The Gear Effect. VI. Conformational Analysis of Molecules with Two Interacting Isopropyl Groups

A. Lidén,[1a] C. Roussel,[1b] T. Liljefors,[1a] M. Chanon,[1c] R. E. Carter,[1d] J. Metzger,[1b] and J. Sandström*[1a]

Contribution from the Divisions of Organic Chemistry 1 and 2, Chemical Center, University of Lund, S-220 07 Lund 7, Sweden, I.P.S.O.I., Université d'Aix-Marseille III, St. Jérome, 13013 Marseille, France, and Ecole Normale Supérieure, Le Bardo, Tunis, Tunisia. Received July 7, 1975

Abstract: The conformations and barriers to conformational interchange of the isopropyl groups in a series of *N,N*-diisopropylamides and -thioamides, and also in some 3,4-diisopropylthiazole derivatives, have been studied by DNMR, by NOE measurements, and by molecular-mechanics calculations. In most cases two or three stable conformers are observed, and their populations and barriers to interconversion show a rational dependence on the sizes of the surrounding atoms and groups. The calculated conformational energies agree reasonably well with the observed populations, if due consideration is given to an experimentally observable solvent effect. The calculations also indicate that the rotation of the isopropyl groups is nonsynchronous.

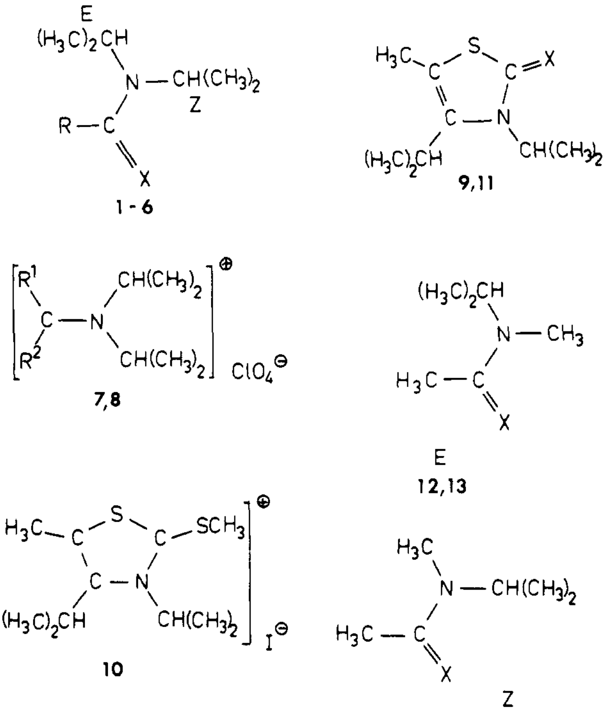
In a series of papers,[2] studies of the conformational interplay between isopropyl groups in the 3 and 4 positions of Δ^4-thiazoline-2-thiones and neighboring atoms and groups have been reported, and in particular the interaction between two adjacent isopropyl groups has been subjected to scrutiny.[2e,f] Similar interactions occur in *N,N*-diisopropylamides and -thioamides, which have been studied by several other research groups.[3] In most of the recent investigations,[3d-g] the results have been interpreted in terms of the model introduced by Siddall and Stewart.[3b] According to this model, the isopropyl groups are regarded as interlocking tetrahedral rotors in synchronous rotation against a trigonal frame (the amide plane). The minimum energy conformations are determined by "the need to exclude as much as possible from this crowded plane".[3c] This model has seemed to us somewhat oversimplified, and one of the goals of the present work is to provide a more flexible model, which takes all interactions in the molecules into account. Furthermore, by work at lower temperatures, we have attempted a more complete description of the conformations of the molecules studied and also the clarification of an obscure point in the original work of Siddall and Stewart[3b] concerning the interpretation of the temperature-dependent spectrum of *N,N*-diisopropylacetamide. The aspect of hindered rotation about the (thio)amide C–N bond is well covered in previous works,[3b-e] and it is not considered here. The systems (**1–13**) which have been investigated are shown in Scheme I. The salts **7** and **8** bear some resemblance to *N,N*-diisopropyldithiocarbamate metal complexes, which have been subjected to DNMR studies.[3g,4]

To aid the assignments of NMR signals to specific conformations and to provide a basis for the suggested conformations, molecular-mechanics calculations have been performed on systems **1–6**. In **1** and **2** nuclear Overhauser effect (NOE) measurements have provided support for conformational assignments.

Experimental Section

Materials. The amides and thioamides used in the present work were prepared mostly in agreement with previous descriptions: **1**,[5a] **2**,[5b] **3**,[3b] **4**,[3d] and **6**.[3g] The solid products (**2** and **4**) were purified by vacuum sublimation and the others by distillation through a Vigreux column. For **3** and **6**, in which rotamers with low populations have been observed, identical NMR spectra were obtained before and after a second distillation. Compound **5** was prepared by reaction of thiophosgene with 2 molar equiv of diisopropylamine in dry benzene, filtration, and addition of 1 equiv of sodium methoxide in absolute methanol. The product was purified by vacuum distillation.

Scheme I



On reaction of **6** with methyl iodide in dry acetone, the iodide corresponding to **7** precipitated. However, in dichlorofluoromethane solution **6** and methyl iodide were partly re-formed, and the iodide was converted by reaction with 70% aqueous perchloric acid in chloroform-acetone-ether to the stable perchlorate **7** (mp 181 °C). The perchlorate **8** (mp 143 °C) was prepared analogously by reaction of **4** with methyl-d_3 iodide, followed by perchloric acid.

For preparation of the thiazolinone **9**, carbon oxysulfide was treated with isopropylamine in absolute ethanol, and the precipitated thiocarbamate (mp 115 °C) was treated with 2-bromo-4-methyl-3-pentanone,[5c] as described for the analogous dithiocarbamates.[5d] The product was purified by chromatography with benzene on activated silica (mp 76 °C). The preparation of the thiazolinethione **11** has already been described,[2g] and the thiazolium iodide **10** was prepared from **11** by reaction with methyl iodide in a sealed tube without solvent (mp 124 °C). Compound **13** was prepared by reaction of **12**[5e] with phosphorus pentasulfide in refluxing toluene and was purified by high-vacuum distillation.

