Intramolecular van der Waals Attraction. Conformational Analysis of Di(primary alkyl) Derivatives of Five- and Six-Membered Heterocyclic Systems

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Four *N,N'*-di(RCH_2)imidazoline-2-thiones and nine *N,N'*-di(RCH_2)thiobarbiturates (R = methyl, isopropyl, *tert*-butyl, 1-adamantyl, phenyl, phenylmethyl, trimethylsilyl, trifluoromethyl, *tert*-butyl + phenyl) have been synthesized and investigated by dynamic NMR and molecular mechanics calculations (MM2/MMP2). Introduction of two geminal methyl groups in the molecules enabled unequivocal assignments of the stable conformers. Two conformers, syn and anti, were usually found, and in most cases the more "crowded" syn conformer predominated. The thiobarbiturates, but not the imidazoline-2-thiones, showed a solvent-dependent syn–anti equilibrium. Molecular mechanics calculations satisfactorily reproduced the syn–anti energy difference. Rationalization of the solvent effect and the results of the molecular mechanics calculations provide support for the operation of van der Waals attraction governing the preference for the syn conformation.

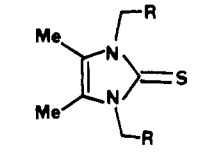
Nonbonded interactions play a major role in determining the equilibrium conformations of organic molecules. The forces of the interactions, which may be repulsive or attractive, have their origin in different contributions: Coulombic forces, repulsion between electron clouds as a result of the Pauli principle (van der Waals repulsion), London dispersion forces (van der Waals attraction), and delocalization of electrons due to interaction between atomic orbitals. For alkyl groups, the Coulombic and electron delocalization contributions are usually small, and the van der Waals forces dominate. Primary alkyl groups attached to planar sp^2 frameworks are found to follow a conformational pattern characterized by torsional angles of ca. 90° between the alkyl groups and the plane of the sp^2 system.[1] When two or more alkyl groups are in close contact, they are usually arranged alternately above and below the plane so as to minimize their mutual steric repulsion. This type of conformation is exemplified for two geminal or vicinal groups by *N,N*-di(primary alkyl)amides and -thioamides[2] or 1,2-dineopentyltetramethylbenzene,[3] for four interacting alkyl groups in tetra(primary alkyl)ethylenes,[4] and for six alkyl groups in hexa(primary alkyl)benzenes.[5,6]

For more distantly spaced alkyl groups, long-range *attractive* forces are operating and may in certain cases be the dominant contribution. A particularly interesting example, in this context, is the 1,3,5-trineopentylbenzene system, in which the rotamer with all three neopentyl groups on the same side of the benzene ring is favored over the 2-proximal, 1-distal rotamer.[7-9]

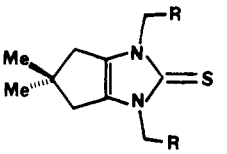
Van der Waals attraction has also been claimed to be responsible for the position of the equilibrium between the valence-bond isomers 1,4- and 1,6-di-*tert*-butylcyclooctatetraene[10-12] and has been discussed in relation to predominant gauche conformations in 1,2-disubstituted ethanes.[13-19]

In the *experimental* studies of conformational problems with possible operation of van der Waals attraction encountered in the organic chemical literature, two observations can be made: (i) The conformational assignment is often not trivial, and incorrect assignment was, for example, initially suggested for the trineopentylbenzene systems, based upon intuitive expectations using the "bulk repulsion approach".[20] In other cases, the question had to be left open, e.g., concerning the syn–anti assignments in di-*cis*-alkenylbenzene derivatives[21] and in 1,3-dibenzylimidazoline-2-thiones.[22] (ii) Strikingly many examples deal with attraction between *tert*-butyl groups,[7-12,21]

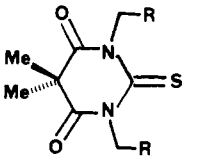
Chart I



1 a–b



2 a–b



3 a–i

	R
a	*t*-Bu
b	*i*-Pr
c	Me
d	1-adamantyl

	R
e	Ph
f	CH_2Ph
g	$SiMe_3$
h	CF_3
i	*t*-Bu, Ph

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Table I. Fractional Populations, Internal Rotational Barriers, and Calculated Energies for the Syn–Anti Equilibria

compd	R	solvent	p_{syn}	$\Delta G°$, kcal mol^{-1} (temp, K)	$\Delta G^{\ddagger}$, kcal mol^{-1} (temp, K)	$\Delta G_{corr}°$,[d] kcal mol^{-1}	ΔE_{calcd},[e] kcal mol^{-1}
1a	*t*-Bu	$(CD_3)_2O$	0.93	1.09 (212)	13.3 (285)	1.39[f]	0.93
		toluene-d_8	0.93	1.07 (208)			
		acetone-d_6	0.93	1.07 (208)			
		methanol-d_4	0.92	1.04 (202)			
1b	*i*-Pr	$(CD_3)_2O$–toluene-d_8	0.59	0.06 (151)	8.9 (172.5)	0.27	−0.01
2a	*t*-Bu	$(CD_3)_2O$–CCl_2F_2[a]	≥0.98	≥1.2 (152)	8.3 (178)	≥1.4	0.75
2b	*i*-Pr	$(CD_3)_2O$–CCl_2F_2[a]			<7.0		
3a	*t*-Bu	$(CD_3)_2O$	0.94	1.02 (192)	12.0 (252)	1.28[f]	0.58
		toluene-d_8	0.88	0.79 (199)			
		$CDCl_3$	0.73	0.44 (225)			
		CD_2Cl_2	0.60	0.15 (191)			
		acetone-d_6	0.83	0.58 (184)			
		CD_3OD	0.88	0.79 (199)			
3b	*i*-Pr	$(CD_3)_2O$–CCl_2F_2[a]	0.75	0.34 (157)	9.7 (185)	0.56	0.18
3c	Me	$(CD_3)_2O$–CCl_2F_2[a]	0.45	−0.05 ± 0.1 (136)	8.1 (171)	0.15±0.1	0.10
3d	1-adamantyl	$(CD_3)_2O$	0.88	0.80 (202)	12.4 (296)	1.08	1.43
		toluene-d_8	0.68	0.30 (205)			
3e	Ph	$(CD_3)_2O$–CCl_2F_2[a]	0.46	−0.05 (155)	9.3 (190)	0.16	0.55 (−0.05)[g]
3f	CH_2Ph	$(CD_3)_2O$–CCl_2F_2[a]	0.32	−0.23 (152)	8.5 (174)	−0.02	
3g	$Si(CH_3)_3$	$(CD_3)_2O$–CCl_2F_2[a]			<7 (140)		0.69
3h	CF_3	$(CD_3)_2O$–CCl_2F_2[a]	0.49	−0.02 (179)	9.3 (198)	0.98[f]	−0.11 (+0.13)[h]
		toluene-d_8	0.78	0.47 (179)			
		$CH_3CO_2CH_3$	0.62	0.18 (179)			
		CD_2Cl_2	0.36	−0.20 (171)			
		acetone-d_6	0.38	−0.17 (173)			
		CD_3OD	0.70	0.30 (175)			
3i	*t*-Bu, Ph	$(CD_3)_2O$–CCl_2F_2[a]	0.68[b]	0.26 (167)	12.2 (280)[c] 9.4 (190)	0.26	0.54

[a] Solvent contained 25–30% CCl_2F_2. [b] Syn form assumed to be the major component (see the text). [c] Higher barrier for the neopentyl rotation, lower for the benzyl rotation. [d] $\Delta G_{corr}° = \Delta G° + RT \ln 2$ except for **3i** (see the text); $\Delta G°$ values in dimethyl-d_6 ether–dichlorodifluoromethane. [e] $\Delta E_{calcd} = E_{steric}(anti) - E_{steric}(syn)$; ϵ 1.5. [f] $\Delta G°$ values extrapolated to ϵ 1.5 by a Zefirov–Samoshin treatment (Figure 2). [g] Same calculation including electrostatic interactions with point charges on the atoms of the benzyl group (see the text). [h] Same calculation but with C–F bond moment 0.

and no systematic study of the effect of other groups, substitution patterns, and shape of the sp^2 framework has appeared.

