Conformational Studies of 3-Alkylrhodanines and an Analogous Mesoionic Compound

Ingrid Pettersson, Knut Rang and Jan Sandström*

Division of Organic Chemistry 3, Chemical Center, University of Lund, P.O. Box 124, S-221 00 Lund, Sweden

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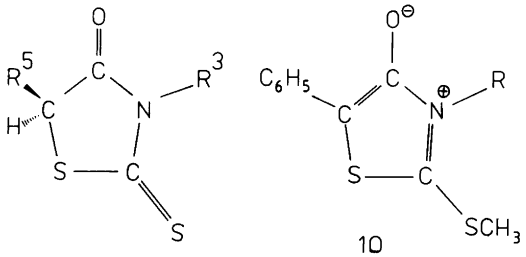
The conformations and barriers to conformational interchange of isopropyl, neopentyl, and isobutyl groups attached to position 3 of 1,3-thiazolidin-4-one-2-thiones (rhodanines) have been studied by temperature-dependent ^{1}H NMR spectra. The iPr groups take up a bisected conformation with the Me groups directed toward the carbonyl group (*A*); the CH_2tBu and CH_2iPr groups take up perpendicular orientations. Diastereomeric forms of the latter (*C* and *D*) result when the rhodanine ring is monosubstituted in position 5. When R^5 = Me, these forms have nearly the same energy, but when R^5 = Ph, the rotamer with the tBu or iPr group on the opposite side of the ring plane (*C*) is favoured. The barriers to rotation of the CH_2tBu group are similar in all compounds, ~40 kJ/mol, although slightly higher when R^5 = Ph; those for the CH_2iPr groups are ~30 kJ/mol. The barrier in an analogous mesoionic 3-neopentyl compound is 45 kJ/mol.

In conjunction with a current investigation of chromatographic enantiomer resolution and chiroptical properties of 3,5-disubstituted rhodanines (thiazolidin-4-one-2-thiones),[1] we have studied conformations and barriers to conformational interchange in 3-isopropyl-, 3-isobutyl-, and 3-neopentylrhodanines without a substituent and with a methyl or phenyl group in position 5 (*1–9*, Scheme 1). In these compounds, orientation and barrier to rotation of the 3-substituent are determined by the sizes and orientations of the flanking C=S and C=O groups, and in order to study the influence of a perturbation of this environment, a mesoionic analogue (*10*) of 3-neopentyl-5-phenylrhodanine (*6*) was included in the investigation. In *10*, the C^2-N^3 bond is shortened and the N^3-C^4 bond is lengthened with respect to the corresponding bonds in *9* (Scheme 2).[2,3] In addition, the effective sizes of S and O can be expected to be different in *9* and *10*.

Results and Discussion

The ^{1}H NMR spectra of the 3-isopropyl derivatives *1–3* (Table 1) show no temperature dependence. The 3-iPr resonance of the 5-H_2 compound *1* consist of a doublet and septet, whereas the chiral compounds *2* and *3* display two equally intense doublets and one septet, due to the presence of diastereotopic methyl groups. In an X-ray crystallographic study of *3*,[3] the 3-iPr group was found to take up an orientation with the CH_3-C-CH_3 angle bisected by the rhodanine plane, and with the methine proton directed towards the thiocarbonyl group (*A*, Scheme 3). This is the expected favoured orientation also in

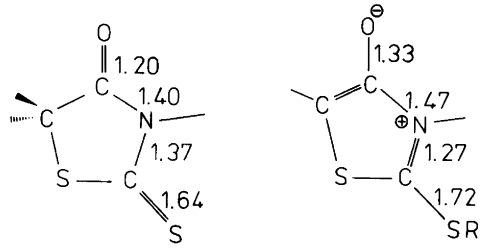


10

R³ \ R⁵	H	Me	Ph
iPr	*1*	*2*	*3*
CH_2tBu	*4*	*5*	*6*
iBu	*7*	*8*	*9*

Scheme 1

*To whom correspondence should be addressed.



Scheme 2.