Dimethyl-d_6 ether was obtained in 70% yield by reaction of methanol-d_4 with 3 M % of deuteriosulfuric acid in a sealed Pyrex

Table I. Chemical Shifts[a] of Compounds **1–8**

Compd	Temp, °C	Rotamer **a**						Rotamer **b**					
		CH_3-*Z*	CH-*Z*	CH_3-*E*	CH-*E*	R (R_1)	p^b	CH_3-*Z*	CH-*Z*	CH_3-*E*	CH-*E*	R (R_1)	p^b
1[c]	−134	1.39	3.49	1.17	3.87	8.08	0.69	1.08	4.79	1.31	3.64	8.41	0.31
2	30							1.23	5.67	1.33	3.85	9.36	1.00
3	−70	1.40	3.36	1.20	3.95	2.07	0.96	1.11	5.03	*d*	*d*	2.15	0.04
4	−100	1.71	3.99	1.27	4.43	2.66	0.24	1.21	6.13	1.45	4.06	2.79	0.76
5	30							1.19	5.54	1.32	3.63	4.01	1.00
6[c]	−80	1.68	4.00	1.25	4.95	2.43	0.75	1.17	6.26	1.55	4.08	2.58	0.22
7	−70	1.48	5.41	1.70	4.51	2.89 2.96	1.00						
8	−80	1.65	~4.5	~1.4	4.77	2.74	0.16	1.44	4.82	1.61	4.42	2.84	0.84
				Rotamer **c**									
6[c]	−80	1.39	6.10	1.45	4.95	2.51	0.03						

[a] In ppm downfield from internal Me_4Si; in $CHCl_2F$ unless stated otherwise. [b] Fractional population. [c] In dimethyl-d_6 ether. [d] Not resolved.

tube at +200 °C for 12 h. It was purified by passage over potassium hydroxide pellets and molecular sieves.

NMR Spectra. All spectra were recorded on a Jeol Model JNM-MH-100 NMR spectrometer, equipped with a standard variable-temperature attachment (VT 3-C), except those used for the complete bandshape analysis on **4**, which were recorded on a Varian XL-100-15 spectrometer. The samples were 0.5–0.7 M with dichlorofluoromethane and in some cases dimethyl-d_6 ether as solvent, and they were carefully degassed by repeated freeze–thaw cycles under high vacuum before being sealed off. Me_4Si was added with the solvent to provide the internal lock signal. The temperatures were measured by monitoring the voltage of the internal thermocouple of the instrument and calibrating it at each measurement against an external thermocouple placed at the height of the receiver coil in a dummy tube containing 0.5 ml of dichlorofluoromethane.

The NOE measurements were performed by repeated integrations of the observed signal, while alternatingly placing the H_1 field in the irradiation position and well to the side of it.

The bandshape analyses were performed by visual curve fitting with spectra (for the two-site cases) calculated on a Hewlett-Packard Model 9820A desk calculator equipped with a Model 9862A plotter and for the three-site cases on a Univac 1108 computer with a Calcomp plotter. The theoretical spectra of single protons and single methyl groups were calculated using the simple McConnell equation for uncoupled two-site exchange.[6] The methyl spectra of the two isopropyl groups were obtained by superposition of four spectra of uncoupled two-site cases, with the same population and lifetime parameters. The effect of coupling was taken into account by suitable amplitude factors. The three-site cases were treated by solving three simultaneous Bloch equations with exchange among all three sites. In practice, all exchanges were of the type **a** $\rightleftharpoons$ **b** $\rightleftharpoons$ **c**, which made necessary the variation of only two lifetimes. The determination of T_2 was performed as described previously.[7] The error limits are given to the 95% confidence level.

Molecular Mechanics Calculations were performed using a program developed by Allinger and coworkers,[8a] employing their 1973 force field.[8b] This force field includes parameters for carbon and hydrogen,[8b] as well as parameters for carbonyl,[8c] alkyl-sulfur[8d] and alkyl-oxygen[8d] groups. The remaining parameters necessary for the calculations were roughly determined by fitting calculated geometries for various amides and thioamides to available experimental geometries. It was found that the relative conformational energies, calculated for the compounds studied in this work, were quite insensitive to moderate variations of the parameters for the amide and thioamide skeletons. A complete optimization of these parameters was therefore not attempted, and their values are not given here. Further refinement of parameters needed for general calculations on amides and thioamides is in progress, and a final set will be presented later. The reported energy minima have been obtained by allowing the molecules to relax from a considerable number of starting geometries. In all cases the energies of the different conformations are given relative to the energy of the most stable conformation.

Results

Most of the compounds show two or three rotamers with respect to the isopropyl groups. However, the NMR spectra in general give no certain indication about the conformation of these rotamers. The safest assignment is in the spectra of amides and thioamides, where a methine septet appears at very low field (δ 4.7–6.2). This must be the methine proton of the (*Z*)-isopropyl group pointing in the direction of the strongly deshielding (thio)carbonyl group.[9] It is also reasonable to assume that in the cations **7** and **8**, the low-field methine proton points in the direction of the C–S bond. Methine and methyls belonging to the same isopropyl group have in all cases been identified by double resonance, and for the amides and thioamides it is without exception observed that the methyl groups combined with the low-field methine always have their resonances at the highest field (δ 1.08–1.23, Table I). In the other rotamers, the (*Z*)-isopropyl methyl groups have their resonances at the lowest field (δ 1.39–1.71), and they are probably staggered with respect to the (thio)carbonyl group.

Without initially being more specific about the conformations, we denote the rotamer with low-field (*Z*)-methyl resonance **a** and the one with high-field (*Z*)-methyl resonance **b**.[10] As with the analogous 3-isopropyl thiazolinethiones,[2a,g] the **a**:**b** ratio decreases on going from a non-hydrogen bonding solvent to deuteriochloroform or dichlorofluoromethane. Thus rotamer **b** is stabilized relative to **a** by 0.5 kcal/mol in **1** and 0.3 kcal/mol in **6** on going from dimethyl-d_6 ether to dichlorofluoromethane as solvent.

Since the molecular-mechanics calculations refer to free molecules, one cannot expect exact agreement between calculated and experimental populations. Indeed, the results discussed above indicate that different rotamers may be quite differently stabilized by solvation. In general, rotamers of type **b** should receive an extra stabilization in solvents like deuteriochloroform and dichlorofluoromethane.

***N,N*-Diisopropylformamide** (**1**) has been studied in dichlorofluoromethane and dimethyl-d_6 ether solutions. Siddall and Stewart[3b] observed no effects of hindered rotation of the isopropyl groups down to −60 °C. Already at this temperature, however, the 100-MHz spectrum shows a broadening of the low-field methine septet [δ 4.14 in $CHCl_2F$,

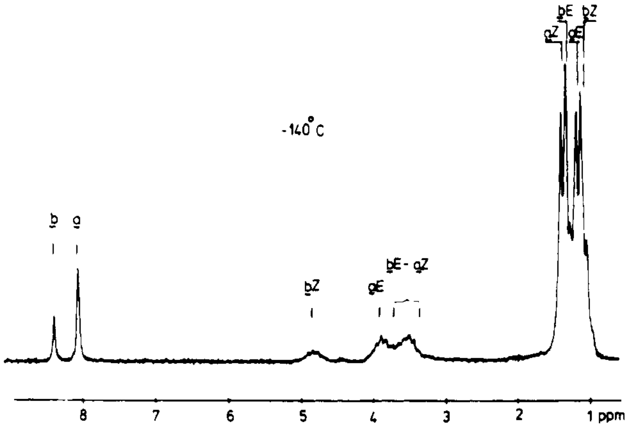


Figure 1. NMR spectrum of **1** in dimethyl-d_6 ether.