This report deals with the design of systems for which van der Waals interactions dominate the conformational distribution and which allow for the systematic study of a large number of groups. Of primary inportance is the demand for unequivocal conformational assignments. We also present results from a computational study by the molecular mechanics method employing the MM2/MMP2 force field of Allinger.[23] The compounds studied are shown in Chart I.

Results

Exploratory Work. Imidazoline-2-thiones. In the early stages of this work we made a dynamic NMR spectroscopic study of 1,3-dineopentyl-4,5-dimethylimidazoline-2-thione (**1a**), showing that at −70 °C this compound exists as an equilibrium between two conformers in the proportions 93:7. As in the cases discussed above, we had no experimental means to unequivocally prove whether the syn or anti conformer is the major component. In order to solve this problem, we prepared the bicyclic analogue **2a**, in which the *gem*-dimethyl groups give rise to different NMR patterns in the syn and anti conformers for symmetry reasons. In the syn form the methyl groups are diastereotopic, and in the anti form they are homotopic. The NMR spectrum of **2a** at −121 °C shows a pair of singlets for the *gem*-dimethyl groups, as expected for the syn conformer and no sign of any anti conformer!

This probe could thus be applied to the study of the steric interaction of several groups, were it not for a rather surprising drawback; the rotational barrier ($\Delta G^{\ddagger}$) of **2a** was as much as 5 kcal mol^{-1} lower than in **1a**, 8.3 and 13.3 kcal mol^{-1}, respectively. This observation indicated that we would have difficulties when groups smaller than the neopentyl group were to be studied because of the inaccessibility of the temperature regions of slow exchange on the NMR time scale. Our suppositions were confirmed for the case of the isobutyl analogues **1b** and **2b**. Although the isobutyl rotation was slow for **1b** below −100 °C, and two conformers with the populations 59:41 were detected, no sign of signal broadening due to slow exchange was noticed for **2b** down to −125 °C. Consequently, we had to seek another model system, as reported below.

Rotamer populations and rotational barriers for the imidazoline-2-thione derivatives are shown in Table I.

Revised Model System. Thiobarbiturates. A simple modification of the model system **2** to achieve higher rotational barriers would be to increase the ring size. In the six-membered thiobarbiturates **3**, smaller exocyclic bond angles could be expected to lead to increased steric interference between the rotating group and the flanking substituents in the transition state for the rotation, and thus to higher barriers. In addition, the NMR probe, the *gem*-dimethyl groups, is closer to the conformational center in **3** and thus might be expected to exhibit higher sensitivity. This system could be synthesized through condensation of 2,2-dimethylmalonic acid with *N*,*N*′-di(primary alkyl)thiourea in acetyl chloride in poor to moderate yields. The compounds **3a–i** were accordingly prepared, and the results of the dynamic NMR study were found to fulfill our expectations in that the rotation of groups as small as the ethyl group was conveniently frozen out.

As solvent for the dynamic NMR study we chose a mixture of dimethyl-d_6 ether containing 25–30% di-

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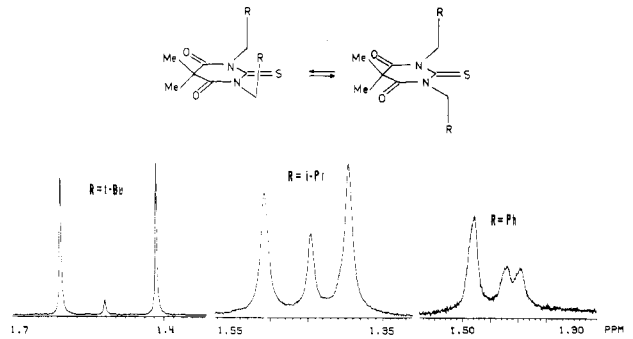

Figure 1. 360-MHz NMR spectrum of **3a**, **3b**, and **3e** showing the signals from the *gem*-dimethyl groups at low temperature, where the rotations of the *N*-alkyl groups are slow.

chlorodifluoromethane (Freon 12) because of its low viscosity at low temperatures and the strong lock signal. Some representative compounds were also studied in other solvents. The results are reported in Table I.

Compound **3a** exhibited a very simple ^{1}H NMR spectrum at room temperature in dimethyl-d_6 ether. It consisted of three singlets at δ 0.98 (*tert*-butyl), δ 1.52 (*gem*-dimethyl), and δ 4.60 (methylene), with the latter one broadened. When the temperature was lowered, all signals broadened and decoalesced. At −70 °C two subspectra could be identified as syn (94%) and anti (6%) conformers. The methylene protons appeared as two AB systems and the *gem*-dimethyl groups as a pair of singlets for the syn and a singlet for the anti conformer. The two signals from the syn form were assigned by an NOE difference experiment. Preirradiation of the *tert*-butyl signal resulted in an NOE enhancement of the low-field signal at δ 1.62 of 2.2% and −0.5% of the high-field signal at δ 1.41. Thus, the low-field signal at δ 1.62 originates from the methyl group syn to the two *tert*-butyl groups, and the negative NOE for the high-field signal is a three-spin effect. A value for $\Delta G^{\ddagger}$ at −21 °C of 12.0 kcal mol^{-1} was evaluated from the band-shape analysis. Band-shape analysis was also used to determine the fractional populations at several temperatures from −60 to −130 °C, which gave the following parameters for the syn ⇌ anti equilibrium: $\Delta G°$(−81 °C) = 1.02 ± 0.05 kcal mol^{-1}; $\Delta H°$ = 0.89 ± 0.1 kcal mol^{-1}; $\Delta S°$ = −1.0 ± 0.5 cal mol^{-1} K^{-1}.

The conformational probe, the *gem*-dimethyl groups, turned out to provide unequivocal syn–anti assignment in most of the cases. Some examples of the appearance of the low-temperature spectra of these groups are shown in Figure 1. In a few cases, however, ^{1}H NMR failed in this respect, and we had to resort to ^{13}C NMR spectroscopy. Thus, the methyl proton signals in **3d** were hidden under the multiplet from the adamantyl protons, but in ^{13}C NMR the 5,5-dimethyl carbons gave unperturbed signals.

Although the rotation of the ethyl groups of **3c** was readily frozen, and a barrier of 8.1 kcal mol^{-1} could be determined from the methylene spectrum, the *gem*-dimethyl groups only gave partly resolved signals after rather heavy apodization, making the determination of conformer populations uncertain. ^{13}C NMR helped in this case also.