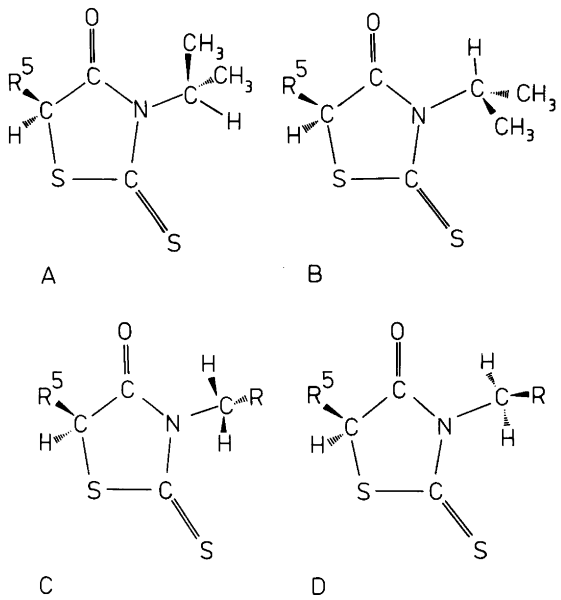
solution,[4–6] and the absence of selective broadening in the low temperature spectrum indicates a very low proportion of the other expected minimum energy conformation (*B*). Analysis of the low-temperature spectra of *5* and *6* (see below) indicate a shift difference between the methine proton resonances in *A* and *B* ≥ 0.5–0.6 ppm, and consequently the proportion of *B* is estimated to be <0.5 % at ~−50 °C, assuming that an exchange broadening of 0.5 Hz would be readily observable.[7]

The 3-neopentyl and 3-isobutyl groups in compounds *4–10* should take up perpendicular orientations as in *C* and *D* (Scheme 3).[5,8,9] For the 5−H_2 compounds *4* and *7* and for *10*, *C* and *D* form a pair of enantiomers, but for *5*, *6*, *8*, and *9* they are diastereomers. Thus, the 3−CH_2 resonance of the 3-neopentyl compound *4* is a singlet at ambient temperature which broadens at lower temperature and appears below −82 °C as an *AB* system. On slow rotation of the 3-substituent, the 5 protons are also diastereotopic, and their resonance appears as an *AB* quartet with a smaller shift difference. A free energy barrier ($\Delta G^{\ddagger}_{rot}$) of

Table 1. ^{1}H NMR spectra of compounds *1–10* (100 MHz) in $CHCl_2F$, except when otherwise stated.

Compound	*T*/°C	R^3	R^5
1[a]	−75	1.43 (6H, d, *J* 6.9 Hz), 5.21 (1H, sept, *J* 6.9 Hz)	3.93 (2H, s)
2[a]	+25	1.46 (3H, d. *J* 7.0 Hz), 1.48 (3H, d, *J* 7.0 Hz), 5.26 (1H, sept, *J* 7.0 Hz)	1.65 (3H, d, *J* 7.3 Hz), 4.03 (1H, q, *J* 7.3 Hz)
3[a]	+25	1.43 (3H, d, *J* 7.0 Hz), 1.48 (3H, d, *J* 7.0 Hz), 5.25 (1H, sept, *J* 7.0 Hz)	5.07 (1H, s), 7.31 (5H, m)
4	+25	0.98 (9H, s),3.93 (2H, s)	3.98 (2H, s)
	−100	3.64, 4.17 (2H, *AB*, J_{AB} 13.4 Hz)	3.91, 4.11 (2H, *AB*, J_{AB} 19.0 Hz)
5	+25	0.95 (9H, s),3.99 (2H, s)	1.65 (3H, d, *J* 7.4 Hz), 4.13 (1H, q, *J* 7.4 Hz)
	−103	3.64, 4,23 (*AB*, J_{AB} 13.3 Hz) 3.69, 4,19 (*AB*, J_{AB} 13.3 Hz)	1.58 (d, *J* 7.4 Hz), 1.72 (d, 7.4 Hz)
6	+25	0.95 (9H, s),3.92, 4.06 (2H, *AB*, J_{AB} 13.4 Hz)	5.17 (1H, s), 7.3–7.4 (5H, m)
	−107	3.69, 4,26 (*AB*, J_{AB} 13.2 Hz)[b] 3.69, 4.30 (*AB*, J_{AB} *ca.* 13 Hz)	5.13, 5.42 (singlets, 4.6:1)
7	+25	0.88 (6H, d, *J* 6.9 Hz), 2.25 (1H, m), 3.82 (2H, d, *J* 7.1 Hz)	3.89 (2H, s)
	−140	broad, $\Delta\delta_{AB}$ ca. 0.6 ppm	
8	+25	0.90 (3H, d, *J* 6.9 Hz), 0.98 (3H, d, *J* 6.9 Hz), 2.28 (1H, m), 3.78 (2H, d, *J* 7.5 Hz)	1.65 (3H, d, *J* 7.2 Hz), 4.13 (1H, q, *J* 7.2 Hz)
	−130	broad, $\Delta\delta_{AB}$ *ca.* 0.6 ppm	
9	−53	0.86 (3H, d, *J* 7.0 Hz), 0.93 (3H, d, *J* 7.0 Hz), 2.29 (1H, m), 3.83, 3.91 (2H, AB part of ABX, J_{AB} 12.9, J_{AX},J_{BX} 7.8 Hz)	5.23 (1H, s), 7.3–7.4 (5H, m)
	−125	broad, $\Delta\delta_{AB}$ *ca.* 0.6 ppm	
10	+25	1.04 (9H, s), 3.92 (2H, s)	7.3 (5H, m)
	−94	3.41, 4.33 (2H, *AB*, J_{AB} 13.0 Hz)	