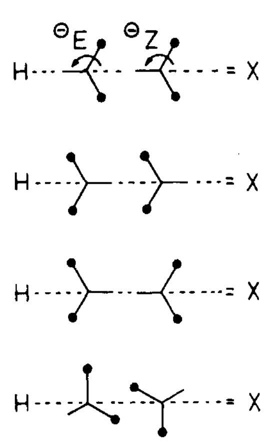
Table II. Free Energy Barriers[a] to Isopropyl Rotation in **1–8**

Compd	Signal studied	Temp, K	τ, s	$\Delta G^\ddagger$, kcal/mol
1[b]	H—C=O	149.6	0.07	7.8
		159.0	0.02	7.9
	$(CH_3)_2CH$	149.6	0.07	7.8
		159.0	0.015	7.8
3	CH_3C=O	193.0	19.2	12.3
		196.5	9.6	12.2
		199.6	4.8	12.1
		203.4	2.4	12.1
		205.7	1.2	12.0
4[c]				13.8
6	CH_3S	240.4	0.58	13.7
		251.3	0.17	13.8
		253.8	0.086	13.5
		264.9	0.041	13.7
		268.4	0.027	13.7
6[d]	CH_3S	210.2	0.56	11.9
		218.9	0.22	12.0
		224.7	0.17	12.2
7	CH_3S	228.6	0.15	12.4
		232.6	0.064	12.2
		244.7	0.024	12.4
		256.2	0.0084	12.5
8	CH_3CS	243.3	0.13	13.2
		248.7	0.062	13.1
		255.0	0.043	13.3

[a] **a** → **b** and in $CHCl_2F$ unless stated otherwise. [b] In $(CD_3)_2O$. [c] See text. [d] **c** → **b**.

3.80 in $(CD_3)_2O$], which has been assigned to the (*Z*)-isopropyl group.[3f] Below −105 °C this septet is split into two with an **a**:**b** ratio of 0.45 in $CHCl_2F$ and 2.22 in $(CD_3)_2O$. The isopropyl methyl signals also show broadening in this temperature region, but due to overlapping, no resolved signals were observed in $CHCl_2F$ solution. In this solvent, overlap with solvent signals precluded an analysis of the formyl proton signal. In $(CD_3)_2O$ solution, on the other hand, the formyl proton gave a well-resolved doublet and the isopropyl methyls a sextet (Figure 1), and these signals allowed the evaluation of the rate of the **a**–**b** exchange by bandshape analysis (Table II).

The molecular-mechanics calculations give four energy minima (**1A**–**1D**) with respect to rotation of the isopropyl groups (Figure 2). If **1D** is excluded because of its high energy, rotamer **b** should have conformation **1B**, whereas rotamer **a** could be either **1A** or a mixture of **1A** and **1C**, which is rapidly equilibrating even at −140 °C. Since the formyl proton in **1B** should be predominantly relaxed by the (*E*)-methyl protons, a NOE experiment should give some information to aid the assignment. Unfortunately, precise information is precluded by the difficulty of selective irradiation in the region of overlapping isopropyl methyl signals and also by the fact that the mean lifetimes of **1a** and **1b** are short compared to T_1 in the accessible temperature region (above −150 °C). However, in the $(CD_3)_2O$ solution at −140 °C, the region of isopropyl methyl absorption (δ 1.05–1.40) was irradiated at intervals of 5 Hz while observing the two formyl proton signals. Both signals showed NOE enhancements, but the minor (**b**) signals showed the largest enhancement at all irradiation frequencies, which can be seen as support for the assignment of conformation **1B** to rotamer **b**. The NOE observed on the formyl proton of rotamer **a** may be an effect of the **a**–**b** exchange and/or of the existence of a considerable proportion of conformation **1C** in rotamer **a**.



X		E, kcal/mol	θ_E	θ_Z
O	1A	0.38	180	180
S	2A	1.48	180	180
O	1B	0	0	0
S	2B	0	0	0
O	1C	0.72	0	180
S	2C	1.78	0	180
O	1D	4.54	212	6
S	2D	4.81	196	26

Figure 2. Calculated minimum energy conformations and conformational energies for **1** and **2**. The isopropyl groups are shown as projections on planes perpendicular to the respective *N–i*-Pr bonds.

***N,N*-Diisopropylthioformamide** (**2**) shows no effect of slow rotation of the isopropyl groups down to −140 °C. This may be due to a low barrier, but in view of the results with **1**, the existence of one strongly preferred rotamer is a more acceptable explanation. The low-field position of the (*Z*)-methine proton (Table I) classifies this rotamer as **b**, and in conjunction with the 25–30% NOE produced in the formyl proton signal on irradiating the (*E*)-methyl proton resonance, this strongly indicates that its conformation is **2B** (Figure 2). In agreement with this, the molecular-mechanics calculations place **2B** 1.48 kcal/mol below the second most stable conformation, to be compared with only 0.38 kcal/mol for the corresponding conformation in the formamide (**1**).

The assigned orientation of the (*Z*)-methine proton is further supported by the negligible ASIS effect observed between dichlorofluoromethane and toluene-d_8 solutions.[3f,11]

***N,N*-Diisopropylacetamide** (**3**). The temperature-dependent spectrum of this compound has been discussed by Siddall and Stewart[3b] and by Ramey et al.[3e] At 60 MHz they observed the high-field methine septet (attributed to the (*E*)-isopropyl group) to become first broad and then sharp again when going from +10 to −60 °C, but no clear-cut temperature effects on the other signals. No splitting of the high-field methine signal was observed. In order to explain the nonobservation of two sets of signals in the slow-exchange limit, Siddall and Stewart advanced a theory, which requires exchange between one rotamer (a *d,l* pair) designated C_3T_6, C_4T_1 and a rapidly equilibrating mixture of two *d,l* pairs called C_1T_4, C_6T_3 and C_2T_5, C_5T_2 (Scheme