The only compound for which the rotation of the nitrogen substituents could not be frozen was the (trimethylsilyl)methyl derivative **3g**. It may seem surprising that the barrier for this group is lower than that of the ethyl group in **3c**. The difference in bond length (the C–Si bond is ca. 0.30–0.35 Å longer than the C–C bond), however, has a significant effect on the strain in the transition state for the rotation. A similar effect was recently reported for the rotational barriers in hexaisopropylbenzene ($\Delta G^{\ddagger} \approx 35$ kcal mol^{-1}) and hexakis(dimethylsilyl)benzene ($\Delta G^{\ddagger}$ = 14.2 kcal mol^{-1}).[24,25]

In the unsymmetrically substituted derivative **3i**, two conformational exchange processes were observed. The room-temperature spectrum consisted of singlets at δ 0.92 (*tert*-butyl), δ 1.50 (*gem*-dimethyl), δ 4.52 (methylene of neopentyl, br), δ 5.64 (methylene of benzyl), and a multiplet at δ 7.14–7.36 (aromatic). Below room temperature the signals at δ 1.50, 4.52, and 5.64 decoalesced, and at −50 °C they appeared as a pair of singlets, an AB system, and a broad, unresolved AB system, respectively. This process was identified as the neopentyl rotation and the barrier, $\Delta G^{\ddagger}$ = 12.2 kcal mol^{-1}, is in good agreement with the neopentyl barrier determined for **3a**. In a second process, observable at 360 MHz between −50 and −100 °C, all signals, except the singlet at δ 1.43, underwent decoalescence to give two subspectra in the proportions 68:32. The barrier was determined as $\Delta G^{\ddagger}$ = 9.4 kcal mol^{-1}, in striking agreement with the barrier to benzyl rotation in **3e**.

As indicated above, the *gem*-dimethyl groups are not a conformational probe in **3i**, since the two methyl groups are diastereotopic in both syn and anti conformers. Our assignments, with the syn conformer as the major constituent, are accordingly less straightforward and are based upon the results of the molecular mechanics calculations (vide infra) and chemical shift considerations.

Solvent Effects. As shown in Table I, the compounds **1a**, **3a**, and **3h** were studied in several solvents. The number of available solvents was limited by the criteria for good solvents for low-temperature NMR.

The data reveal quite a remarkable difference between the two neopentyl compounds **1a** and **3a**. The thiobarbiturate shows an important solvent dependence of the syn–anti equilibrium, whereas solvent effects are absent for the imidazoline-2-thione derivative.

In order to rationalize the solvent effects on the conformational equilibria, we used the method proposed by Zefirov and Samoshin,[26] in which an empirical parabolic function was devised, according to eq 1, where $X = (\epsilon - 1)/(2\epsilon + 1)$ and A and B are empirical parameters. The advantages of this method are as follows: (i) It is derived to be used for conformational correlations and known to give satisfactory results. (ii) The only solvent parameter needed is the dielectric constant, which is known for most solvents even at the low temperatures of interest here. (iii) The method is suitable for extrapolation to gas-phase values. The plots in Figure 2 show that for solvents of low or moderate polarity linear relations are obtained. On the other hand, acetone and, in particular, methanol deviate strongly. Hydrogen bonding seems to be a plausible explanation in the case of methanol, but the effects of acetone suggest other contributions. The solvent mixture dimethyl ether–dichlorodifluoromethane could not be included in the plots, since the dielectric constant for this mixture is unknown. The use of any conceivable value for ϵ (ϵ 9.9 for dimethyl ether[27] and ϵ 2.1 for dichlorodifluoromethane[28]), however, reveals that this solvent also deviates from the linear relation.

$$\Delta G° = A + B(0.5 - X)^{1/2} \quad (1)$$

The linear, low-polarity parts of the plots were used for extrapolation to gas-phase values. The dielectric constant

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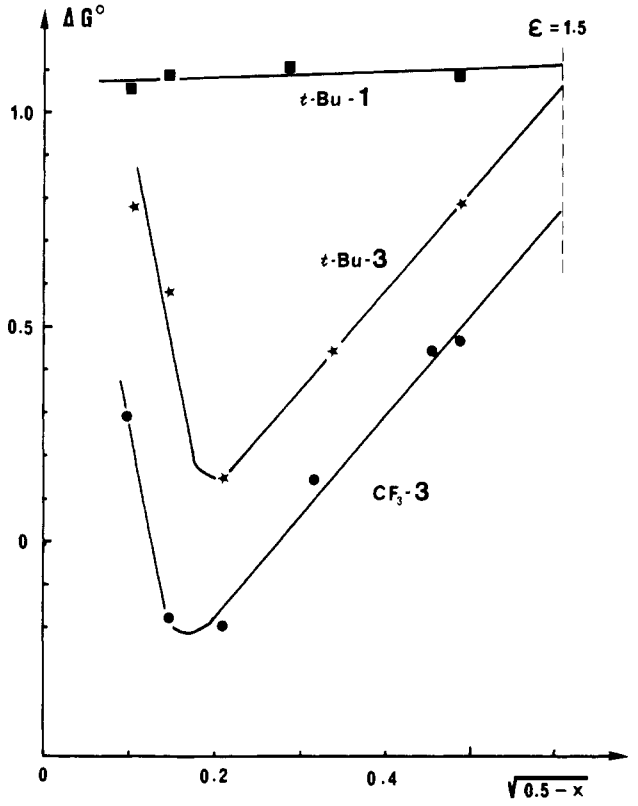

Figure 2. Plots of $\Delta G°$ versus solvent polarity according to Zefirov and Samoshin[26] for **1a**, **3a**, and **3h**. $X = (\epsilon - 1)/(2\epsilon + 1)$.

for the gas phase was set to 1.5 in order to conform with the value used in the molecular mechanics calculations (vide infra). The extrapolated gas-phase value for **3a**, $\Delta G°$ = 1.06 kcal mol^{-1}, is quite similar to the value in dimethyl ether–dichlorodifluoromethane, 1.02 kcal mol^{-1}, and reasonable agreement was also found for the adamantylmethyl compound **3d**, 0.59 (gas phase) and 0.80 kcal mol^{-1} (solution), even though the gas-phase value was extrapolated from only two solvents.

There is a striking parallelism between the curves for **3a** and **3h**, also in the region for high-polarity solvents. This is a little surprising, since the trifluoroethyl groups of **3h** are appreciably polar, and a medium-dependent electrostatic contribution would be expected to have an influence on the syn–anti equilibrium. These findings indicate that the solvent dependence of the equilibrium stems from an interaction between the solvent and the thiobarbiturate system, and not from a solvent effect on the interaction between the alkyl groups. This view is also supported by the absence of solvent effects in **1a**.

The reason for the difference in behavior between **1a** and **3a** is by no means obvious. Imidazoline-2-thiones are considerably more polar than thiobarbiturates. The dipole moment of the former system is ca. 5 D,[29] but unfortunately the dipole moment of the thiobarbiturate system is unknown. However, if we consider the dipole moments of a series of (thio)uracils,[30,31] we may conclude that the values for 5,5-dialkylthiobarbiturates are not far from the value for 5,5-diethylbarbituric acid (1.1 D[32]). Preliminary CNDO/2 and ab initio (STO-3G) calculations from our laboratory support these estimated values. The thiobarbiturate system is probably better described as a multipolar molecule, and possibly the carbonyl groups are sites for more efficient solvation than the thiocarbonyl group.

