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Temperature coefficient of NH chemical shifts of thioamides and amides in relation to structure

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Abstract

NH chemical shift temperature coefficients have been measured in a large series of N-substituted-3-piperidinethiopropionamides in which the N···N distances are short but of varied length, as well as in a couple of the corresponding amides and in some simpler amides and thioamides. Geometries are calculated by means of ab initio DFT methods. The N-substituted-3-piperidinethiopropionamides show in most cases strong intramolecular N–H···N hydrogen bonds according to IR spectra and ab initio calculations. For compounds with rather short N···N distances the S=C–N–H moiety is non-planar. Dihedral angles as small as 160° are found. The NH chemical shift coefficients measured in non-polar solvents in all the N-substituted-3-piperidinethiopropionamides are more negative (−8 to −17 ppb/K) than in non-hydrogen bonded thioamides. For the latter in non-polar solvents like $CDCl_3$ and toluene the temperature coefficients are as small as −1 to −4 ppb/K. The large negative effects can be related not only to the non-planarity of the thioamide group in a way that the more pronounced the non-planarity the more negative the temperature coefficients, but also to strong hydrogen bonding and the fact that the acceptor is a nitrogen. For similar amides with non-planar amide groups and nitrogen acceptor large negative temperature coefficients are likewise seen. In polar solvents like DMF the effects in simple thioamides are uniform and close to −6 ppb/K, whereas in the more complex compound like **4p**(**t**) the temperature coefficient is close to 0. An essential feature of measuring temperature coefficients of compounds without strong intramolecular hydrogen bonds in non-polar solvents and at low temperatures is to keep the concentration low enough to avoid dimerisation.

Keywords: NH chemical shifts; NH temperature coefficients; Intramolecular hydrogen bonding; Ab initio calculations; Thioamides; Amides

1. Introduction

NH chemical shifts of amides as a function of temperature have attracted much attention as a monitor of hydrogen bonding [1–18]. Coefficients more positive than −4 to −5 ppb/K have especially in protein structure work been taken as evidence for intramolecular hydrogen bonding [3–8]. The effects in proteins were originally related to solvent access [1–3]. More recently it has been pointed out that conformational changes may play an important role [5,6]. In order to make predictions more reliable a combination of parameters have been suggested [4], but the temperature coefficients are so far not fully understood. Gellman et al. [14–18] have performed very extensive investigations of amides and peptides in non-polar solvents and demonstrated that equilibrium between inter and intramolecular hydrogen bonding or dimerisations could give both small and large temperature coefficients depending on the ΔH of the two hydrogen bonded states. These authors decided upon a value of −5 ppb/K in non-polar solvents for an ideal intramolecularly hydrogen bonded amide, whereas for compounds with no hydrogen bond they found values of approx. −2 ppb/K. They point to the necessity of keeping the concentration low, typically below 2 mg/ml for small amides as dimerisation otherwise could lead to wrong results (see below).

Temperature coefficients of thioamides have been investigated in a couple of cases [10,11]. In the present study a number of intramolecularly hydrogen bonded N-substituted-3-piperidine, morpholine thiopropionamides [19] have been investigated. Structures of all the compounds are calculated using ab initio DFT methods [20–22]. As reference non-hydrogen bonded thioamides are also

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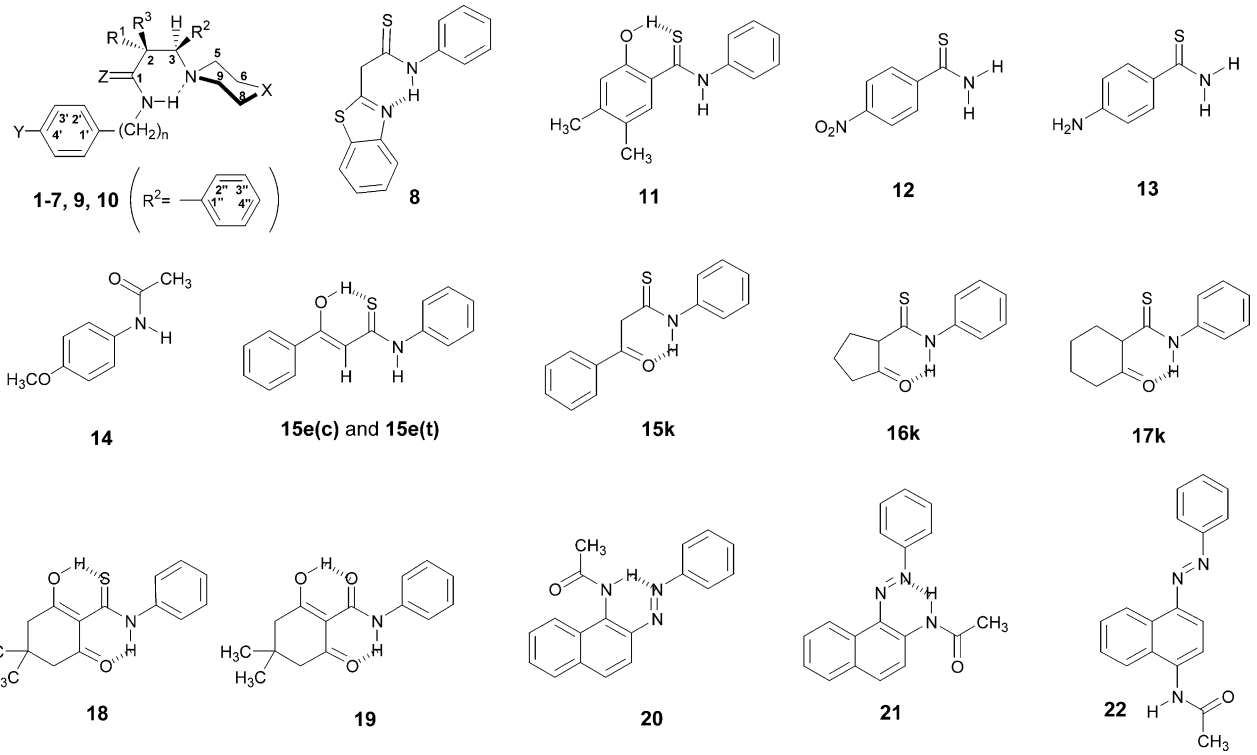
studied. In addition, a couple of strongly hindered cyclic amides similar to the thioamides are investigated together with *ortho*-substituted naphthalenes with azo and acetamido groups.