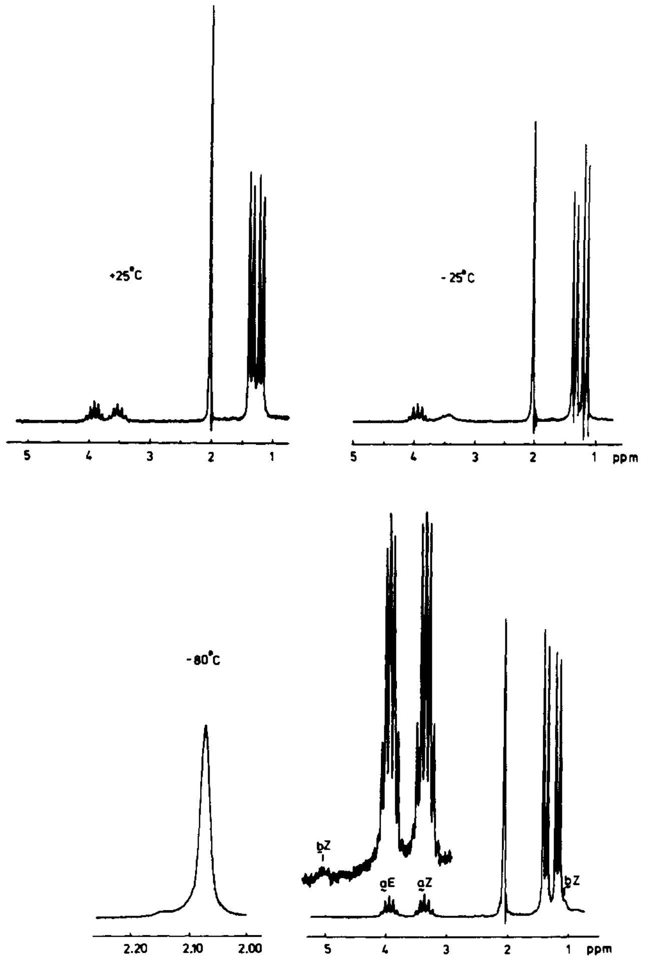
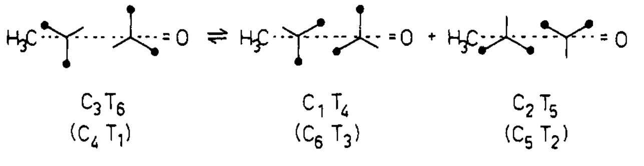


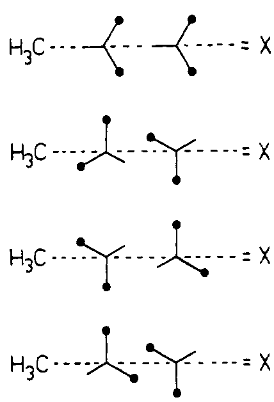
Figure 3. NMR spectra of 3 in dichlorofluoromethane.

Scheme II



II). Furthermore, a change in population is assumed, which leaves one of the rotamers (C_2T_5?) strongly dominant at −60 °C. This model, however, requires an improbably large difference in entropy between the rotamers, and furthermore it rests on an erroneous assignment of the (*Z*)- and (*E*)-isopropyl group signals. Graham and Miller[3f] have shown by a study of the ASIS effect that the assignment of Siddall and Stewart must be reversed, i.e., the average (*Z*)-methine proton signal appears at higher field than the (*E*)-methine, whereas the reverse applies to the methyl proton signals.

We have observed the following temperature-dependence in the 100-MHz spectrum of 3 in dichlorofluoromethane. Below −20 °C the (*Z*)-isopropyl methyl signal (δ 1.40) broadens due to a process giving rise to a low intensity doublet partly concealed by the (*E*)-methyl doublet, but which appears as a shoulder on the high-field side of the latter below −70 °C (Figure 3). The acetyl methyl signal also broadens slightly and below −70 °C displays a doublet in the intensity ratio 96:4 with the small signal 7.5 Hz to lower field. The broadening of the (*Z*)-methine signal is accompanied at lower temperatures (below ca. −55 °C) by the appearance of a low-intensity multiplet (only three signals visible) at δ 5.03. This gives a singlet on irradiation of the small high-field doublet of the (*Z*)-isopropyl methyl protons. On lowering the temperature to −140 °C, no further splittings are observed.



X		E, kcal/mol	θ_E	θ_Z	
O	**3A**	0	180	180	
S	**4A**	0	200	169	(stag.)
S	**4A**	0	180	180	(ecl.)
O	**3B**	+3.34	345	15	
S	**4B**	+1.50	339	24	(stag.)
S	**4B**	+2.45	341	22	(ecl.)
O	**3C**	+2.92	12	207	
S	**4C**	+2.46	29	199	(stag.)
S	**4C**	+3.31	28	195	(ecl.)
O	**3D**	+4.29	201	21	
S	**4D**	+2.83	201	24	(stag.)
S	**4D**	+3.11	198	26	(ecl.)

Figure 4. Calculated minimum energy conformations and conformational energies for 3 and 4.

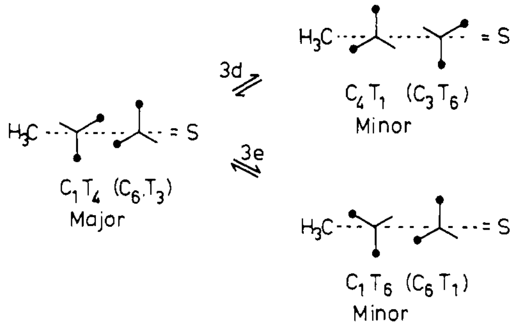
These observations are all in agreement with a single exchange between two rather unequally populated rotamers. By curve fitting of the acetyl methyl signal at several temperatures around −70 °C, $\Delta G^{\ddagger} = 12.2 \pm 0.2$ kcal/mol is obtained for the major to minor rotamer exchange (Table II). Taking into account the change in rotamer population with increasing temperature ($\Delta S°$ assumed zero), curve-fitting of the (*Z*)-methine septet at higher temperatures gives $\Delta G^{\ddagger}$ values in the region 12.0 to 12.2 kcal/mol. The minor rotamer is evidently of type **b**, and according to the molecular-mechanics calculations (Figure 4), the most likely conformation is **3B**, whereas the major rotamer should be best represented by **3A**, bearing in mind the relative stabilization of **3b** by solvation in dichlorofluoromethane. In the notation given by Siddall and Stewart,[3b] the observed exchange should be between the *d,l* pairs C_3T_4 + C_4T_3 (major) and C_1T_6 + C_6T_1 (minor).

In agreement with the interpretation given above are the observations by Siddall and Stewart that the temperature for broadening of the high-field methine signal is raised by hydrogen bonding solvents and even more by complexing with uranyl nitrate. This may be due to a relative stabilization of rotamer **b** or to an increase of the barrier to isopropyl rotation, but most probably to both of these factors.

***N,N*-Diisopropylthioacetamide** (**4**) has been studied by Siddall and Stewart[3d] and by Ramey et al.[3c] Both groups observe exchange processes which are ascribed to exchange between two rotamers, the major one with a low-field methine septet being of type **b**. Siddall and Stewart favor the *d,l* pairs C_1T_4, C_6T_3 (major); C_3T_6, C_4T_1 (minor) (Scheme III), whereas Ramey et al. propose the equilibrium C_1T_4, C_6T_3 (major) $\rightleftharpoons$ C_1T_6, C_6T_1 (minor). However, the latter assignment is rendered unlikely by the high-field position of the minor (*Z*)-methine septet (δ 4.0 in $CDCl_3$).[3d]

We have recorded the spectrum of **4** in dichlorofluoromethane at a large number of temperatures between +35 and −140 °C, and in this region the spectra are affected by an exchange between two rotamers only, the major one being of type **b**. By curve fitting on the *C*-methyl and isopropyl methyl signals, preexchange lifetimes have been evaluated for 12 different spectra obtained in the temperature region −20 to +16 °C. The calculated free energy barriers all fall within 13.79 ± 0.09 kcal/mol without observable trend, and a least-squares plot of the data using the Eyring equation gives $\Delta H^{\ddagger} = 13.2 \pm 0.8$ kcal/mol and $\Delta S^{\ddagger} = 2.4 \pm 3.0$ cal mol^{-1} K^{-1}. Evidently the results do not allow the conclusion that the activation entropy is sig-

Scheme III



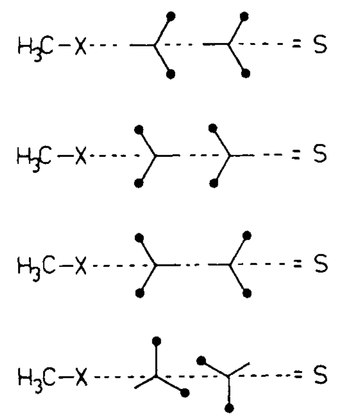
nificantly different from zero. No elaborate bandshape analysis using the methine septets as well was undertaken because these (and to some extent also the isopropyl methyl signals) are significantly affected by the thioamide rotation in the upper temperature region of the isopropyl rotation.