Molecular Mechanics Calculations. The theoretical treatment of the van der Waals attraction is not trivial. Quantum mechanical methods require the inclusion of configuration interaction, since the dispersion energy essentially arises from electron correlation. Thus, ab initio calculations, with a minimal basis set and without inclusion of configuration interaction, failed to account for the equilibrium between the 1,4- and 1,6-isomers of dialkylcyclooctatetraene, whereas the semiempirical PCILO method, which is based on a configuration interaction approach, fairly well reproduced the relative stabilities of the isomers.[12]

The best established examples in which molecular structure is governed by van der Waals attraction, the conformational distribution in 1,3,5-trineopentylbenzene derivatives[8] and the valence isomerism of 1,4- and 1,6-dialkylcyclooctatetraene,[11] were successfully treated by molecular mechanics calculations.

In the MM2 version used in this work (Allinger's 1977 force field), the van der Waals energy is calculated from eq 2, in which the first term accounts for the short-range,

$$U(r) = \epsilon[Ae^{-\alpha r/r_0} - B(r_0/r)^6] \quad (2)$$

repulsive forces and the second term accounts for the attractive dispersion forces. In this equation, -1.1ϵ defines the minimum energy value, r_0 the minimum energy distance, and α, A, and B are constants.

The heterocyclic systems studied in this work are not ideally suited for molecular mechanics calculation in that no established force field exists. We have treated the heterocyclic rings as rigid, planar frameworks using idealized geometries, although it is known that (thio)barbiturates are slightly puckered when disubstituted in the 5-position.[33] Instead of constructing an ad hoc force field for the ring systems, we preferred to introduce this approximation. We have concentrated the study to the ground-state properties, because the force-field limitations are expected to pose more serious problems in the transition state.

The calculations yielded two groups of conformations for all compounds studied, corresponding to the syn and anti conformers. In each group, some of the compounds had two or three stable conformers with an energy difference of less than 1.5 kcal mol^{-1}. The primary alkyl substituents were essentially perpendicular to the ring, in agreement with earlier findings.[1] The relative stabilities of the syn and anti conformers are shown in Table I, together with experimental $\Delta G°$ values statistically corrected for the fact that the anti conformers are chiral (C_2 symmetry) and the syn conformers are not (C_s symmetry), in all cases except for the unsymmetrically substituted compound **3i**. The experimental $\Delta G°$ values were measured in dimethyl-d_6 ether–dichlorodifluoromethane solution, and a direct comparison with calculated enthalpy differences in the gas phase requires some comments. First, the entropy contribution was found to be small, 1 cal mol^{-1} K^{-1} in favor of the syn form in the case of **3a**, which is in line with what is generally observed for conformational equilibria. Second, the solvent studies reported above showed that the $\Delta G°$ values determined in this solvent were close to the values extrapolated to ϵ 1.5 for **3a** and **3d** but not for **3h**. The latter compound requires special considera-

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tion, however, since the rotor groups contain the polar trifluoromethyl groups.

The agreement between calculated and experimental values is satisfactory; the only somewhat larger discrepancy concerns compound **3h**, which will be treated separately. A detailed analysis of the partitioning of the conformational energies will only reflect the force-field properties and has no physical meaning, and we have resisted such an analysis, even though it is tempting as a support for the presence of van der Waals attraction. In general terms, however, the larger groups, such as *tert*-butyl and adamantyl, are placed close together in the syn conformer, with the nearest hydrogen atoms separated by about 3 Å, close to the van der Waals minimum. The energy for two interacting hydrogen atoms at the van der Waals minimum is −0.06 kcal mol^{-1} in the MM2 force field. Most of the 169 interactions of two *tert*-butyl groups and 625 interactions of two adamantyl groups are, however, at longer distances and give only smaller energy contributions. The larger number of interactions in the adamantyl derivative seems to be compensated for by the higher flexibility of the *tert*-butyl groups so as to optimize the attraction. The distance between the tertiary carbon atoms in the *tert*-butyl and adamantyl groups is 6.0–6.1 Å (compounds **1a**, **2a**, **3a**, and **3d**), and the distance between the secondary carbon atoms in the isopropyl groups is 5.5 Å (compounds **1b** and **3b**).

The only compound containing appreciably polar rotor groups is **3h**. The trifluoromethyl groups have net group moments that result in dipole–dipole effects, which should disfavor the syn conformer, and lead to a syn–anti dependence on the polarity of the solvent. Using C–F bond moments of the MM2 force field and performing calculations for various dielectric media, we obtained values for ΔE_{calcd} from −0.11 (ϵ 1.5) to +0.13 kcal mol^{-1} (ϵ 99). The trend is opposite to the one found experimentally for moderate- and low-polarity solvents, and the total range in ΔE_{calcd} is rather small. These observations further support our conclusion that the solvent effects on the thiobarbiturates are due to specific interactions between the solvent and the polar groups of the thiobarbiturate ring. The use of normal C–F bond moments may be questioned, since trisubstitution should lead to a leveling effect. In order to estimate the magnitude of the effect we performed identical calculations, but with zero bond moments for the C–F bonds. This resulted in a moderate change of the ΔE_{calcd} value from −0.11 to +0.13 kcal mol^{-1}. Still, the discrepancy between experiment and theory is comparatively large.

The MM2 (MMP2) force field predicts the syn conformer of the dibenzyl compound **3e** to be 0.55 kcal mol^{-1} more stable than the anti conformer. Although this value does not drastically deviate from the experimental value, we recommend scepticism toward MM2 (MMP2) computations of phenyl–phenyl interactions, since this force field has been shown to give an incorrect description of benzene–benzene and phenyl–phenyl interactions.[4,34] This deficiency may be overcome by the addition of electrostatic interactions, using point charges on carbon and hydrogen atoms. The inclusion of electrostatic interaction between the phenyl rings in **3e** by the addition of point charges[34] gives ΔE_{calcd} = −0.05 kcal mol^{-1}.

Discussion

The results presented above show that most of the compounds studied prefer the more "crowded" syn conformation and that this preference is due to intramolecular forces. The solvent effects illustrated in Figure 2 indicate that the relative stability of the syn conformer is even higher in a "gas-phase" dielectric medium than in the solvents used here. It should be borne in mind, however, that the values extrapolated to ϵ 1.5 do not represent values for the isolated molecule in the gas phase. The significant internal pressure in solution shifts the equilibrium toward the conformer with smallest molecular volume.[35,36] We failed, however, to see any regular relationship between $\Delta G°$ and the internal pressure of the solvents. Therefore, we intend to examine the pressure dependence of the equilibrium. In order to complete the discussion of the phase dependence, it should be noted that both 1,3-diethylbarbiturate and 1,3-diethylthiobarbiturate assume the syn arrangement in the crystal.[37] The thiobarbiturate is enolized and has a planar ring, but the oxo analogue has an sp^3-hybridized 5-carbon atom, which is also slightly out of the average plane of the other ring atoms.

A point of interest is the trend that the dominance of the syn conformer is more important for the larger alkyl groups. A similar effect was also noted by Allinger et al. in the case of the 1,4- and 1,6-dialkylcyclooctatetraene equilibrium.[11] These authors also noted that the trend in van der Waals attraction energy parallels the total number of interactions between the alkyl groups. The observed trends, however, reflect interactions at different positions on the potential energy curve for the various alkyl groups, since the groups are displaced by essentially the same distance, determined by the structure of the heterocyclic framework. For example, the *tert*-butyl groups are rather close to the optimum distance in **1a**, **2a**, and **3a**, but this is not the case for the methyl groups in **3c**.