The idea is to study NH temperature coefficients in a series of thioamides and amides covering a range from weak to strong intramolecular hydrogen bonding and nitrogen as the hydrogen bond acceptor and to compare these results with those of simple amides with only possibility of intermolecular hydrogen bonding and finally with amides and thioamides in which the acceptor is an oxygen atom (Fig. 1). Furthermore, the type of acceptor, sp^2 hybridised



Compound	R^1	R^2	R^3	X	Y	Z	n
1ap	H	H	H	CH_2	H	S	0
2ap	H	Ph	H	CH_2	H	S	0
2am	H	Ph	H	O	H	S	0
2apme	H	Ph	H	$CHCH_3$	H	S	0
2amCl	H	Ph	H	O	Cl	S	0
2apNO_2	H	Ph	H	CH_2	NO_2	S	0
2bep	H	Ph	H	CH_2	H	S	1
2bem	H	Ph	H	O	H	S	1
3ap	CH_3	H	H	CH_2	H	S	0
3am	CH_3	H	H	O	H	S	0
4ap(t)	-$(CH_2)_4$-		H	CH_2	H	S	0
4am(t)	-$(CH_2)_4$-		H	O	H	S	0
4bep(t)	-$(CH_2)_4$-		H	CH_2	H	S	1
4bep(c)	H	-$(CH_2)_4$-		CH_2	H	S	1
5ap(t)	CH_3	Ph	H	CH_2	H	S	0
5am(c)	H	Ph	CH_3	O	H	S	0
6ap(t)	-$(CH_2)_3$-		H	CH_2	H	S	0
6am(t)	-$(CH_2)_3$-		H	O	H	S	0
6bep(t)	-$(CH_2)_3$-		H	CH_2	H	S	1
6bem(t)	-$(CH_2)_3$-		H	O	H	S	1
7ap	H	CH_3	H	CH_2	H	S	0
7bep	H	CH_3	H	CH_2	H	S	1
7bem	H	CH_3	H	O	H	S	1
9amCl	H	Ph	H	O	H	O	0
10ap(t)	-$(CH_2)_4$-		H	CH_2	H	O	0

Fig. 1. Investigated compounds.

oxygen or nitrogen or sp^3 hybridised nitrogen is covered by the above-mentioned compounds.

2. Experimental

Theoretical calculations. The molecular geometries were optimised using the GAUSSIAN98 suite of programs [20] and B3LYP Density Functional Theory (DFT) [21,22] and the 6-31G* basis set.

Experiments. Melting points were determined on a Boetius hot stage apparatus and are uncorrected. Infrared spectra were taken with a Specord M80 instrument. Mass spectra (70 eV) were recorded with a HP 6890 (Hewlett-Packard) GCMS spectrometer equipped with a mass detector HP 5973. Elemental analyses were performed on EuroEA 3000 series, EuroVector CHNS-O Elemental Analyser.

NMR. ^{1}H, ^{13}C NMR spectroscopic measurements were performed on a Bruker DPX 400 spectrometer equipped with a 5 mm ^{1}H/BB-inverse probehead, operating at 400.13 and 100.62 MHz with a digital resolution of 0.12 and 0.97 Hz per point for ^{1}H and ^{13}C, respectively, or on a Bruker AC 250 or a Varian Mercury 300 instrument primarily using $CDCl_3$ as solvent. Low temperature spectra were recorded in $CDCl_3$, CD_2Cl_2 or in toluene-d_8. TMS was used as internal reference in all measurements. Two-dimensional spectra were acquired using standard Bruker software. Heteronuclear correlation (^{13}C, ^{1}H COSY) was optimised for a coupling 145 Hz. In ^{1}H, ^{1}H NOESY experiment (**2apme**, C_6D_6) the mixing time of 0.6 s was applied. Enhanced resolution spectra were obtained by Lorentzian to Gaussian transformation (LB = −2.5, GB = 0.64) using Bruker software for PC.

Compounds. Compounds **1**–**7** were synthesized by addition of amines to corresponding α,β-unsaturated thioamides according to the method described earlier [19]. Yield and the reaction conditions of new compounds are presented in Table 1. Compounds **8** [23], **11** [11], **12** and **13** [24], **15** [11], **16**, **17** and **18** [11], **19** and **20** [25] are described elsewhere. Compound **14** was purchased from Aldrich, Weinheim, Germany.

Table 1
Yields and reaction conditions of new compounds

Amine[a]/solvent	Molar ratio of thioamide to amine	Temperature (°C) (reaction time)	Product yield (%) (ratio of diastereoisomers)
p/Neat	1:10	20 (6 h)	**2apme**, 82
m/Neat	1:8	20 (1 d)	**2amCl**, 90
p/Methanol	1:20	20 (0.5 h) then −10 (0.5 h)	**2apNO$_2$**, 64
p/Neat	1:3	20 (1.5 h) then −10 (3 d)	**3am**, 80
m/Neat	1:10	20 (2 d)	**5ap(t)**, 70, (50:50)
p/Neat	1:10	20 (3 d)	**5am(c)**, 74, (50:50)
p/Neat	1:8	20	**7ap**, 86

[a] p, piperidine; m, morpholine.