[a]Solvent CD_2Cl_2. [b]Major rotamer.



Scheme 3.

38 ± 1 kJ/mol to rotation of the 3-neopentyl group is found by band shape analysis of the exchange-broadened spectra.

For the 3-isobutyl group in *7*, $\Delta G^{\ddagger}_{rot}$ is lower, but below −121 C°, the iBu CH_2 protons give a very broad *AB(X)* system, giving $\Delta G^{\ddagger}_{rot}$ 31 ± 2 kJ/mol. No splitting of the 5−H resonance is observed.

The 3−CH_2 protons in *5* are diastereotopic also when the rotation of the 3-substituent is fast on the NMR time scale, but due to accidental equivalence, the resonance appears as a singlet at ambient temperature. Below −79 °C, two *AB* spectra of nearly equal intensity appear, and the 5−Me resonance changes from a doublet to a doublet of doublets, also with equal intensity. Evidently, the two diastereomeric rotamers *C* and *D* in this case have very equal energies. This is also the reason for the equivalence of the 3−CH_2 protons under conditions of fast exchange, when the weighted average environments of H_a and H_b are nearly equal. Bandshape analysis of the 5−Me resonance gave $\Delta G^{\ddagger}_{rot}$ 39 ± 1 kJ/mol.

The spectrum of the 3-isobutyl analogue *8* displays a doublet for the 3−CH_2 protons at ambient temperature (accidental equivalence), which broadens strongly at lower temperatures. At slow exchange, two overlapping *AB* parts of *ABX* spectra should result, but the barely resolved bands appearing below −130 °C do not permit a detailed analysis. Assuming the same chemical shifts as for *5*, we could calculate $\Delta G^{\ddagger}_{rot}$ = 30 ± 2 kJ/mol.

The 3-neopentyl-5-phenyl compound *6* behaves differently. At ambient temperature, the 3−CH_2 protons give an *AB* spectrum with an *AB* shift difference of 0.14 ppm, which changes below −80 C° to two overlapping *AB* spectra with much larger and quite similar chemical shift differences (0.57 and 0.61 ppm) but with an intensity ratio 4.6:1 at −107 °C. The 5−H resonance similarly changes from a singlet to a doublet with the same intensity ratio. In this system, the diastereomers *C* and *D* have different energies (ΔG° = −2.1 kJ/mol), and $\Delta G^{\ddagger}_{rot}$ (maj → min) = 42 ± 1 kJ/mol. The energy difference and also the higher barrier must be related to steric interaction between the phenyl ring and the 3-neopentyl group. According to the X-ray crystallographic study of *3*,[3] the plane of the phenyl ring is nearly orthogonal to that of the rhodanine ring, and a model shows that the nearest ortho proton in this arrangement approaches the tBu group in the *D* form of *6* within repulsive distance. This would indicate that the *C* form is the favoured rotamer.

The 3−CH_2 resonance of the 3−iBu analogue *9* appears as the *AB* part of an *ABX* spectrum with an *AB* shift difference of 0.08 ppm at −53 °C. Assuming that the *C* form is the dominating one and that the *AB* shifts for the *C* and *D* forms are the same as for *6* and independent of the temperature, we can calculate ΔG° (*C* → *D*) = 0.4 kJ/mol. At lower temperatures, the CH_2 resonance broadens and appeared below −120 °C as a partly resolved set of two overlapping *AB* spectra with an *AB* shift of the order of 0.6 ppm. The effect of the *AX* and *BX* couplings cannot be observed, but assuming the same parameters as at higher temperatures, $\Delta G^{\ddagger}_{rot}$ (*C* → *D*) = 30 ± 2 kJ/mol can be calculated.