In the preceding sections we have rationalized the observed effects in terms of van der Waals attraction. Support for this was mainly found in the molecular mechanics calculations. It is by no means the only conceivable attractive, nonbonded interaction between proximate atoms or groups of atoms. Electrostatic interactions play a role when polar or charged groups are present, and charge-transfer interactions were recently proposed to account for the aryl–aryl gauche conformation of *N*-(1-phenyl-2-propyl)nicotinamide chloride.[38] Other stabilizing effects need the use of a quantum chemical approach. The interaction between molecular orbitals of appropriate symmetry, particularly those of lone pairs and unsaturated bonds, can be attractive in nature.[39] Typically, this phenomenon has been successfully used to account for the gauche effect (e.g., in 1,2-difluoroethane) and the cis effect (e.g., in 1,2-difluoroethylene). However, neither of these concepts seems to be applicable to our systems, at least if we restrict the discussion to the pure alkyl derivatives of **1**, **2**, and **3a–d**. In the trifluoroethyl compound **3h**, the situation is less clear. Obviously, an electrostatic contribution should destabilize the syn conformer, and nonbonded MO interactions cannot, a priori, be excluded. The close parallelism of the curves in Figure 2, however, suggests that neither of these effects is of significance in this case.

Repulsive interactions with the thiobarbiturate framework prohibit the phenyl groups in **3e** from assuming the most favourable perpendicular arrangement[4,34] in the syn conformer. In order to avoid this interaction with the

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framework, we synthesized compound **3f** in which the phenyl groups are displaced from the ring by another methylene group. With this modification we had hoped to find a molecule with a strong attractive interaction between the phenyl groups. Apparently we failed, perhaps due to unfavorable entropy contributions.

In compound **3i**, which has the mixed benzyl–neopentyl substitution pattern, the omission of point charges is unimportant, and the interaction should be correctly described by van der Waals potentials alone, just as for the dialkyl interactions in compounds **1**, **2**, and **3a–d**. We thus consider the ΔE_{calcd} value (0.54 kcal mol^{-1}) as reliable as those of the dialkyl compounds, and as strong support for the preference of the syn conformer.

The rotational barriers span a range from <7 to 13.3 kcal mol^{-1} and were determined at quite different temperatures (−102 to +12 °C). Since the only measured quantity is the Gibbs free energy of activation, a direct comparison requires that the entropies of activation are of similar magnitude and close to zero. This is a reasonable assumption, but it has to be kept in mind in any comparison.

The barrier heights of the corresponding imidazoline-2-thiones and thiobarbiturates are of similar magnitude. This similarity probably conceals two opposite effects. On the one hand, the larger ring size of **3** leads to closer flanking substituents and increases the barrier. On the other hand, the oxygen atom is a considerably smaller group than the methyl group, which has an opposite effect on the barrier. In both cases, the sulfur atom is the larger adjacent group, and rotation takes place via the opposite substituent.[1]

The most striking aspect is the large difference in barrier heights between the systems **1** and **2**. Apparently, the opening of the bond angle upon ring closure of the five-membered ring has a dramatic effect.

This study gives clear evidence that two primary alkyl groups in general prefer the syn conformation when they are 1,3-substituents in a five- or six-membered ring. In a broader perspective, it turns out that for two primary alkyl groups attached to a planar sp^2 framework, the substitution pattern determines whether attraction or repulsion will predominate, provided that other factors cancel. Thus, repulsion seems to predominate in the syn conformation when the groups are geminal,[2,4] cis–vicinal,[4] or ortho[3,5,6] to each other, leading to preferred anti conformations, whereas attraction usually predominates in the syn conformation when the groups are trans–vicinal[4] or meta[7–9] (and possibly para) to each other. The importance of these conformational relations for the chemical properties and biological activities of these molecules remains to be explored.

Conclusions

An overwhelming majority of the compounds studied in this work has been unequivocally shown to prefer the more crowded syn conformation, including groups of very diverse sizes, symmetries, and electronic properties.

The effects of solvent polarity and the results of the molecular mechanics calculations indicate that the conformational preference is due to intramolecular, attractive interactions between the groups. Molecular mechanics calculations give satisfactory agreement with experiments and provide support for the operation of van der Waals attraction as the most important factor determining the conformational equilibrium.

Experimental Section

Syntheses. The imidazoline-2-thione derivatives were prepared by condensation of the appropriate *N,N'*-di(primary alkyl)thioureas with either acetoin (for compounds **1**) or 2-hydroxy-4,4-dimethylcyclopentanone,[40] according to a previously described route.[41] The reagents were refluxed in hexanol under azeotropic water-eliminating conditions. After workup moderate yields of the desired products were obtained.

1,3-Dineopentyl-4,5-dimethylimidazoline-2-thione (1a) was prepared from *N,N'*-dineopentylthiourea (2.2 g, 0.01 mol) and acetoin dimer (0.5 g, 0.0057 mol). The reaction mixture was evaporated, and the crude product was purified by flash chromatography on silica (methylene chloride–light petroleum ether) to give 0.45 g (19%) of the title compound after recrystallization from 80% ethanol: mp 117–118 °C; ^{1}H NMR ($(CD_3)_2O$) δ 1.04 (s, 18 H), 2.12 (s, 6 H), 3.0–5.0 (4 H, br d); mass spectrum, *m/e* (relative intensity) 268 (27), 253 (7), 235 (30), 197 (6), 183 (9), 179 (19), 165 (30), 156 (8), 142 (22), 141 (12), 128 (16), 127 (12), 109 (5), 97 (8), 43 (100). Anal. Calcd for $C_{15}H_{28}N_2S$: C, 67.1; H, 10.50; N, 10.43; S, 11.95. Found: C, 66.8; H, 10.33; N, 10.3; S, 12.1.

1,3-Diisobutyl-4,5-dimethylimidazoline-2-thione (1b) was prepared from *N,N'*-diisobutylthiourea (1.9 g, 0.01 mol) and acetoin dimer (0.9 g, 0.01 mol). The solvent was removed and the residue chromatographed on silica (methylene chloride–light petroleum ether) to give 0.60 g (25%) of the title product as a viscous yellow oil: ^{1}H NMR ($(CD_3)_2O$–CCl_2F_2) δ 0.90 (d, 12 H, J = 6.9 Hz), 2.08 (s, 6 H), 2.43 (doublet of septets, 2 H, J = 6.9 Hz), 3.80 (d, 4 H, J = 6.9 Hz); mass spectrum, *m/e* (relative intensity) 240 (31), 207 (6), 184 (9), 169 (5), 151 (12), 142 (8), 129 (12), 128 (100), 95 (9), 68 (11), 57 (17), 55 (18), 42 (36), 41 (77). Anal. Calcd for $C_{13}H_{24}N_2S$: C, 64.9; H, 10.06; N, 11.65; S, 13.34. Found: C, 64.6; H, 9.93; N, 11.4; S, 13.3.