2.1. 3-(4-Methylpiperidin-1-yl)-3,N-diphenylthiopropionamide (*2apme*)

Pale yellow solid, mp 108–111 °C from acetonitrile. δ_H (400.1 MHz, 300 K, $CDCl_3$) 0.90 (3H, d, J = 5.9 Hz, 7-CH_{3eq}), 1.18 (1H, qd, J = 11.2, 3.9 Hz, H-8$_{ax}$), 1.20–1.25 (1H, m, H-7$_{ax}$), 1.32 (1H, qd, J = 11.2, 3.8 Hz, H-6$_{ax}$), 1.62–1.75 (2H, m, H-6$_{eq}$, H-8$_{eq}$), 1.78 (1H, td, J = 11.2, 2.4 Hz, H-9$_{ax}$), 2.31 (1H, td, J = 11.3, 2.7 Hz, H-5$_{ax}$), 2.96 (1H, brd, J = ca. 11.5 Hz, H-5$_{eq}$), 3.12 (1H, brd, J = ca. 11.5 Hz, H-9$_{eq}$), 3.17 (1H, dd, J = 17.3, 2.2 Hz, H-2$_{eq}$), 3.66 (1H, dd, J = 17.3, 12.1 Hz, H-2$_{ax}$), 4.15 (1H, dd, J = 12.1, 2.2 Hz, H-3$_{ax}$), 7.13 (2H, dd, J = 7.5, 1.3 Hz, 2 × H-2″), 7.24 (1H, dt, J = 7.4, 1.0 Hz, H-4′), 7.27–7.38 (3H, m, 2 × H-3″, H-4′), 7.42 (2H, t, J = 8.3 Hz, 2 × H-3′), 7.88 (2H, dd, J = 8.3, 1.1 Hz, 2 × H-2′), 13.75 (1H, brs, NH).

δ_H (400.1 MHz, 300 K, C_6D_6) 0.68 (3H, s, 7-CH_{3eq}), 0.66–0.77 (1H, m, H-7$_{ax}$), 0.88 (1H, qd, J = ca. 11.8, 3.7 Hz, H-8$_{ax}$), 1.08 (1H, qd, J = ca. 11.8, 4.0 Hz, H-6$_{ax}$), 1.20–1.31 (2H, m, H-8$_{eq}$, H-6$_{eq}$), 1.32 (1H, td, J = 11.7, 2.3 Hz, H-9$_{ax}$), 1.84 (1H, td, J = 11.7, 2.4 Hz, H-5$_{ax}$), 2.28 (1H, brd, J = ca. 11.7 Hz, H-5$_{eq}$), 2.52 (1H, brd, J = ca. 11.3 Hz, H-9$_{eq}$), 3.22 (1H, dd, J = 17.0, 2.3 Hz, H-2$_{eq}$), 3.39 (1H, dd, J = 17.0, 12.0 Hz, H-2$_{ax}$), 3.65 (1H, dd, J = 12.0, 2.3 Hz, H-3$_{ax}$), 6.69–6.73 (2H, m, 2 × H-2″), 6.99 (1H, tt, J = 7.4, 1.0 Hz, H-4′), 7.08–7.11 (3H, m, 2 × H-3″, H-4″), 7.22–7.26 (2H, m, 2 × H-3′), 8.35 (2H, dd, J = 8.7, 1.0 Hz, 2 × H-2′), 13.39 (s, 1H, NH); [Found: C, 74.62; H, 7,75; N, 8.37; S, 9.36. $C_{21}H_{26}N_2S$ requires C, 74.51; H, 7.74; N, 8.28; S, 9.47%]; ν_{max}(KBr pellet) 2944, 2920, 2730 br, 1594, 1562, 1492, 1380, 756, 740, 708 cm^{-1}; GCMS-decomposition (retro-Michael addition).

2.2. N-(4-chlorophenyl)-3-morpholin-4-yl-3-phenylthiopropionamide (*2amCl*)

Pale yellow solid, mp 133–137 °C from acetonitrile. δ_H (400.1 MHz, rt, $CDCl_3$) 2.48 (2H, brs, CH_2N), 2.70–2.78 (2H, m, CH_2N), 3.21 (1H, dd, J = 17.1, 2.7 Hz, H-2$_{eq}$), 3.64 (1H, dd, J = 17.1, 11.3 Hz, H-2$_{ax}$), 3.70–3.83 (4H, m, 2 × CH_2O), 4.11 (1H, dd, J = 11.3, 2.7 Hz, H-3$_{ax}$), 7.14 (2H, dd, J = 7.9, 2.9 Hz, 2 × H-2″), 7.33–7.41 (5H, m, C_6H_4Cl, C_6H_5), 7.81 (2H, d, J = 8.8 Hz, 2 × H-2′), 13.06 (1H, s, NH); [Found: C, 63.02; H, 5,91; N, 7.30; S, 8.89. $C_{19}H_{21}ClN_2OS$ requires C, 63.23; H, 5.86; N, 7.76; S, 8.88%]; ν_{max}(KBr pellet) 2888, 2750 br, 1608, 1556, 1490, 1388, 1116, 776, 760, 740, 710 cm^{-1}; GCMS-decomposition (retro-Michael addition).

2.3. N-(4-nitrophenyl)-3-phenyl-3-piperidin-1-yl-thiopropionamide (**2apNO$_2$**)

Pale yellow solid, mp 163–166 °C from acetonitrile. δ_H (400.1 MHz, rt, $CDCl_3$) 1.45 (2H, brs, CH_2), 1.70 (4H, brs, 2 × CH_2), 2.40 (2H, brs, CH_2N), 2.75 (2H, brs, CH_2N), 3.18 (1H, dd, J = 17.3, 1.7 Hz, H-2$_{eq}$), 3.67 (1H, dd, J = 17.3, 12.3 Hz, H-2$_{ax}$), 4.15 (1H, brd, J = ca. 10.9 Hz, H-3$_{ax}$), 7.13 (2H, brd, J = ca. 6.0 Hz, 2 × H-2″), 7.25–7.42 (3H, m, 2 × H-3″, H-4″), 8.19 (2H, d, J = 9.1 Hz, $C_6H_4NO_2$), 8.29 (2H, d, J = 9.1 Hz, $C_6H_4NO_2$), 14.40 (1H, brs, NH); [Found: C, 64.92; H, 6,34; N, 11.40; S, 8.77. $C_{20}H_{23}N_3O_2S$ requires C, 65.01; H, 6.27; N, 11.37; S, 8.68%]; ν_{max}(KBr pellet) 2936, 2650 br, 1584, 1514, 1336, 1110, 854, 744, 706 cm^{-1}; GCMS-decomposition (retro-Michael addition).