The 3−CH_2 proton resonance of the mesoionic compound *10* is a singlet at ambient temperature but changes below −46 °C to an *AB* system with a shift difference of 0.92 ppm, giving $\Delta G^{\ddagger}_{rot}$ 45 ± 1 kJ/mol. This barrier is distinctly higher than those of the other 3-neopentyl compounds, indicating a more congested environment in the transition state. In the rhodanines, the iPr and tBu groups of the 3-substituent must pass on the

side of the smaller of the flanking groups, the carbonyl group, during the $C \rightleftharpoons D$ exchange. Therefore it is unexpected that the barrier should be raised when the critical N3–C4 bond is lengthened, unless this effect is compensated for by increased van der Waals radius of the oxygen atom due to the enhanced negative charge on this atom in the mesoionic compound. The shortened C2–N3 bond contributes to the increased barrier by raising the energy of interaction between the 3–CH_2 protons and the sulfur atom in the transition state, but this effect is expected to be smaller.

Conclusion

This study shows that secondary alkyl groups, with the isopropyl group as model, take up one strongly preferred bisected orientation when attached to the nitrogen atom in rhodanines. Primary alkyl groups, exemplified by neopentyl and isobutyl groups, take up perpendicular orientations. In the 5-phenyl compounds, the diastereomeric rotamers have different energies, whereas the interaction with the 5-methyl group seems to be negligible. The effects of these conformations on the CD spectra of the chiral rhodanines will be discussed in a forthcoming publication.[1]

Experimental

Neopentylammonium N-*neopentyldithiocarbamate* (11) and its isobutyl analogue (12) were prepared in yields >90 % by reaction between the appropriate amines (2 mol) and CS_2 (1 mol) in dry ether as described for the isopropyl analogue.[3] The identities of the salts were ascertained by their ^{1}H NMR spectra (60 MHz, $CDCl_3$). *11*: δ 0.97 (9H, s), 1.06 (9H, s), 2.87 (2H, s), 3.45 (2H, broad d, J ~5 Hz), 6.70 (3H, s), 7.7 (1H, broad). *12*: δ 0.95 (6H, d, J 7.0 Hz), 1.02 (6H, d, J 7.0 Hz), 1.98 (2H, m), 2.88 (2H, d, J 7.5 Hz), 3.46 (2H, m, broad), 7.7 (4H, broad).

Several different methods were tried to prepare the rhodanines *1–9*; those presented here have been selected mainly on the basis of yield and purity of the product. The identity and purity of the products were checked by MS and ^{1}H NMR spectra (Table).

3-Isopropylthiazolidin-4-on-2-thione (1). Bromoacetic acid (0.005 mol) was dissolved with sodium bicarbonate (0.0055 mol) in water (5 ml). Solid isopropylammonium *N*-isopropyldithiocarbamate[3] (0.005 mol) was added with cooling (0 °C) and stirring. After dissolution, the temperature was allowed to rise to +25 °C. After 3 h, the solution was added with stirring to warm (+75 °C) 6 N HCl (15 ml), and the mixture briefly heated to 90 °C.[11] After cooling, extraction with chloroform gave nearly pure *1* in 73 % yield; colourless needle-shaped prisms, m.p. 63–64 °C after recrystallization from absolute ethanol. MS: 175 (M, 21), 100 (72), 86 (14), 60 (25), 47 (22), 46 (68), 45 (38), 43 (74), 42 (73), 41 (100), 39 (64).

3-Isopropyl-5-methylthiazolidin-4-on-2-thione (2). Ethyl 2-bromopropanoate (0.005 mol) in absolute ethanol (4 ml) was added to a solution of isopropylammonium *N*-isopropyldithiocarbamate (0.005 mol) in absolute ethanol (25 ml). The progress of the reaction was followed by monitoring the UV absorption of the diminishing dithiocarbamate bands at 255 and 275 nm and the increasing rhodanine bands at 265 and 300 nm. After 48 h, the reaction was complete; evaporation gave a 75 % yield of *2*, m.p. 86–87 °C after recrystallization from absolute ethanol (colourless needle-shaped prisms). MS: 189 (M, 22), 100 (100), 86 (17), 61 (31), 60 (63), 59 (33), 45 (29), 43 (56), 42 (32), 41 (87), 39 (49).