In molecular-mechanics calculations on **4** the conformation of the thioacetyl methyl can be expected to be of importance for the relative conformational energies of **4**A-D. Unfortunately, there are no reliable experimental data available on the methyl conformation in thioacetyl compounds. We determined the H—CC═S torsional constant from a recent microwave investigation on thioacetaldehyde and thioacetone, which provides barriers for methyl rotation.[12] No structural data were, however, given in this paper. Therefore, two alternatives were employed, one in which the most stable methyl group conformation was assumed to be analogous to the one found in acetyl compounds, i.e., with one CH bond eclipsing the C═S bond,[13] and another in which a staggered conformation was taken to be of lowest energy. The two alternatives are denoted (ecl) and (stag) in Figure 4. In both cases, however, the same minimum energy conformations for the isopropyl groups were found (with minor angle changes) and in the same order of energies.

Qualitatively, the results of the calculations and the NMR spectra indicate that the same *d,l* pairs are involved as in the case of **3**, but that the major and minor rotamers must be interchanged.[3h]

For **3** the free energy difference between **b** and **a** is +1.26 kcal/mol and for **4** −0.40 kcal/mol. The difference between these values, 1.66 kcal/mol, should be compared with the energy differences 0.89 kcal/mol and 1.84 kcal/mol calculated on the basis of the eclipsed and staggered models, respectively. Thus, at least qualitatively, the molecular-mechanics calculations predict conformations which are in good agreement with experiment.

Methyl *N,N*-diisopropylthioncarbamate (5) gave only one rotamer down to −140 °C in dichlorofluoromethane solution. This is of type **b**, and according to the molecular-mechanics calculations, the conformation (**5B**) is analogous to that found for **2** (Figure 5).



λ		E, kcal/mol	θ_E	θ_Z
O	5A	+1.55	180	180
S	6A	0	180	180
O	5B	0	0	1
S	6B	+0.26	0	0
O	5C	+1.90	0	180
S	6C	+2.72	1	181
O	5D	+4.59	196	26
S	6D	+2.83	204	23

Figure 5. Calculated minimum energy conformations and conformational energies of **5** and **6**. .

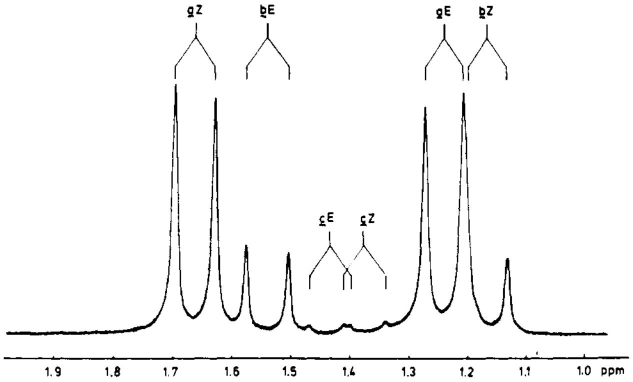


Figure 6. The isopropyl methyl region of the NMR spectrum of **6** in dimethyl-d_6 ether. at −80 °C.

Methyl *N,N*-diisopropyldithiocarbamate (6) has been subjected to a qualitative study by Tanaka and Watanabe,[3g] who found a spectrum rather similar to that of **4**, but with a reversed rotamer ratio. We find in dichlorofluoromethane an **a**:**b** ratio of 1.44 (2.7 in carbon disulfide[3g] as well as in dimethyl-d_6 ether) compared with 0.43 for **4**. However, inspection of the *S*-methyl and isopropyl methyl signals at lower temperatures reveals a further exchange process, which affects the spectrum in the temperature region below −45 °C. Between the **a** and **b** *S*-methyl signals, a small singlet apprears, due to a third rotamer denoted **c**. The intensity ratio **a**:**b**:**c** is 59:37:4 in dichlorofluoromethane and 75:22:3 in dimethyl-d_6 ether.[14] Two doublets also appear between the (*E*)-isopropyl methyl doublet of rotamer **a** and the corresponding doublet of **b** (Figure 6). On irradiation of the high-field **c** doublet, the **b** (*Z*)-methine septet is narrowed due to off-resonance decoupling, and on its high-field side the *Z*-methine signal of **c** appears as a singlet (δ 6.10). Irradiation of the low-field **c** doublet gives off-resonance narrowing of the (*E*)-methine septet of **a** (δ 4.95), but no (*E*)-methine signal due to **c** appears. Apparently it is overlapped by the larger septet. In agreement with this, irradiation at δ 4.95 decouples the low-field **c** doublet at δ 1.45, whereas the high-field **c** doublet (δ 1.39) is decoupled by irradiation at δ 6.10. Thus rotamer **c** must have its (*Z*)-methine group pointing in the direction of the C═S bond, and the position of the (*E*)-methine group should be similar to that of the corresponding group in the rotamer **a**. The rather low-field position of these methines (≈ δ 5) compared with that in rotamer **a** of **4** (δ 4.43) indicates that they point in the direction of the C-S bond. The similar shifts of the **c** methyl groups (δ 1.39 and 1.45) also indicate that they reside in similar environments.