2.4. 2-Methyl-3-morpholin-4-yl-N-phenylthiopropionamide (**3am**)

Pale yellow solid, mp 97–98 °C from *n*-hexane: ethyl acetate. δ_H (400.1 MHz, 300 K, $CDCl_3$) 1.41 (3H, d, J = 6.9 Hz, CH_3), 2.49–2.57 (2H, m, CH_2N), 2.59 (1H, dd, J = 13.0, 3.3 Hz, H-3$_{eq}$), 2.71–2.79 (2H, m, CH_2N), 2.76 (1H, dd, J = 13.0, 10.2 Hz, H-3$_{ax}$), 2.85–2.94 (1H, m, H-2$_{ax}$), 3.72–3.82 (4H, m, 2CH_2O), 7.22 (1H, t, J = 7.4, H-4′), 7.37–7.41 (m, 2H, 2 × H-3′), 7.75 (2H, dd, J = 8.7, 1.2 Hz, 2 × H-2′), 12.44 (1H, brs, NH); [Found: C, 63.29; H, 7,57; N, 10.42; S, 12.04. $C_{14}H_{20}N_2OS$ requires C, 63.60; H, 7.62; N, 10.60; S, 12.13%]; ν_{max}(KBr pellet) ca. 2700 br, 1592, 1568, 1492, 1404, 1366, 1292, 1116, 860, 716 cm^{-1}; *m/z* (EI, 70 eV) 264 (7), 231 (13), 100 (100), 77 (8).

2.5. trans-2-Methyl-3,N-diphenyl-3-piperidin-1-yl-thiopropionamide [**5ap(t)**]

This compound was obtained after fractional crystallization of the mixture of diastereoisomers from methanol: water. White solid, mp 163–166 °C from methanol:water. δ_H (400.1 MHz, 300 K, $CDCl_3$) 1.31 (3H, d, J = 6.9 Hz, CH_3), 1.36 (2H, brs, CH_2-7), 1.51–1.71 (4H, m, CH_2-6, CH_2-8), 2.33–2.70 (4H, m, CH_2-5, CH_2-9), 3.37–3.48 (1H, m, H-2$_{ax}$), 3.89 (1H, d, J = 10.7 Hz, H-3$_{ax}$), 7.16 (2H, brd, J = ca. 6.7 Hz, 2 × H-2″), 7.23–7.30 (1H, m, H-4′), 7.31–7.48 (5H, m, 3-C_6H_5, N-C_6H_5), 7.75 (2H, dd, J = 8.6, 1.2 Hz, 2 × H-2′), 13.89 (1H, brs, NH); [Found: C, 74.63; H, 7,64; N, 8.38; S, 9.57. $C_{21}H_{26}N_2S$ requires C, 74.51; H, 7.74; N, 8.28; S, 9.47%]; ν_{max}(KBr pellet) 3240, 2932, ca. 2750 br, 1490, 1416, 764, 704 cm^{-1}; *m/z* (EI, 70 eV) 338 (1, M$^+$), 305 (8), 177 (5), 174 (100), 91 (12), 77 (5).

2.6. cis-2-Methyl-3-morpholin-4-yl-3,N-diphenylthiopropionamide [**5am(c)**]

This compound was obtained after fractional crystallization of the mixture of diastereoisomers from *n*-hexane:ethyl acetate. Pale yellow solid, mp 193–196 °C from *n*-hexane:ethyl acetate. δ_H (400.1 MHz, 300 K, $CDCl_3$) 1.40 (3H, d, J = 6.7 Hz, CH_3), 2.48–2.65 (4H, m, 2 × CH_2N), 3.40 (1H, q, J = 6.7 Hz, H-2), 3.71–3.79 (5H, m, H-3, 2 × CH_2O), 7.15–7.31 (6H, m, 3-C_6H_5, N-C_6H_5), 7.34 (2H, t, J = 7.6 Hz, 2 × H-3′), 7.46 (2H, d, J = 7.7 Hz, 2 × H-2′), 11.25 (1H, brs, NH); ν_{max}(KBr pellet) 3428 br, 3216 br, 2956, 2816, 596, 1496, 1412, 1288, 1106, 862, 756, 704 cm^{-1}; [Found: C, 70.57; H, 7,25; N, 8.22; S, 9.23. $C_{20}H_{24}N_2OS$ requires C, 70.55; H, 7.10; N, 8.23; S, 9.42%]; *m/z* (EI, 70 eV) 340 (1, M$^+$), 307 (5), 252 (2), 176 (100), 117 (8), 91 (8), 17 (5).

2.7. N-phenyl-3-piperidin-1-yl-butyramide (**7ap**)

Pale yellow solid, mp 105–107 °C from *n*-hexane:ethyl acetate. δ_H (400.1 MHz, 300 K, $CDCl_3$) 1.02 (3H, d, J = 6.6 Hz, CH_3), 1.47–1.78 (6H, m CH_2-6, CH_2-7, CH_2-9), 2.48 (2H, brs, CH_2N), 2.75–2.84 (2H, m, CH_2N), 2.88 (1H, dd, J = 17.4, 2.6 Hz, H-2$_{eq}$), 3.02 (1H, dd, J = 17.4, 11.0 Hz, H-2$_{ax}$), 3.15–3.27 (1H, m, H-3$_{ax}$), 7.21 (1H, t, J = 7.5 Hz, C_6H_5), 7.39 (2H, t, J = 8.2 Hz, C_6H_5), 7.83 (2H, dd, J = 8.7, 1.1 Hz, C_6H_5), 13.89 (1H, brs, NH); [Found: C, 68.75; H, 8.52; N, 10.51; S, 12.15. $C_{15}H_{22}N_2S$ requires C, 68.65; H, 8.45; N, 10.68; S, 12.22%]; ν_{max}(KBr pellet) 2932, 2650 br, 1596, 1570, 1428, 1402, 736, 692 cm^{-1}; GCMS-decomposition (retro-Michael addition).

