.60	87.9	−63.5	179.1
	syn	10.92		87.4	−61.9	177.5

[a] Energy difference between most stable *syn* and *anti* forms. [b] Dihedral angle C(9)–N(1)–C(10)–C(11). [c] Dihedral angle N(1)–C(10)–C(11)–C(12). [d] Dihedral angle N(1)–C(10)–C(11)–C(13).

Table 5 Rotational barriers (kJ mol^{-1}) for **1**–**4** calculated by MM2(91)

Compound	$\Delta E^{\ddagger}_{syn\rightarrow anti}$ [a]	$\Delta E^{\ddagger}_{anti\rightarrow syn}$ [b]
1	30.5	37.2
2	35.9	57.5
3	31.5	37.4
4	42.2	57.8

[a] Past the C=O group. [b] Past the C=S group.

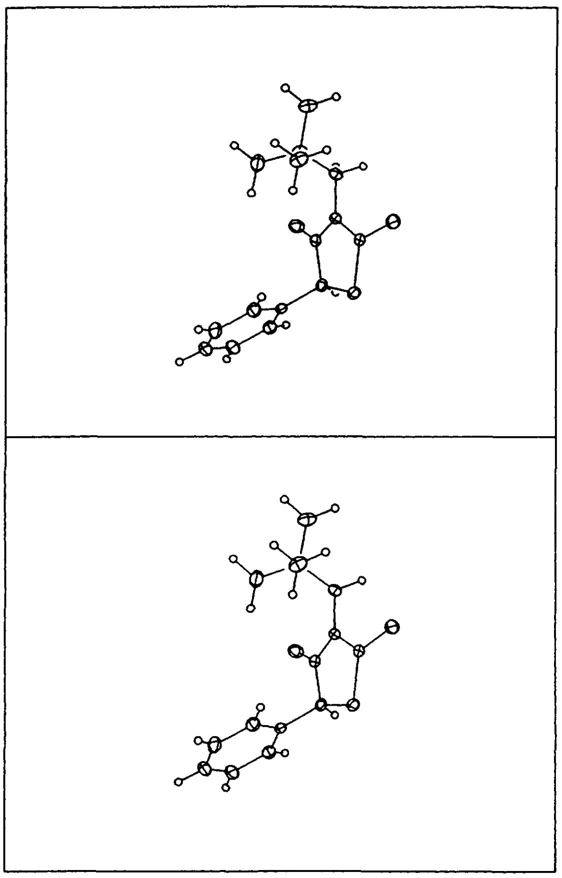


Fig. 2 Stereopicture of the crystal structure of **4**

mol^{-1} lower than that of the corresponding *anti* form (Table 4), in excellent agreement with the experimental result (assuming that the *syn* form is really the most stable one in solution). The difference is almost entirely due to a larger contribution of attractive van der Waals energy in the *syn* than in the *anti* form, −15.56 compared to −12.96 kJ mol^{-1}. A considerable portion of the attractive interaction in the *syn* form is calculated to originate in interactions between C(6) and H(61) in the phenyl ring on one side and H(121), H(141), C(12), and C(14) in the *tert*-butyl group on the other (Fig. 1).

The MM2(91) calculations gave a geometry for the *syn* form which showed good agreement with the crystal geometry with the exception of the phenyl group, which showed a C(6)–C(1)–C(7)–C(9) dihedral angle of −47.8°. This leads to a shortening of the H(61) ··· H(121) and H(61) ··· H(141) distances to 244 and 276 pm respectively, the corresponding C(6) ··· C(12) and C(6) ··· C(14) distances being 428 and 478 pm. The barrier to rotation of the phenyl group is quite low, 24 kJ mol^{-1} according to MM2(91), and the difference between calculated and the crystal geometry may be ascribed to crystal forces in the latter case.

The calculations predict the lowest-energy *syn* forms to be more stable than the *anti* forms also for **1**, **2** and **3** (Table 4). The value for **3** agrees reasonably well with the experimental one provided the major form is *syn*, but the values for **1** and **2** are somewhat too large. The subdivision of the steric energies from the MM2 calculations shows that in all cases the attractive van der Waals energy is larger in the *syn* than in the *anti* forms, but unlike what was found for **4**, the other contributions also show differences. Three energy minima were found for the 3-isobutyl compounds **1** and **3**, corresponding to the three possible staggered orientations of the Pr^i group with respect to the CH$_2$N group. The forms with one methyl group *anti* to the C(10)–N bond (θ_2 *ca.* ±60°, θ_3 *ca.* 180°, Fig. 3) were considerably more stable than the forms with two *gauche* oriented methyl groups (θ_2 and θ_3 *ca.* ±60°).

The barriers to rotation of the 3-CH$_2$R groups were calculated by driving the C(9)–N(1)–C(10)–C(11) dihedral angle from the *syn* to the *anti* form and *vice versa*. As expected, the route involving passage of the R group past the thiocarbonyl group requires a considerably higher energy than the passage past the carbonyl group. The lower calculated *syn* ⟶ *anti* barriers (Table 5) agree well with the experimental ones (Table 1).