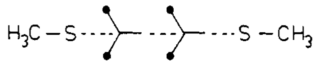
Combining the results of molecular-mechanics calculations with the observations in the NMR spectra, one can conclude that rotamer **a** should have conformation **6**A, rotamer **b** conformation **6B**, and rotamer **c** conformation **6D** (Figure 5). The latter conformation is favored relative to **6C** by the energy of solvation. The rotamer **b** observed at higher temperatures must be an equilibrium mixture of **6B** and **6D**, and the appearance of the subset of signals due to rotamer **c** must be due to the slowing down of the rotation of the (*E*)-isopropyl group in this mixture. This conclusion is supported by the absence of a significant broadening of the (*Z*)-methine septet of rotamer **a** below −10 °C. Since the resonances of the (*Z*)-methines in rotamers **a** and **c** are ca. 200 Hz apart, an exchange between these would have caused a strong broadening of the **a** methine septet in spite

Table III. Chemical Shifts[a] and Fractional Populations for **9–11**

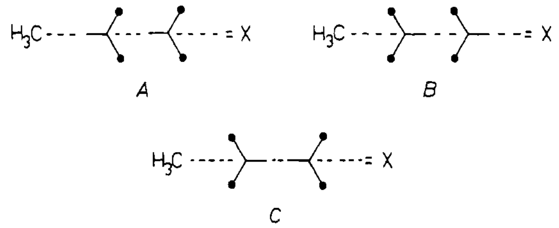
		a$_1$						**a**$_2$						**b**					
		CH$_3$			CH			CH$_3$			CH			CH$_3$			CH		
Compd	Temp, °C	3	4	5	3	4	p	3	4	5	3	4	p	3	4	5	3	4	p
9	−90	1.52	1.31	2.16	4.11	~3.2	0.18	1.52	1.28	2.07	4.30	3.27	0.68	1.41	1.32	2.18	5.04	2.82	0.15
10	−80	1.78	1.51	2.61	5.11	3.38	0.16	1.80	1.45	2.52	5.19	3.54	0.37	1.73	1.46	2.62	4.96	3.62	0.47
11	−80	1.85	1.35	2.22	~4.7	3.20	0.06	1.85	1.34	2.11	4.70	3.33	0.12	1.50	1.36	2.86	6.07	3.50	0.82

[a] In CHCl$_2$F.

Scheme IV



Scheme V



of the large population difference (cf. **3**).

One discrepancy between calculations and observations is found in the small calculated energy difference between conformations **6**A and **6**B (0.26 kcal/mol) compared with 2.45 or 1.50 kcal/mol for **4**, in spite of the fact that the observed **a**:**b** ratios for these compound (1.59 and 0.32 in CHCl$_2$F) should require the larger energy difference for **6.** This may be ascribed to differences in energies of solvation. On the other hand, the shifts observed for the (*Z*)-methine protons of **b** and **c** (δ 6.26 and 6.10) are in qualitative agreement with the positions calculated by molecular mechanics (Figure 5), the B methine being in the thioamide plane and the D methine 23° out of it.

Diisopropylamino[bismethylthio]methylium perchlorate (**7**) shows at ambient temperature one set of isopropyl and *S*-methyl signals, but below −40 °C two sets of equal intensity. This is most likely due to exchange between two equivalent rotamers (Scheme IV), similar to those proposed for a related process in some *N*,*N*-diisopropyldithiocarbamate metal complexes.[3g,4,15] This geometry is also found in a crystallographic study of a nickel *N*,*N*-diisopropyl dithiocarbamate complex.[16]

Because geometric and force field parameters are lacking, no molecular-mechanics calculations have been performed for this and the following systems.

Diisopropylaminomethylthio-d_3-ethylium perchlorate (**8**) shows one *C*-methyl singlet and two sharp sets of isopropyl signals somewhat above ambient temperature (+47 °C). The methine septets (δ 4.56 and 4.74) and also the isopropyl methyl doublets (δ 1.51 and 1.57) overlap partly. These two sets are attributed to the (*E*)- and (*Z*)-isopropyl groups rendered nonequivalent by a high barrier to rotation around the C–N(i-Pr)$_2$ bond. Below ambient temperature the spectrum broadens, and below −35 °C the appearance of the spectrum is in agreement with a slow exchange between two rotamers (**a** and **b**) in the ratio 1:5.3. The *C*-methyl resonance is a doublet with this intensity ratio and with the major signal (**b**) at lower field. In the isopropyl methyl region (δ 1.4–1.7) two **b** doublets are well separated, whereas the high-field **a** doublet is completely covered by the high-field **b** doublet and the low-field **a** doublet appears on the low-field side of the low-field **b** doublet (Table I). Two **b** methine septets appear at δ 4.42 and 4.82, i.e., with a greater separation than the original *E* and *Z* septets, but no **a** septets are visible. Irradiation at δ 1.45 causes the low-field septet to change into two singlets in the ratio 1:5.3 at δ 4.82 (**b**) and 4.77 (**a**), whereas irradiation in the region δ 1.60–1.65 changes the high-field septet into *one* singlet (δ 4.42). Since the two septets have equal intensities, the high-field **a** septet must nearly coincide with the high-field **b** septet. From the temperature dependence of the spectrum, it follows that the low-field septet must contain **a***Z* + **b***E* or **a***E* + **b***Z*, whereas the corresponding alternatives for the high-field septet are the same, but in the reverse order. The same combinations are valid for the isopropyl methyl doublets.

In the absence of a strongly deshielding group, it is difficult to assign conformations to rotamers **a** and **b**. However, it is reasonable to assume that four energy minima similar to those found for **3** and **4** must be considered (Figure 4). In all systems hitherto studied, a methyl group or a proton, which is opposed by the methyl groups of an adjacent isopropyl group, resonates at lower field than one, which is opposed by the isopropyl methine (ref 2g, 17, 18, and Table I). On the basis of these observations, the *C*-methyl group of **b** should oppose the (*E*)-isopropyl methyls, and this rotamer should have a conformation of one of the types B or C. The relatively large shift difference between the **b** septets favors conformation B, i.e., the low-field septet is **a***E* + **b***Z*. Thus the low-field minor methyl doublet is **a***Z*, and a conformation of type A is the most likely one for rotamer **a.** This assignment is further strengthened by the relatively large shift difference between the **a** methyl doublets. In conformation D the difference should be quite small (cf. rotamer **c** of **6**).

3,4-Diisopropyl-5-methyl-Δ^4-thiazolin-2-one (**9**) shows a single set of signals at ambient temperature. Below −40 °C two sets appear in the ratio 15:85, and at −50 °C a decoalescence of the major subset is observed, leading to three sets of signals (Table III). As usual, the rotamer with a low-field methine (δ 5.04) is denoted **b,** and this corresponds to the minor subset, which appeared at the first decoalescence. Of the two other rotamers, the one with the 5-methyl resonance at low field is denoted **a**$_1$, and the third one **a**$_2$. As discussed previously,[2e,g] simple strain energy calculations for the thione analogue predict three minimum energy conformations (Scheme V), and they are probably relevant for **9** as well. The combinations **a**$_1$–C, **a**$_2$–A, and **b**–B fit the experimental data, e.g., the relatively low-field resonance of the 5-methyl group in **a**$_1$ and **b** (δ 2.16 and 2.18) compared with that in **a**$_2$ (δ 2.07), and also the low-field resonances of the 3-isopropyl methyl groups in **a**$_1$ and **a**$_2$ (δ 1.52), which point into the deshielding zone around the carbonyl group, compared with the one in **b** (δ 1.41), in which the methyl groups point in the opposite direction.