Amides: **9amCl** and **10ap(t)** were obtained from corresponding thioamides by using method described by Papadopoulos [26] with some modifications.

General procedure. To the homogenous mixture, resulting from 0.23 g (5.7 mmol) of NaOH (pellets) and 0.1 g (0.33 mmol) of thioamide and 8 cm^3 99.8% ethanol, 0.7 cm^3 of H_2O_2 (30%) was added at room temperature. After 20 min further 0.7 cm^3 of H_2O_2 was added and the mixture was kept at room temperature for an additional 20 min. In this time the small amounts of the products precipitated. Finally the resulting mixture was acidified with diluted HCl causing the gas evolution and the solid dissolving. After 10 min the mixture was slightly alkalised with solid NaOH and was left overnight to precipitate yielding white solid.

2.8. N-(4-chlorophenyl)-3-morpholin-4-yl-3-phenyl-propionamide (**9amCl**)

Yield 76%. White solid, mp 204–206 °C from *n*-hexane:ethyl acetate. δ_H (400.1 MHz, rt, $CDCl_3$) 2.48 (2H, brs, CH_2N), 2.55 (1H, dd, J = 16.7, 3.2 Hz, H-2$_{eq}$), 2.62–2.72 (2H, m, CH_2N), 3.19 (1H, dd, J = 16.7, 11.2 Hz, H-2$_{ax}$), 3.70–3.85 (4H, m, 2 × CH_2O), 4.01 (1H, dd, J = 11.2, 3.2 Hz, H-3$_{ax}$), 7.15 (2H, brd, J = 7.8 Hz, 2 × H-2″), 7.25–7.40 (5H, m, C_6H_4Cl, C_6H_5), 7.52 (2H, d, J = 8.7 Hz, 2 × H-2′), 10.95 (1H, s, NH); [Found: C, 65.96; H, 6.28; N, 8.06. $C_{19}H_{21}ClN_2O_2$ requires C, 66.18; H, 6.14; N, 8.12%]; ν_{max}(KBr pellet) 3440 br, 2888, 1680, 1592, 1544, 1492,

1116, 828, 784, 748, 712 cm^{-1}; *m/z* (EI, 70 eV) 344 (4, M^+), 285 (9), 257 (10), 176 (100), 131 (47), 103 (22), 86 (64).

2.9. 2-Piperidin-1-yl-cyclohexanecarboxylic acid phenylamide [*10ap(t)*]

Yield 75%. White solid, mp 153–157 °C from *n*-hexane:ethyl acetate. δ_H (400.1 MHz, rt, $CDCl_3$): 1.10–1.35 (3H, m, C*H*H-7, H-13_{ax}, H-10_{ax}), 1.45–1.90 (9H, m, CH_2-6, CH*H*-7, CH_2-8, CH_2-11, CH_2-12), 1.97 (1H, br s, H-13_{eq}), 2.32 (1H, td, $J = 11.3$, 4.0 Hz, H-2_{ax}), 2.51 (2H, br s, CH_2N), 2.57–2.70 (2H, m, H-10_{eq}, H-3_{ax}), 2.78–2.88 (2H, m, CH_2N), 7.05 (1H, t, $J = 7.4$ Hz, C_6H_5), 7.26–7.34 (2H, m, C_6H_5), 7.61 (2H, d, $J = 7.8$ Hz, C_6H_5), 12.58 (1H, br s, NH). [Found: C, 75.60; H, 9.22; N, 9.66. $C_{18}H_{26}N_2O$ requires C, 75.48; H, 9.15; N, 9.78%]; ν_{max}(KBr pellet) 3284, 3216, 2932, 2872, 2796, 1654, 1604, 1544, 1442, 760, 744, 692 cm^{-1}; *m/z* (EI, 70 eV) 286 (41, M^+), 194 (7), 166 (16), 124 (100), 84 (35).

3. Results

The temperature coefficients of non-intramolecularly hydrogen bonded compounds have been measured at concentrations of 2 mg/ml. In case higher concentrations are used then the plot vs. temperature usually becomes non-linear so an internal check is present. In non-polar solvents like $CDCl_3$ and toluene we find very small and negative temperature coefficients −1 to −4 ppb/K for simple thioamides like **11**, **15e(c)** and **15e(t)**. In the series of N-substituted-3-piperidinethiopropionamides the effects are seen to range from −8.5 to −17 ppb/K in non-hydrogen bonding solvents with the more negative ones observed for **4ap(t)**, **4am(t)**, **5ap(t)**, **5am(t)** and **4bep(t)**. For the morpholine derivatives the temperature coefficients are normally more negative than for the corresponding piperidine derivatives (see Table 2). For the compounds **2ap** > **2am** the numerical order of the temperature coefficient is as shown. Differences are also seen for aniline (a) and benzyl (be) derivatives, but these are much less systematic and they are most likely related to structure (see later). For the weakly hydrogen bonded compounds like **8** the temperature coefficient is −7.5 pp/K (Table 2).

It is noteworthy for compounds **1–10** that in most cases the change in the NH chemical shifts are uniform in the measured temperature interval (Fig. 2). One exception is **5am(c)** in which the change with temperature is decreasing due to conformational averaging (see later).

The temperature coefficients do not vary significantly with the solvent as long as this is not strongly hydrogen bonding as seen for **2ap** in $CDCl_3$ and THF-d_8 and for **4ap(t)** in toluene-d_8 (see Table 2). For the sterically hindered amides **9amCl** and **10ap(t)** we again find large negative values, −12 and −9 ppb/K, respectively.