NOE enhancements

Irradiation of the *tert*-butyl resonance gave a 0.88% enhancement of the aromatic proton resonance (total *tert*-butyl intensity = 1.0), and irradiation of the 5-H resonance gave a 10.5% enhancement of the aromatic proton resonance. The first result undoubtedly points to a considerable proximity of *tert*-butyl and aromatic protons, as required for the *syn* form. However, at 300 K the major and minor forms exist in a ratio of 7:3 in dichlorofluoromethane ($\Delta S°$ assumed to be near zero), and the ratio in CDCl$_3$ solution can be expected to be very similar. After consideration of the uncertainty about the barriers to rotation of the phenyl and *tert*-butyl groups, the conclusion was reached that the NOE enhancement is not strong enough to exclude that the minor forms is responsible for the effect.

Summing up, the results of the MM2 calculations and the crystal structure support the conclusion that the *syn* form of **4** is

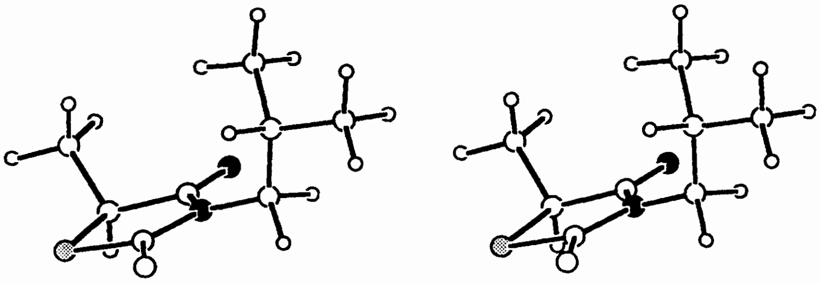


Fig. 3 Stereostructure of the most stable conformer of the *syn* form of (*S*)-**1**

the most stable one, while the NOE results are more ambiguous with respect to the equilibrium in solution.

Acknowledgements

Financial support of this investigation by the Swedish Natural Science Research Council (to J. S.) and by the National Science Council of the Republic of China (to S.-L. W.) is gratefully acknowledged. We are grateful to Dr Karl-Erik Bergquist for help with the NOE spectra.

References

1 I. Pettersson, K. Rang and J. Sandström, *Acta Chem. Scand., Ser. B*, 1986, **40**, 751.
2 Z. Aksaç, E. Pinar and S. Içli, *Org. Magn. Reson.*, 1983, **21**, 548.
3 I. Dogan, N. Pustet and A. Mannschreck, *J. Chem. Soc., Perkin Trans. 2*, 1993, 1557.
4 U. Berg and J. Sandström, *Adv. Phys. Org. Chem.*, 1989, **25**, 1 (see, in particular, p. 56).
5 R. E. Carter, B. Nilsson and K. Olsson, *J. Am. Chem. Soc.*, 1975, **97**, 6155.
6 R. E. Carter and P. Stilbs, *J. Am. Chem. Soc.*, 1976, **98**, 7515.
7 B. Aurivillius and R. E. Carter, *J. Chem. Soc., Perkin Trans. 2*, 1978, 1033.
8 M. H. Lyttle, A. Streitwieser, Jr. and R. Q. Kluttz, *J. Am. Chem. Soc.*, 1981, **103**, 3232.
9 N. L. Allinger, M. Frierson and F. A. Van Catledge, *J. Am. Chem. Soc.*, 1982, **104**, 4592.
10 C. Tosi, *J. Comput. Chem.*, 1984, **5**, 248.
11 J. E. Anderson and P. A. Kirsch, *J. Chem. Soc., Perkin Trans. 2*, 1992, 1951.
12 U. Berg and I. Pettersson, *J. Org. Chem.*, 1987, **52**, 5177.
13 *International Tables for X-Ray Crystallography*, Kynoch Press, Birmingham, 1974, vol. 4 (present distributor Kluwer Academic Publishers, Dordrecht).
14 G. M. Sheldrick, SHELXTL-Plus Crystallographic System, version 4. Siemens Analytical International Inc., Madison, WI, USA, 1990.
15 The program is available from Intstar Software, IDEON Research Park, S-223 70 Lund, Sweden.
16 U. Burkert and N. L. Allinger, *Molecular Mechanics*, ACS Monograph 177, Am. Chem. Soc., Washington, DC, 1982.
17 The program is available from the Quantum Chemistry Program Exchange (University of Indiana, Bloomington, IN 47405).
18 S. Karlsson, T. Liljefors and J. Sandström, *Acta Chem. Scand., Ser. B*, 1977, **31**, 399.
19 I. Pettersson and J. Sandström, *Acta Chem. Scand., Ser. B*, 1984, **38**, 397.
20 K. Rang, J. Sandström, L. Thell and Q. Yang, *Acta Chem. Scand., Ser. B*, 1985, **39**, 123.
21 G. Gattow, G. Kiel and W. Rach, *Z. Anorg. Allg. Chem.*, 1983, **506**, 145.

Paper 4/07922A
Received 30*th December* 1994
Accepted 23*rd March* 1995