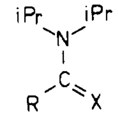
The free energy barriers to the exchange $\mathbf{b} \rightleftharpoons (\mathbf{a}_1 + \mathbf{a}_2)$ and $\mathbf{a}_1 \rightleftharpoons \mathbf{a}_2$ have been determined by curve fitting on the

Table IV. Barriers[a] to Isopropyl Rotation in **9-11** in $CHCl_2F$

Compd	Temp, K	τ, s	$\Delta G^{\ddagger}$, kcal/mol
9[b]	248.3	0.031	12.7
	254.7	0.022	12.9
	261.5	0.008	12.8
9[c]	194.5	1.11	11.3
	204.3	0.37	11.4
	210.0	0.19	11.5
	218.0	0.10	11.6
10[b]	272.2	0.62	15.6
	292.4	0.084	15.7
	298.0	0.044	15.6
10[c,d]	220.6	0.15	12.0
11[b]	288.8	0.43	16.4
	298.6	0.19	16.5
	302.6	0.16	16.6
11[c]	226.7	0.06	11.9
	237.7	0.03	12.1

[a] By curve fitting on the 5-methyl resonance. [b] For the reaction **b** → (**a**$_1$ + **a**$_2$). [c] For the reaction **a**$_1$ → **a**$_2$. [d] From a complete bandshape analysis, $\Delta H = 10.5 \pm 0.4$ kcal/mol; $\Delta S = -5.0 \pm 2.0$ cal mol^{-1} K^{-1}.

Scheme VI



5-methyl signals (Table IV), but due to the small shift differences no evaluation of activation enthalpies and entropies was attempted.

2-Methylthio-3,4-diisopropyl-5-methylthiazolium iodide (**10**) shows qualitatively the same behavior as **9.** The rotamer assignments were made from the exchange pattern and from the shifts of the 5-methyl group, since the deshielding effect of the methylthio group is much smaller than those of the carbonyl and thiocarbonyl groups. The shielding is probably also complicated by the ring current effect of the aromatic thiazolium ring.

A complete bandshape analysis of the **a**$_1$-**a**$_2$ exchange gave an activation entropy of -5 ± 2 cal mol^{-1} K^{-1}, in good agreement with the value (-4.4 ± 1.4 cal mol^{-1} K^{-1}) found for the isopropyl group rotation in 3,4-diisopropyl-Δ^4-thiazoline-2-thione.[2f]

3,4-Diisopropyl-5-methyl-Δ^4-thiazoline-2-thione (**11**). The **b** ⇌ (**a**$_1$ + **a**$_2$) exchange in this molecule has already been discussed.[2g] The **a**$_1$ ⇌ **a**$_2$ exchange has nearly the same free-energy barrier as in **9** and **10,** and the chemical shifts used for rotamer assignments are in good qualitative agreement with those of **9.** The 3-isopropyl methyl doublets of **a**$_1$ and **a**$_2$ coincide completely (δ 1.85), which follows from the intensities and also from the observation that this doublet remains sharp throughout the temperature region in which the **a**$_1$-**a**$_2$ exchange affects the spectrum.

Discussion

It follows from the above that four general types of minimum energy conformations, denoted A-D (Figures 2, 4, and 5), are available to two interacting isopropyl groups. The precise geometries and the relative energies depend on the sizes and shapes of the flanking groups.

Because of the symmetry of the amides and thioamides (Scheme VI), it may be meaningful to compare the steric effects of R and X. An inspection of the populations shows that conformations of type B are favored by a large X (S) combined with a small R (H, OCH_3), whereas the reverse holds for conformations of type A. The first type of combination (X = S, R = N=R′) is found in a thioamide, which has recently been subjected to an x-ray crystallographic study,[19] and the conformation of the isopropyl groups is of type B. When ordered according to effective size R and X give the series H < CH_3O < =O < CH_3 < CH_3S < =S. However, this order may well be reversed in some places in other combinations, since the effective size of a group depends among other things on its possibilities to avoid strong steric interactions by angle bending, i.e., it is a function of the other substituents in the molecule.

Table V. Chemical Shifts[a] of **12** and **13**

Compd	$(CH_3)_2$CH	$(CH_3)_2CH$	CH_3—C=X	CH_3N	p
12*Z*	1.02	4.82	1.94	2.69	0.56
12*E*	1.14	4.04	1.98	2.78	0.44
13*Z*	1.17	5.92	2.59	3.03	0.53
13*E*	1.25	4.51	2.67	3.26	0.47

[a] In $CHCl_2F$, temp = 30 °C.

Scheme VII

The order of the free energies of activation to isopropyl rotation follows roughly the above order of substituent sizes, i.e., a combination of two large substituents (CH_3S, =S) gives a high barrier and two small substituents (H, =O) a low one.

An inspection of Table III shows that the populations of rotamers **a**$_1$ and **a**$_2$ of the thiazole derivatives diminish in the series X = O, SCH_3, S (Scheme VII), i.e., in good conformity with the order of substituent sizes derived from the amides and thioamides. The barriers to rotation of the 3-isopropyl groups, **b** → (**a**$_1$ + **a**$_2$), increase in the same order, whereas the **a**$_1$ → **a**$_2$ barrier is nearly constant, as expected for a rotation of the 4-isopropyl group.

The conformers of types A and B in general are the dominant ones. Similar conformations have recently been found in tetraisopropylethylene[20,21] and in a diisopropylphosphorane.[22] Conformers of type C are only observed in the series **9-11,** with the relative population increasing with decreasing size of the 2 substituent (S > SCH_3 > O). A rotamer of type D has only been observed in **6,** and in general it should be favored by large flanking groups. In the diseleno analogue of **6** a third rotamer has been observed in a relative population of 0.15 in CS_2 at −60 °C,[14] and probably it is also of type D, though the authors propose a C_2T_5-C_5T_2 pair (see Scheme II), which should give rise to eight isopropylmethyl signals instead of the observed four. Localization of the methine proton signals of this rotamer could probably resolve the problem.

It was demonstrated in a previous paper[2g] that the rotation of the isopropyl groups in two 3,4-diisopropylthiazolinethiones is not synchronous. This conclusion was reached by a comparison with the barriers in the 3-isopropyl-4-methyl analogues and with the barrier to rotation of the 4-isopropyl group in **11.** In an attempt to use the same technique for the amides and thioamides, *N*-methyl-*N*-isopropylacetamide (**12**) and -thioacetamide (**13**) were studied. Both compounds show spectra of two rotamers (*E* and *Z*) with respect to the (thio)amide bond at ambient temperature, but on lowering the temperature to −140 °C, no further exchange processes can be observed. This may be due to strongly preferred conformations of the isopropyl groups in the *Z* as well as the *E* positions in both the amide and the thioamide and/or to low barriers to rotation in all cases. A comparison of the chemical shifts of the isopropyl and *C*-methyl groups of **12** and **13** (Table V) with those of **3** and **4** gives some indications. The assignments for **12** are those given by La Planche and Rogers[23] on the basis of ASIS effects, and the resonances of **13** are assigned by reference to the strong deshielding effect of the thiocarbonyl group. It appears that the methine of **12***Z* (δ 4.82) falls between the **a***Z* (3.36) and **b***Z* (5.03) methines of **3**, whereas the other signals of **12** fall outside the ranges of the **a** and **b** rotamers of **3**. The same result is obtained on a comparison between **13** and **4**. Evidently, the chemical shifts in the diisopropyl compounds are generally shifted appreciably downfield by the steric compression.[17] However, from the positions of the methine resonances, it may be concluded that the isopropyl groups in the *Z* rotamers of **12** and **13** are preponderantly in a conformation of type **b**.