For simple amides like **14** and **22** we find temperature coefficients of −5 and −3 ppb/K. This can be compared to the value of −2.5 and −3.5 ppb/K found for *N*-methylacetamide in CD_2Cl_2 and CD_3CN [18]. However, using DMF-d_4 forming strong hydrogen bonds to the solute the temperature coefficient for the simple thioamides like **12**, **13** in DMF are typically −6 to −8 ppb/K similar to those found in **15e(c)** and **15e(t)**. For **4ap(t)**, **2bep** and **2bem** the temperature coefficients change to −4 and −2 ppb/K in DMF-d_8 (Table 2). Martinez-Martinez et al. [12] investigated oxamides and simpler amides in DMSO and found temperature coefficients between −0.5 and −5.9 ppb/K.

Thioamides with a NH group forming a hydrogen bond to oxygen have previously been investigated in **16k**, **17k** and **18** [11]. For **16k** the temperature coefficient was −4 ppb/K, for **17k** only −2.6 ppb/K and for **18** −2 ppb/K, all very close to zero and all in non-polar solvents.

Intramolecularly hydrogen bonded amides are exemplified by **19–21** giving temperature coefficients of −1, −3 and −4.8 ppb/K (Table 2). **20** shows a linear behaviour at low concentrations, which at a concentration of 4.4 mM it becomes non-linear.

3.1. OH temperature coefficient

A couple of the present compounds have OH groups. For **11** the temperature coefficient is −4 in $CDCl_3$ and −7 ppb/K in toluene and close to zero in **15e(c)** and **15e(t)**. For **11** and **15e(c)** the temperature coefficient is uniform in the temperature interval irrespective of the concentration, but this is not the case for **15e(t)**, which decreases numerically at high concentration at low temperature.

3.2. Structure assignment

The formation of quasi-heterocyclic ring due to intramolecular NH···N hydrogen bonding is observed for compounds described in this work. The same fact was noticed in the case of derivatives described earlier [19]. Based on coupling constants between protons at C-2 and C-3 the quasi-axial and -equatorial positions of the protons were assigned. A more detailed analysis of **2apme** based on 1D and 2D (^{1}H, ^{1}H NOESY) ^{1}H and ^{13}C spectra allowed to assign all ^{1}H and ^{13}C signals and estimate conformation of quasi-heterocyclic and 4-methylpiperidine rings and their orientation to each other. The NMR analysis performed in C_6D_6 was facilitated as 4-methylpiperidine exhibited no exchange process at room temperature and most of signals did not overlap. Based on conformational analysis derived from J_{HH} couplings and the NOE effects (Fig. 3) the chair shape of piperidine ring with equatorially substituted nitrogen atom was recognized as well as the perpendicular orientation of quasi-heterocyclic ring in relation to piperidine one. This picture correlates well with the calculated structure (Fig. 3) and that obtained from X-ray studies [27].

Table 2
NH temperature coefficients, NH chemical shifts and NH stretching frequencies and ab initio calculated bond length and bond angles

Compound	ΔNH/*T* (ppb/K)	Angle S=C–N–H	R_{N-H} (Å)	$R_{N\cdots N}$ (Å)	ν_{NH}[a] (cm^{-1})	δNH (ppm)[b]	Solvent
1ap	−9	174.5	1.0302	2.876	–	13.44	$CDCl_3$
2ap	−8.8	177.9	1.0326	2.855	2750	13.77	$CDCl_3$
2apme[c]	−8.3					13.70	$CDCl_3$
2am	−10	177.9	1.0298	2.876		12.94	$CDCl_3$
2apNO$_2$	−9	176.9	1.0348	2.846	2680	14.30	$CDCl_3$
2amCl	−10.6	177.9	1.0311	2.866	2780	13.06	$CDCl_3$
3ap	−11	173.4	1.0294	2.857	2790	13.37	$CDCl_3$
3am	−12.5	173.7	1.0280	2.867	2790	12.44	$CDCl_3$
4ap(t)	−14	160.6	1.0301	2.799	2630	14.51	$CDCl_3$
4ap(t)	−11.3	–	–	–	–	14.02	Toluene-d_8
4ap(t)	−2.0	–	–	–	–	11.57	DMF-d_4
4am(t)	−17	161.2	1.0289	2.804	2700	12.75	$CDCl_3$
5ap(t)	−16.3	170.8	1.0310	2.804	2740	13.72	$CDCl_3$
5am(c)[d,e]	−8				3377[f]	11.04	$CDCl_3$
6ap(t)	−10	174.6	1.0283	2.927		12.98	$CDCl_3$
6am(t)	−8.8	174.5	1.0269	2.942		12.33	$CDCl_3$
7ap	−9	177.3	1.0307	2.875	2750	13.86	$CDCl_3$
2bep	−8.7	179.8	1.0285	2.823		12.00	$CDCl_3$
2bep	−4				2780	11.05[g]	DMF-d_4
2bem	−10.4	177.2	1.0207	2.844	2900	11.28	$CDCl_3$
2bem	−4					10.55	DMF-d_4
4bep(t)	−15	164.4	1.0308	2.759	–	12.9	$CDCl_3$
4bep(c)	−8.6	179.8	1.0315	2.772	–	12.95	$CDCl_3$
6bep(t)	−10	172.2	1.0268	2.896	–	11.36	$CDCl_3$
6bem	−10.6	172.9	1.0260	2.906	3160[h]	10.68	$CDCl_3$
7bem	−8.8	175.6	1.0265	2.851		11.63	$CDCl_3$
8	−7.5	176.4	1.0233	2.867	–	11.51	$CDCl_3$
9amCl	−12.2	175.2	1.0254	2.884	2970	10.88	$CDCl_3$
10ap(t)	−9.3	175.1	1.0278	2.801	2800	12.58	$CDCl_3$
11[d]	−2					11.14	$CDCl_3$
12	−6 and −7[i]					9.94, 10.25	DMF-d_4
13[d]	−5.8 and −8[i]					9.16, 9.22	DMF-d_4
14[d]	−5					7.20	$CDCl_3$
15k	Non-linear	173.7	1.0216	2.827	–	10.99	$CDCl_3$
15k	−6	–	–	–		11.48	DMF-d_4
15e(t)[j]	−6	173.4	1.0131	–		12.07[k]	DMF-d_4
15e(t)	−2	–	–			8.24[l]	$CDCl_3$
15e(c)	−6	173.5	1.0139	–		11.33[k]	DMF-d_4
15e(c)	−2 to −4	–	–			8.32[l]	$CDCl_3$
16k[m]	−4	172.7	1.0230	2.762		10.34	$CDCl_3$
17k[m]	−2.6	172.0	1.0240	2.708		11.25	$CDCl_3$
18[m]	−2	173.6	1.0315	2.586		13.97	CD_2Cl_2
19[m]	−1	180.0	1.0232	2.870		9.69	CD_2Cl_2
20	−3	159.3	1.0217	2.690		8.16	$CDCl_3$
21[d]	−4.8					13.00	$CDCl_3$
22[d]	−3					7.73[k]	$CDCl_3$