The preparation of *3* in 30 % yield is described in Ref. 3; however, with the method described above for *2*, the yield of *3* was nearly quantitative.

3-Neopentylthiazolidin-4-on-2-thione (4). Sodium bromoacetate (0.005 mol) and neopentylammonium *N*-neopentyldithiocarbamate (0.005 mol) were reacted in 85 % aqueous methanol (35 ml) for 3 h, followed by acidification with 5 N HCl (1.7 ml). Evaporation of the methanol was followed by extraction with ether (3×20 ml). Evaporation of the dried ether extract gave a non-crystalline product consisting, according to the NMR spectrum, of the uncyclized product, carboxymethyl *N*-neopentyldithiocarbamate. Heating with acetic anhydride (5 ml) at 70 ± 5° for 3 h affected cyclization, and complete evaporation left a colourless liquid; yield 30 % after flash chromatography with toluene as eluent. MS: 203 (M, 13), 105 (16), 74 (16), 69 (13), 57 (92), 55 (33), 46 (33), 45 (25), 43 (42), 42 (45), 41 (100), 39 (49).

3-Neopentyl-5-methylthiazolidin-4-on-2-thione (5). Preparation as described for *1* gave a liquid product in 59 % yield after flash chromatography on silica with toluene/chloroform (96:4) as eluent. MS: 217 (M, 13), 161 (21), 72 (23), 61 (22), 60 (55), 59 (20), 57 (90), 56 (34), 55 (48), 45 (22), 43 (34), 41 (100), 39 (44).

3-Neopentyl-5-phenylthiazolidin-4-on-2-thione (6) was prepared as *4*. In this case also, cyclization at room temperature failed, and the isolated intermediate was reacted with dicyclohexyl carbodiimide in chloroform, finally under reflux for 23 h. Evaporation and recrystallization from absolute ethanol gave *6* in 58 % yield as colourless prisms, m.p. 135–136 °C. MS: 279 (M, 11), 122 (33), 121 (25), 91 (26), 90 (43), 57 (80), 55 (30), 45 (34), 43 (44), 41 (100), 39 (44).

3-Isobutylthiazolidin-4-on-2-thione (7) was obtained as a colourless liquid in quantitative yield by the same method as was used for *2*. MS: 189 (M, 15), 134 (65), 106 (14), 72 (24), 60 (26), 56 (47), 55 (25), 46 (42), 45 (35), 43 (26), 42 (44), 41 (100), 39 (63).

3-Isobutyl-5-methylthiazolidin-4-on-2-thione (8) was obtained as a colourless liquid in 54 % yield, using the same method as for *2*. MS: 203 (M, 7), 148 (48), 72 (30), 61 (70), 60 (46), 59 (25), 57 (20), 56 (66), 55 (53), 45 (34), 43 (31), 41 (100), 39 (57).

3-Isobutyl-5-phenylthiazolidin-4-on-2-thione (9) was obtained as *2* in 77 % yield as colourless prisms, m.p. 99–100 °C after recrystallization from absolute ethanol. MS: 265 (M, 8), 210 (13), 134 (13), 121 (15), 91 (100), 90 (29), 77 (11), 72 (10), 63 (10), 55 (17), 51 (10), 45 (29), 41 (57), 39 (37).

Anhydro-2-methylthio-3-neopentyl-4-hydroxy-5-phenylthiazoline hydroxide (10). 3-Neopentyl-5-phenylrhodanine (*6*, 0.0025 mol) and methyl iodide (0.003 mol) were added to *N* sodium ethoxide in absolute ethanol (2.5 ml) at −15 °C. The orange solution was kept at −18 °C for 72 h then evaporated. The red semisolid residue was subjected to flash chromatography on silica with chloroform/ethyl acetate (88:12) as eluent and a solid product was obtained in 74 % yield; dark yellow prisms, m.p. 103–105 °C after recrystallization from absolute ethanol. MS: 293 (M, 17), 223 (29), 150 (14), 121 (50), 77 (19), 74 (18), 71 (67), 55 (14), 43 (100), 41 (39), 39 (17).