1,3-Dineopentyl-4′,4′-dimethyl-3′*H*-4′,5′-dihydrocyclopenta[1′,2′-*d*]imidazoline-2-thione (2a) was obtained from 2-hydroxy-4,4-dimethylcyclopentanone (1.3 g, 0.01 mol) and *N,N'*-dineopentylthiourea (2.2 g, 0.01 mol). Chromatography on silica (methylene chloride–light petroleum ether) and recrystallization from ethanol yielded 2.1 g (68%) of the title compound: mp 149–151 °C, ^{1}H NMR ($(CD_3)_2O$–CCl_2F_2) δ 1.00 (s, 18 H), 1.28 (s, 6 H), 2.58 (s, 4 H), 3.87 (s, 4 H); mass spectrum, *m/e* (relative intensity) 308 (40), 275 (30), 219 (14), 205 (14), 181 (11), 57 (17), 55 (19), 43 (100). Anal. Calcd for $C_{18}H_{32}N_2S$: C, 70.0; H, 10.46; N, 9.08; S, 10.39. Found: C, 69.5; H, 10.29; N, 9.5; S, 10.7.

1,3-Diisobutyl-4′,4′-dimethyl-3′*H*-4′,5′-dihydrocyclopenta[1′,2′-*d*]imidazoline-2-thione (2b) was prepared from 2-hydroxy-4,4-dimethylcyclopentanone (1.2 g, 0.009 mol) and *N,N'*-diisobutylthiourea (1.7 g, 0.009 mol). The product was chromatographed on silica (methylene chloride–light petroleum ether) and recrystallized from ethanol to give 1.3 g (52%) of pale yellow crystals, which darken in the light: mp 60–61 °C; ^{1}H NMR ($(CD_3)_2O$–CCl_2F_2) δ 0.89 (d, 12 H, J = 7.0 Hz), 1.26 (s, 6 H), 2.33 (doublet of septets, 2 H, J = 7.0 Hz), 2.49 (s, 4 H), 3.71 (d, 4 H, J = 7.0 Hz); mass spectrum, *m/e* (relative intensity) 281 (26), 280 (100), 247 (12), 224 (22), 191 (15), 168 (86), 167 (28), 153 (11), 57 (29), 41 (92). Anal. Calcd for $C_{16}H_{28}N_2S$: C, 68.5; H, 10.06; N, 9.99; S, 11.43. Found: C, 68.1; H, 9.87; N, 9.7; S, 11.6.

The thiobarbituric acid derivatives were prepared from dimethylmalonic acid and the appropriate *N,N'*-di(primary alkyl)thiourea by heating in a large excess of acetyl chloride for 1–18 h.[42] After cooling, the mixture was triturated with water and the pasty mass flash chromatographed on silica (methylene chloride–light petroleum ether), giving usually poor yields of the desired product.

In most of the reactions a byproduct was observed, which is probably a rearranged isomer with one alkyl group migrated to the sulfur atom. This byproduct could usually be removed by chromatography on an acidic aluminum oxide column.

5,5-Dimethyl-1,3-dineopentyl-4,6-dioxohexahydropyrimidine-2-thione (3a) was synthesized from *N,N'*-dineopentylthiourea (0.6 g, 0.0027 mol) and dimethylmalonic acid (0.4 g, 0.003 mol). Recrystallization from 60% ethanol gave nearly white crystals of **3a**: 60 mg (7%); mp 69–70 °C; ^{1}H NMR ($(CD_3)_2O$) δ 0.98 (s, 18 H), 1.52 (s, 6 H), 4.60 (br s, 4 H); mass spectrum, *m/e* (relative intensity) 312 (12), 241 (9), 227 (8), 223

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(12), 200 (27), 155 (10), 126 (10), 86 (12), 71 (19), 70 (62), 69 (41), 57 (100), 55 (35), 43 (90), 41 (90).

1,3-Diisobutyl-5,5-dimethyl-4,6-dioxohexahydropyrimidine-2-thione (3b) was prepared from *N,N'*-diisobutylthiourea (0.95 g, 0.005 mol) and dimethylmalonic acid (1 g, 0.007 mol). After chromatography on silica, a yellow oil was obtained. According to TLC and ^{1}H NMR, the product contained ca. 25% of an impurity (according to NMR, probably the isomer with one isobutyl group migrated to the sulfur atom). Flash chromatography on acidic alumina effectively eliminated the impurity and yielded a viscous, yellow oil: 0.47 g (35%); ^{1}H NMR ($(CD_3)_2O$–CCl_2F_2) δ 0.91 (d, 12 H, J = 7.1 Hz), 1.49 (s, 6 H), 2.32 (doublet of septets, 2 H, J = 7.2 Hz), 4.27 (d, 4 H, J = 7.2 Hz); mass spectrum, m/e (relative intensity) 284 (10), 229 (31), 173 (20), 116 (11), 114 (12), 86 (21), 70 (68), 57 (49), 55 (41), 43 (32), 42 (71), 41 (100). Anal. Calcd for $C_{14}H_{24}N_2O_2S$: C, 59.1; H, 8.50; N, 9.85; S, 11.27. Found: C, 58.9; H, 8.42; N, 9.7; S, 11.0.

1,3-Diethyl-5,5-dimethyl-4,6-dioxohexahydropyrimidine-2-thione (3c) was prepared from *N,N'*-diethylthiourea (1.5 g, 0.007 mol) and dimethylmalonic acid (0.9 g, 0.007 mol). Recrystallization of the crude product from ethanol gave pale yellow crystals: 0.35 g (22%); mp 46–48 °C; ^{1}H NMR ($(CD_3)_2O$–CCl_2F_2) δ 1.21 (t, 6 H, J = 7.0 Hz), 1.45 (s, 6 H), 4.43 (q, 4 H, J = 7.0 Hz); mass spectrum, m/e (relative intensity) 228 (28), 195 (17), 185 (9), 169 (6), 131 (14), 97 (11), 86 (11), 70 (100), 69 (41), 60 (22), 56 (10), 44 (83), 42 (83), 41 (61). Anal. Calcd for $C_{10}H_{16}N_2O_2S$: C, 52.6; H, 7.05; N, 12.3; S, 14.0. Found: C, 52.4; H, 7.00; N, 12.0; S, 14.2.

1,3-Bis(1-adamantylmethyl)-5,5-dimethyl-4,6-dioxohexahydropyrimidine-2-thione (3d) was prepared from *N,N'*-bis(adamantylmethyl)thiourea (0.6 g, 0.0016 mol) and dimethylmalonic acid (0.21 g, 0.0016 mol). The first eluted band from the flash chromatography was recrystallized from ethanol and yielded slightly yellow crystals: 25 mg (3%); mp 148–151 °C; ^{1}H NMR ($(CD_3)_2O$–CCl_2F_2) δ 1.5–2.0 (m, 36 H), 4.43 (br s, 4 H); ^{13}C NMR ($(CD_3)_2O$–CCl_2F_2, −69 °C) δ 19.50, 25.38, 29.79 (5-CH_3), 29.50 (3'-CH), 37.72 37.80 (4'-CH_2), 37.88 (1'-C), 42.09, 42.26 (2'-CH_2), 49.84, 50.25 (5-C), 57.19, 58.14 (NCH_2), 173.19 (C=O), 185.31 (C=S); mass spectrum, m/e (relative intensity) 468 (7), 467 (4), 453 (5), 435 (3), 398 (3), 333 (3), 319 (4), 305 (3), 233 (3), 176 (3), 164 (6), 149 (30), 135 (100), 119 (6), 107 (20), 93 (50), 91 (18), 79 (43), 70 (25), 69 (25), 67 (32), 55 (21), 44 (22).