[a] Almost all resonances are very broad.
[b] At 300 K.
[c] Structure not calculated. Assumed to be similar to **2ap**.
[d] Structure not calculated.
[e] Exists as a mixture of a closed and an open form.
[f] Open form.
[g] Measured at 273 K. *j* broad at 298 K. Measured at 273 K.
[h] Sharp resonance.
[i] Assigned to the H(Z) proton.
[j] Assignment according to Ref. [11].
[k] Broad at 298 K. Measured at 273 K.
[l] Broad at 298 K. Measured at 213 K.
[m] Data taken from Ref. [11].

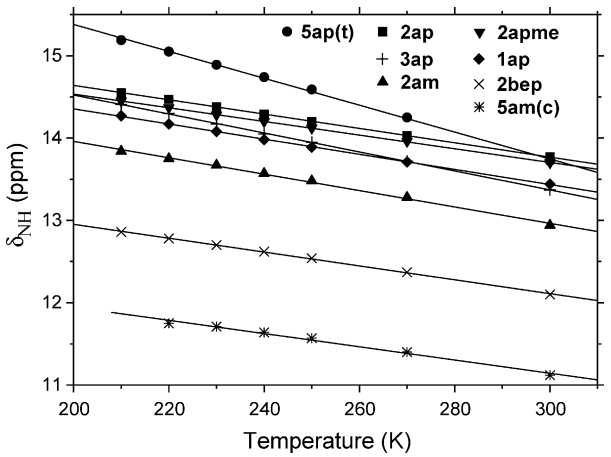


Fig. 2. Plot of NH chemical shifts vs. temperature (K) for selected compounds in $CDCl_3$.

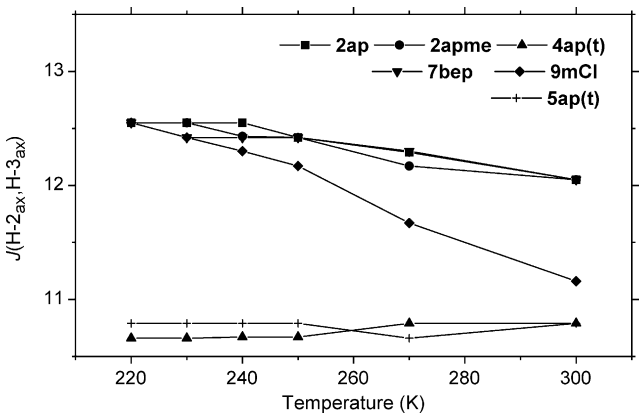


Fig. 4. Plot of ^3J(H-2_{ax},H-3_{ax}) (Hz) vs. temperature (K) for selected compounds.

3.3. Coupling constants and structural implications

^3J(H-2,H-3). This coupling constant at ambient temperature in $CDCl_3$ is typically between 10.4 and 12.1 Hz for the *trans* coupling and 2.2 and 2.8 Hz for *gauche* coupling for **2ap**, **2am**, **2apme**, **2bep**, **3ap**, **5ap(t)**, **7ap**, **9amCl** and **10ap(t)**. For **3am** it is 10.29 and 3.37 Hz and for **2bem** 11.17 and 3.14 Hz (similar to those shown in Ref. [19]). For **4ap(t)** no coupling could be measured because of overlap at ambient temperature. At 240 K ^3J(H-2, H-3) couplings of 10.4 and 3.3 Hz could be measured, showing a *trans* structure. For **1ap** the couplings could be calculated from the AA′XX′ system as 4.7 and 6.6 Hz showing an equilibrating structure. For **5am(c)** the two coupling constants are identical, 7.35 Hz measured at 250–220 K. At higher temperature overlap prevents measurement. For **2bep** dissolved in DMF the coupling constants are 7.3 and 7.5 Hz showing that this compound is no longer forming an intramolecular hydrogen bond. This is also confirmed from the NH chemical shifts. A similar pattern is seen in DMSO for **4ap(t)**.

Important for the following discussion is the temperature variation of ^3J(H-2,H-3). For a number of compounds the *trans* coupling goes up slightly as the temperature is lowered, whereas for others the coupling constant remains constant (Fig. 4).

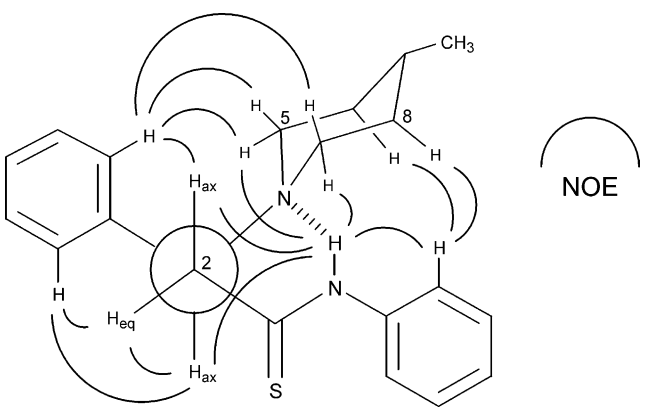


Fig. 3. Calculated (ab initio) structure of **2apme** together with a structure estimated from NOESY constraints.