The feasibility of a synchronous rotation was instead tested by molecular-mechanics calculations on **6**. The program does not yet permit a continuous rotation of groups, but it is possible to rotate one group in steps of ca. 30 °C and allow the relaxation of the molecules with respect to all geometric parameters except the driving dihedral angle. Rotating the *Z* isopropyl group from conformation A, it was found that the (*E*)-isopropyl group followed the *Z* group at rotations of 30 and 60°, but that it had switched back to the original position at 90° rotation. Thus this rotation is not synchronous, a conclusion which is probably also valid for the less compressed amides and thioamides, and the barriers observed are those to rotation of the most hindered isopropyl group. This problem will be attacked on a broader basis in connection with attempts to calculate the rotational barriers in several diisopropylamides and -thioamides.

Acknowledgments. We are grateful to C.N.R.S. de France (International A.T.P. No. 9111) and to the Swedish Natural Science Research Council for financial support, and to FK Bengt Klarin for valuable preparative assistance. We also thank Professor N. Allinger for placing his molecular mechanics program at our disposal and Dr. Flemming Nicolaisen, Chemical Laboratory V, The H. C. Orsted Institute, Copenhagen, for communicating his results to us prior to publication.

References and Notes

(1) (a) Organic Chemistry 1, Chemical Center, Lund; (b) I. P. S. O. I., Marseille; (c) Ecole Normale Supérieure, Tunis; (d) Organic Chemistry 2, Chemical Center, Lund.

(2) (a) C. Roussel, Thesis, Université de Provence, Marseille, 1973; (b) C. Roussel, M. Chanon, and J. Metzger, *Tetrahedron Lett.*, 1861 (1971); (c) *ibid.*, 3843 (1972); (d) *FEBS Lett.*, **29**, 253 (1973); (e) A. Liden, C. Roussel, M. Chanon, J. Metzger, and J. Sandström, *Tetrahedron Lett.*, 3629 (1974); (f) R. E. Carter, T. Drakenberg, and C. Roussel, *J. Chem. Soc., Perkin Trans. 2,* 1690 (1975); (g) C. Roussel, A. Lidén, M. Chanon, J. Metzger, and J. Sandström, *J. Am. Chem. Soc.*, preceding paper in this issue.

(3) (a) R. M. Hammaker and B. A. Gugler, *J. Mol. Spectrosc.*, **17,** 356 (1965); (b) T. H. Siddall, III, and W. E. Stewart, *J. Chem. Phys.*, **48,** 2928 (1968); (c) T. H. Siddall, III, W. E. Stewart, and F. D. Knight, *J. Phys. Chem.*, **74,** 3580 (1970); (d) T. H. Siddall, III, and W. E. Stewart, *J. Org. Chem.*, **35,** 1019 (1970); (e) K. C. Ramey, D. J. Louick, P. W. Whitehurst, W. B. Wise, R. Mukherjee, J. F. Rosen, and R. M. Moriarty, *Org. Magn. Reson.*, **3,** 767 (1971); (f) L. L. Graham and M. R. Miller, *ibid.*, **4,** 327 (1972); (g) T. Tanaka and N. Watanabe, *ibid.*, **6,** 165 (1974); (h) F. Nicolaisen, *Acta Chem. Scand.*, in press.

(4) R. M Golding, P. C. Healy, P. W. G. Newman, E. Sinn, and A. H. White, *Inorg. Chem.*, **11,** 2435 (1972).

(5) (a) M. Liler, *J. Chem. Soc. B,* 334 (1971); (b) W. Walter and G. Maerten, *Justus Liebigs Ann. Chem.*, **669,** 66 (1963); (c) C. Roussel, A. Babadjamian, M. Chanon, and J. Metzger, *Bull. Soc. Chim. Fr.*, 1087 (1971); (d) C. Roussel, R. Gallo, M. Chanon, and J. Metzger, *ibid.*, 1902 (1971); (e) J. v. Braun, F. Jostes, and H. Wagner, *Ber.*, **61,** 1423 (1928).

(6) H. M. McConnell, *J. Chem. Phys.*, **28,** 430 (1958).

(7) A. Lidén and J. Sandström, *Tetrahedron,* **27,** 2893 (1971).

(8) (a) N. L. Allinger, M. T. Tribble, M. A. Miller, and D. H. Wertz, *J. Am. Chem. Soc.*, **93,** 1637 (1971); (b) D. H. Wertz and N. L. Allinger, *Tetrahedron,* **30,** 1579 (1974); (c) T. Liljefors and N. L. Allinger, to be published; (d) N. L. Allinger, personal communication.

(9) W. Walter, E. Schaumann, and H. Paulsen, *Justus Liebigs Ann. Chem.*, **727,** 61 (1969).

(10) Experimentally observed rotamers are referred to by lower-case letters and calculated minimum energy conformations by capital letters.

(11) P. Laszlo, *Prog. Nucl. Magn. Reson. Spectrosc.*, **3,** 231 (1967).

(12) H. W. Kroto, B. M. Landsberg, R. J. Suffolk, and A. Vodden, *Chem. Phys. Lett.*, **29,** 265 (1974).

(13) R. W. Kilb, C. C. Lin, and E. B. Wilson, Jr., *J. Chem. Phys.*, **26,** 1695 (1957).

(14) After this study was finished, the observation of three rotamers in **6** and in its diseleno analogue was reported by Y.-I. Takeda and T. Tanaka, *Org. Magn. Reson.*, **7,** 107 (1975). Their interpretation, however, is at variance with the one given here.

(15) The Arrhenius activation energies given for the nickel and cobalt complexes (4.6 and 6.0 kcal/mol)[4] are unrealistically low.

(16) P. W. G. Newman and A. H. White, *J. Chem. Soc., Dalton Trans.*, 2239 (1972).

(17) S. Winstein, P. Carter, F. A. L. Anet, and A. J. R. Bourn, *J. Am. Chem. Soc.*, **87,** 5247 (1965).

(18) A. Mannschreck, L. Ernst, and E. Keck, *Angew. Chem.*, **82,** 840 (1970).

(19) J. Sletten, *Acta Chem. Scand., Ser. A,* **28,** 989 (1974).

(20) R. F. Langler and T. T. Tidwell, *Tetrahedron Lett.*, 777 (1975).

(21) D. S. Bomse and T. H. Morton, *Tetrahedron Lett.*, 781 (1975).

(22) A. H. Cowley, R. W. Braun, and J. W. Gilje, *J. Am. Chem. Soc.*, **97, 434** (1975).

(23) L. A. La Planche and M. T. Rogers, *J. Am. Chem. Soc.*, **85,** 3728 (1963).