1,3-Dibenzyl-5,5-dimethyl-4,6-dioxohexahydropyrimidine-2-thione (3e) was prepared from *N,N'*-dibenzylthiourea (1.3 g, 0.005 mol) and dimethylmalonic acid (1 g, 0.0076 mol). Recrystallization from ligroin gave pale yellow crystals: 53 mg (4%); mp 125–126 °C; ^{1}H NMR ($(CD_3)_2O$–CCl_2F_2) δ 1.46 (s, 6 H), 5.61 (s, 4 H), 7.15–7.36 (m, 10 H); mass spectrum, m/e (relative intensity) 352 (21), 261 (9), 191 (10), 148 (11), 132 (22), 106 (11), 91 (100), 86 (17), 70 (17), 65 (22), 42 (23), 41 (29).

1,3-Bis(2-phenylethyl)-5,5-dimethyl-4,6-dioxohexahydropyrimidine-2-thione (3f) was prepared from *N,N'*-bis(2-phenylethyl)thiourea (1.4 g, 0.005 mol) and dimethylmalonic acid (0.7 g, 0.0053 mol). The solvent from the chromatographed product was removed, which left 0.16 g (8%) of a viscous, yellow oil: ^{1}H NMR ($(CD_3)_2O$–CCl_2F_2) δ 1.35 (s, 6 H), 2.98 (m, 4 H), 4.59 (m, 4 H), 7.12–7.31 (m, 10 H); mass spectrum, m/e (relative intensity) 380 (4), 276 (3), 207 (4), 128 (3), 104 (100), 103 (10), 91 (10), 77 (10), 70 (31), 42 (23). Anal. Calcd for $C_{22}H_{24}N_2O_2S$: C, 69.5; H, 6.36; N, 7.4; S, 8.4. Found: C, 69.2; H, 6.17; N, 7.1; S, 8.2.

1,3-Bis[(trimethylsilyl)methyl]-5,5-dimethyl-4,6-dioxohexahydropyrimidine-2-thione (3g) was prepared from *N,N'*-bis[(trimethylsilyl)methyl]thiourea (0.5 g, 0.0025 mol) and dimethylmalonic acid (0.35 g, 0.0026 mol). Flash chromatography (methylene chloride–light petroleum ether) gave two pure fractions, a yellow oil of the title compound (25 mg, 3%) and 90 mg of an impurity, probably the isomer with one (trimethylsilyl)-methyl group migrated to the sulfur atom. The title compound had the following characteristics: ^{1}H NMR ($(CD_3)_2O$–CCl_2F_2) δ 0.09 (s, 18 H), 1.50 (s, 6 H), 4.06 (s, 4 H); mass spectrum, m/e (relative intensity) 344 (2), 329 (53), 301 (2), 299 (2), 287 (2), 271 (2), 228 (2), 213 (2), 199 (2), 184 (3), 170 (2), 156 (25), 143 (3), 129 (3), 126 (3), 116 (5), 114 (3), 102 (9), 100 (10), 87 (16), 86 (22), 82 (20), 73 (100), 70 (37), 59 (91), 45 (60), 41 (52).

1,3-Bis(2,2,2-trifluoroethyl)-5,5-dimethyl-4,6-dioxohexahydropyrimidine-2-thione (3h) was prepared from *N,N'*-bis(2,2,2-trifluoroethyl)thiourea (1.0 g, 0.0042 mol) and dimethylmalonic acid (0.4 g, 0.003 mol). Flash chromatography yielded pale brown oily crystals: 71 mg (70%); mp 52–54 °C; ^{1}H NMR ($(CD_3)_2O$–CCl_2F_2) δ 1.54 (s, 6 H), 5.30 (q, 4 H, J = 8.4 Hz); ^{13}C NMR (CD_2Cl_2, −96 °C) δ 23.16, 23.66, 23.88 (3 s, 5-CH_3), 47.18 (q, NCH_2, J = 35.4 Hz), 49.29, 49.39 (2 s, 5-C), 123.63 (q, CF_3, J = 281.2 Hz), 169.92, 179.28 (s, C=O), 179.28 (s, C=S); ^{19}F NMR ($(CD_3)_2O$–CCl_2F_2, reference CCl_2F_2) δ 116.5 (t, J = 8.4 Hz); mass spectrum, m/e (relative intensity) 336 (8), 83 (7), 71 (69), 69 (16), 42 (100).

1-Benzyl-5,5-dimethyl-3-neopentyl-4,6-dioxohexahydropyrimidine-2-thione (3i) was prepared from *N*-benzyl-*N'*-neopentylthiourea contaminated by ca. 20% of a mixture of *N,N'*-dibenzyl- and *N,N'*-dineopentylthiourea (1.2 g) and dimethylmalonic acid (0.7 g, 0.0053 mol). Flash chromatography (silica, methylene chloride–light petroleum ether) gave ca. 250 mg of a mixture (3 to 2 according to NMR). Chromatography on acidic alumina (methylene chloride) gave a yellow oil: 57 mg; ^{1}H NMR ($(CD_3)_2O$–CCl_2F_2) δ 0.92 (s, 9 H), 1.50 (s, 6 H), 4.52 (br s, 2 H), 5.64 (s, 2 H), 7.15–7.35 (m, 5 H); mass spectrum, m/e (relative intensity) 332 (10), 299 (2), 241 (6), 106 (17), 92 (11), 91 (100), 86 (15), 70 (49), 69 (22), 65 (19), 57 (40), 44 (33), 43 (45), 42 (45), 41 (67). Anal. Calcd for $C_{18}H_{24}N_2O_2S$: C, 65.0; H, 7.28; N, 8.4; S, 9.6. Found: C, 64.5; H, 7.03; N, 8.3; S, 9.6.

The thiourea derivatives were prepared by heating the corresponding primary amine with carbon disulfide in ethanol. *N,N'*-Diethylthiourea was commercial (Fluka), and the following compounds have been described previously and had characteristics in agreement with those published: *N,N'*-dibenzylthiourea,[43] *N,N'*-diisobutylthiourea,[44] *N,N'*-dineopentylthiourea,[45] *N,N'*-bis(2-phenylethyl)thiourea,[46] and *N,N'*-bis(2,2,2-trifluoroethyl)-thiourea.[47]

***N,N'*-Bis(1-adamantylmethyl)thiourea** was prepared from 1-adamantylmethylamine (1 g, 0.006 mol) and excess carbon disulfide (0.2 mL) by heating to reflux in 10 mL of ethanol overnight. After the mixture was cooled to room temperature, a white powder crystallized: 1.1 g (98%); mp 244–246 °C; ^{1}H NMR ($CDCl_3$) δ 1.4–2.2 (m, 30 H), 3.10 (d, 4 H, J = 5.8 Hz), 5.7–6.0 (br s, 2 H). Anal. Calcd for $C_{23}H_{36}N_2S$: C, 74.14; H, 9.74; N, 7.52; S, 8.60. Found: C, 73.9; H, 9.59; N, 7.7; S, 8.8.