The mass spectra were recorded with a Finnigan model 4021 mass spectrometer. The ^{1}H NMR spectra were recorded with a Jeol MH−100 spectrometer, with the samples of compounds *4–10* ~0.6 M in dichlorofluoromethane and with TMS added to provide the internal lock. The samples were degassed by several cycles of freezing and thawing under high vacuum before being sealed off. The temperatures were measured as previously described.[12] The rate constants, k_{rot}, for rotation of the 3-alkyl groups in compounds *4–10* were evaluated by fitting calculated band shapes to the experimental ones in the regions of the largest band broadening. The following exchange systems were employed for band shape calculations. For *4*, both the 3−CH_2 and 5−CH_2 groups give $AB \rightleftharpoons BA$ systems, as does the 3−CH_2 group for *10*. The 3−CH_2 protons in *5* and *6* participate in $AB \rightleftharpoons CD$ exchanges, but k_{rot} for *5* was evaluated from the $AX \rightleftharpoons BY$ system displayed by the 5-methyl protons, and for *6* from the $A \rightleftharpoons B$ system displayed by the proton in position 5. The 3−CH_2 protons in *7* participate in $ABX \rightleftharpoons BAX$ systems, but the spectrum at −121 °C was not sufficiently resolved to allow the evaluation of the spectral parameters; at lower temperature, general broadening occured. The exchange-broadened spectra of the 3−CH_2 protons were therefore calculated assuming the same $\Delta\nu_{AB}$ and J_{AB} as for *4* and $J_{AX} = J_{BX} = 7.8$ Hz as for *9*. With these parameters a reasonable fit could be obtained. The 3−CH_2 protons of *8* and *9* participate in $ABX \rightleftharpoons CDY$ systems and were treated as such, assuming $J_{AX} = J_{BX} = J_{AY} = J_{BY} = 7.8$ Hz.

The evaluation of T_2 values was performed as previously described.[13] The free energy of activation, $\Delta G^{\ddagger}_{rot}$, was calculated using the Eyring eqn.[14] in the form (1). The error limits for the 3-neopentyl group rotational barriers in *4–6* and *10* were mainly based on the estimated maximum

$$\Delta G^{\ddagger}_{rot} = RT \ln (k_B T/h\, k_{rot}) \qquad (1)$$

error in the temperatures, whereas the error limits for the 3-isobutyl group rotational barriers in *7–9* were also based on estimates of maximum errors in the NMR parameters.

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References

1. Isaksson, R., Rang, K. and Sandström, J. *To be published.*
2. Abrahamsson, S., Westerdahl, A., Isaksson, G. and Sandström, J. *Acta Chem. Scand. 21* (1967) 442.
3. Rang, K., Sandström, J., Thell, L. and Yang, Q. *Acta Chem. Scand. B 39* (1985) 123.
4. Roussel, C., Lidén, A., Chanon, M., Metzger, J. and Sandström, J. *J. Am. Chem. Soc. 98* (1976) 3847.
5. Berg, U., Liljefors, T., Roussel, C. and Sandström, J. *Acc. Chem. Res. 18* (1985) 80.
6. Djafri, A., Roussel, C. and Sandström, J. *J. Chem. Soc., Perkin Trans. 2* (1985) 273.
7. Sandström, J. *Dynamic NMR Spectroscopy,* Academic Press, London 1982, p. 81.
8. Roussel, C., Gallo, R., Metzger, J. and Sandström, J. *Org. Magn. Reson. 14* (1980) 120.
9. Roussel, C., Blaive, B., Gallo, R., Metzger, J. and Sandström, J. *Org. Magn. Reson. 14* (1980) 166.
10. Berg, U., Grimaud, M. and Sandström, J. *Nouv. J. Chim. 3* (1979) 175.
11. Gattow, G., Kiel, G. and Rach, W. *Z. Anorg. Allg. Chem. 506* (1983) 145.
12. Lidén, A., Roussel, C., Liljefors, T., Chanon, M., Carter, R. E., Metzger, J. and Sandström, J. *J. Am. Chem. Soc. 98* (1976) 2853.
13. Lidén, A. and Sandström, J. *Tetrahedron 27* (1971) 2893.
14. Glasstone, S., Laidler, K. J. and Eyring, H. *The Theory of Rate Processes,* McGraw-Hill, New York 1941, p. 195.

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