***N,N'*-Bis[(trimethylsilyl)methyl]thiourea** was prepared from trimethylsilylmethylamine (3 g, 0.029 mol) and carbon disulfide (1.1 g, 0.014 mol) by heating to reflux in 15 mL of ethanol for 3 h. After evaporation, the oily residue was flash chromatographed on silica (methylene chloride–ethyl acetate), which gave the title compound as nearly colorless crystals: 0.8 g (28%); mp 127–129 °C; ^{1}H NMR ($CDCl_3$) δ 0.11 (s, 18 H), 2.90 (d, 4 H, J = 5.3 Hz), 5.80 (br s, 2 H). Anal. Calcd for $C_9H_{24}N_2SSi$: C, 49.03; H, 10.97; N, 12.70; S, 14.54. Found: C, 49.3; H, 10.69; N, 12.6; S, 14.4.

***N*-Benzyl-*N'*-neopentylthiourea** was prepared from benzylamine (2 g, 0.019 mol), neopentylamine (1.65 g, 0.019 mol), and carbon disulfide (1.5 g, 0.020 mol) by heating to reflux in 25 mL of ethanol for 3 h. According to NMR, the three possible thioureas were formed in statistical proportions. After flash chromatography and recrystallization from ethanol (70%), a white powder was obtained, which contained ca. 10% of each of the two symmetrically substituted thioureas. This product was characterized by NMR and used without further purification: ^{1}H NMR ($CDCl_3$) δ 0.90 (s, 9 H), 3.21 (d, 2 H, J = 6.0 Hz), 4.61 (d, 2 H, J = 5.9 Hz), 5.9–6.2 (br s, 2 H), 7.29 (s, 5 H).

NMR spectra were recorded on a Nicolet 360 WB or a Varian XL 300 spectrometer. The samples were about 0.04 M in dimethyl-d_6 ether containing ca. 25% dichlorodifluoromethane. They were degassed by the high-vacuum freeze–thaw technique before being sealed.

The temperature scales of the instruments were calibrated by the use of a methanol–dimethyl-d_6 ether sample, which in turn had been calibrated by the technique described in ref 48.

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Table II. ^{1}H NMR Properties of the Studied Compounds at Low Temperature (Solvent: $(CD_3)_2O$–CCl_2F_2)

		chemical shift, δ						
		R		CH_3		CH_2		
compd	temp, °C	syn	anti	syn	anti	syn	anti	J_{AB}, Hz
1a	−9.3	1.015	1.015	2.145	2.167	3.43	3.45	13.9 (syn)
						4.65	4.51	13.9 (anti)
1b[a]	−121	0.90	0.71	1.91	1.86	4.2–4.35		
2a	−121	0.97		1.19		3.22		13.9 (syn)
				1.28		4.52		
2b[b]		0.88		1.26		3.64		
3a	−81	0.955	0.928	1.41	1.52	4.30	(4.30)	13.3 (syn)
				1.62		4.99	4.80	13.3 (anti)
3b	−116	0.95	0.82	1.40	1.455	4.10–4.35		
				1.52				
3c	−129	1.16		1.375	1.385	(4.22	4.22)	
				1.410		(4.29	4.29)	
3d	−69	1.4–2.0		(1.4–2.0)		4.12	4.09	13.7 (syn)
						4.87	4.69	13.5 (anti)
3e	−118	7.20–7.40		1.41	1.495	5.47	5.40	14.2 (syn)
				1.43		5.79	5.68	14.2 (anti)
3f	−113	2.78, 4.36		1.29	1.38	3.06	3.06	
		7.19–7.37		1.415		4.37	4.37	
3g[b]	−141	0.09		1.23		4.02		
3h	−102			1.459	1.478	5.30	5.13	
				1.493		5.63	5.50	
3i	−102	0.94	0.97 (*t*-Bu)	1.43	1.43	4.30	4.24	13.3 (syn)
				1.54	1.58	4.83	4.74	13.4 (anti)
		7.15–7.42 (Ph)				5.54	5.34	14.7 (syn)
						5.83	5.75	14.7 (anti)

[a] Solvent: $(CD_3)_2O$–toluene-d_8 (3:1). [b] Average signals from syn and anti.

Table III. New Force-Field Parameters

torsional angle	V_1	V_2	V_3, kcal mol^{-1}
N(sp^2)–C(sp^3)–Si–C(sp^3)	0.000	0.000	0.167
Si–C(sp^3)–N(sp^2)–C(C=O)	0.000	0.000	1.000
N(sp^2)–C(sp^3)–C(sp^3)–F	0.000	0.000	0.300
N(sp^2)–C(sp^3)–C(sp^2)–C(sp^2)	0.000	0.000	0.600
C(sp^2)–C(sp^3)–N(sp^2)–C(C=O)	0.000	0.000	1.000
C(sp^3)–C(sp^3)–C(sp^2)–N(sp^2)	0.400	0.030	0.500
H–C(sp^3)–C(sp^2)–N(sp^2)	0.000	0.000	0.530
C(sp^3)–C(sp^2)–N(sp^2)–C(sp^3)	0.000	0.000	0.000

Low-temperature NMR parameters are shown in Table II.

Band-shape analysis and evaluation of thermodynamic parameters were performed as previously described.[49,50] Band-shape analysis was used to determine both rate constants and conformer populations at low temperature. The programs used have been described previously,[22,51] and the band fitting was carried out on a PDP 11/34 computer with a GT 42 graphics terminal. Estimated errors are ±0.1 kcal mol^{-1} in $\Delta G^{\ddagger}$ and ±0.05 kcal mol^{-1} in $\Delta G°$ if not otherwise stated.[50]

NOE difference experiments were run by automatic frequency alteration using the following sequence: preirradiation, delay (50 ms), pulse, acquisition of one transient, delay (10 s). After ca. 100 passes through the cycle, the fid's were Fourier transformed and identically phased and the spectra subtracted.

Molecular mechanics calculations were performed with the MM2/MMP2 program developed by Allinger and co-workers[23] employing their 1977 force field. The torsional parameters not included in MM2 were taken from the literature.[52-54] The new parameters that are not included in the rigid imidazoline-2-thione or thiobarbiturate rings are given in Table III. Input structures for MM2/MMP2 were constructed with the molecular modeling program MIMIC.[55]

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Registry No. **1a**, 110457-99-3; **1b**, 110458-14-5; **2a**, 110458-00-9; **2b**, 110458-01-0; **3a**, 110458-02-1; **3b**, 110458-03-2; **3c**, 110458-04-3; **3d**, 110458-06-5; **3e**, 110458-07-6; **3f**, 110458-08-7; **3g**, 110458-10-1; **3h**, 110458-11-2; **3i**, 110458-13-4; acetoin dimer, 51555-24-9; *N*,*N*′-diisobutylthiourea, 29214-81-1; *N*,*N*′-dineopentylthiourea, 25347-86-8; 2-hydroxy-4,4-dimethylcyclopentanone, 54639-78-0; dimethylmalonic acid, 595-46-0; *N*,*N*′-diethylthiourea, 105-55-5; *N*,*N*′-bis(adamantylmethyl)thiourea, 110458-05-4; *N*,*N*′-dibenzylthiourea, 1424-14-2; *N*,*N*′-bis(2-phenylethyl)thiourea, 18085-24-0; *N*,*N*′-bis[(trimethylsilyl)methyl]thiourea, 110458-09-8; *N*,*N*′-bis(2,2,2-trifluoroethyl)thiourea, 79652-02-1; *N*-benzyl-*N*′-neopentylthiourea, 110458-12-3.

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