3.4. Ab initio calculations

Structure calculation. Ab initio calculations of the B3LYP DFT type [20–22] have been performed to obtain optimised geometries. The structures calculated with respect to N···N distances are similar to those obtained from PM3 calculations [28] (see below) except that N···N distances systematically are 0.01 Å shorter in the semi empirical calculations apparently caused by shorter H···H distances between H-2′, H-6′ of the *N*-phenyl ring and H-6,H-8_{ax} in the PM3 calculations, thereby leading to a slightly more compact structure. This distance is short as is seen from NOESY spectra (Fig. 3). This finding lends support to the search for optimal structures using semi-empirical PM3 methods [28]. This has been useful in order to search the conformational space in order not to end up in local minima.

An important feature is the acidity of the NH group. This is greatly enhanced by the phenyl ring in derivatives of aniline type. The NH bond is found to be largely coplanar with the benzene ring in these compounds. An additional factor is the hybridisation of the thioamide nitrogen. In a number of key compounds the S=C–N–H dihedral angle is found to be considerably less than 180° (see below). The N–H bond length is calculated to be close to 1.03 Å illustrating the hydrogen bond formation. This is seen in contrast to simple non-hydrogen bonded compounds like *N*-phenylthioacetamide in which the N–H bond length is calculated as 1.01 Å.

For **7bem** two structures (one with the methyl group at C-3 equatorial, relative to the six-membered hydrogen bond ring) and one with the methyl group axial are found to have very similar energies with the latter 5.5 kJ of lower energy. However, this conformation was not found in the first

Table 3
Calculated ^{1}H nuclear shielding tensor elements and isotropic shielding

Compounds	*XX*	*YY*	*ZZ*	Isotropic shielding
2apNO$_2$	6.9	22.3	31.5	20.2
2am	8.0	23.3	31.2	20.9
2amCl	7.7	23.0	31.5	20.8
4ap(t)	7.8	23.2	31.3	20.8
4am(t)	8.3	23.5	31.2	21.00
5ap(t)	7.1	23.0	31.7	20.4
7ap	7.8	23.6	31.7	20.9
2bep	11.7	21.6	31.6	21.6
2bem	11.1	24.8	32.2	22.7
4bep(c)	8.9	24.6	32.0	21.8
4bep(t)	9.4	24.5	32.2	21.9
6bep	11.9	25.8	32.1	23.3
8	9.4	25.9	29.0	21.4
9amCl	10.8	23.0	34.0	22.6
12	21.8, 20.7	23.9, 25.9	32.2, 32.9	26.0, 26.5
15k	12.7	26.3	28.4	22.5
15e(t)	17.5	28.3	30.8	25.2
15e(c)	18.1	28.8	29.0	25.3
16k	10.9	26.1	28.1	21.7
17k	9.2	25.8	28.0	21.0
18	5.7	23.1	29.6	19.5
19	13.2	26.2	30.6	23.4
20	7.9	25.6	29.2	20.9

attempt. For **8** the calculations oscillated between two very similar low energy structures.

^{1}H nuclear shielding tensors. ^{1}H nuclear shielding tensors of the NH protons are given in Table 3. The values for the N-substituted-3-piperidinethiopropionamides of aniline type show a small change in the smallest tensor value related to the change in the N···N distance. Derivatives of benzyl type fall in between. However, going to compounds like **15k**, **16k**, **17k**, **18**, **19** and **20** the tensor elements are changed considerably. The smallest tensor element is increasing for these again related to the N···N distance, but the two other tensor elements are now much more alike giving a cylindrical type of shielding surface. This change in the tensor elements reflects also the influence of the acceptor atom.

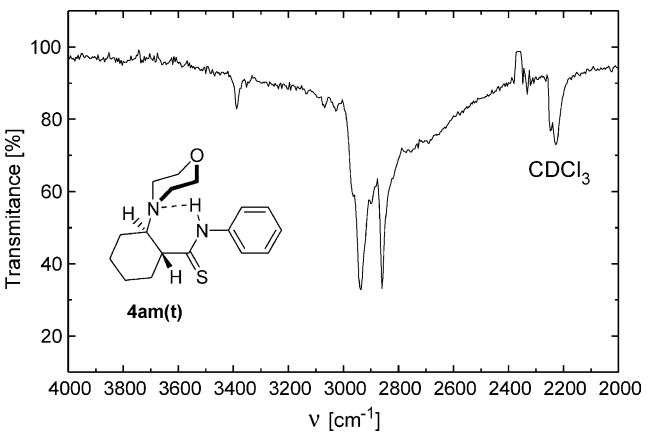


Fig. 5. IR spectrum of **4am(t)** measured in $CDCl_3$ solution.

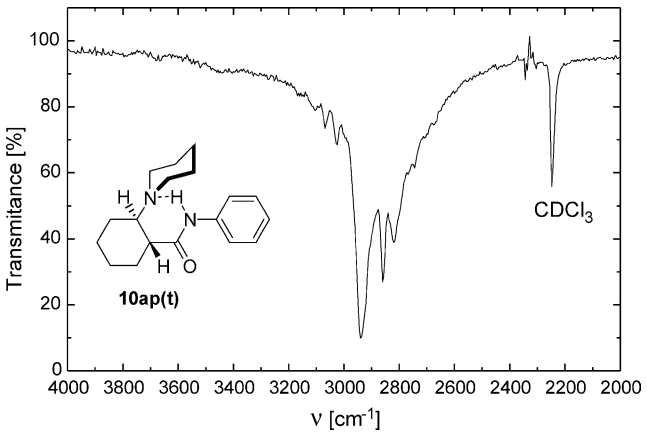


Fig. 6. IR spectrum of **10ap(t)** measured in $CDCl_3$ solution.

3.5. Infrared spectra

IR data have been obtained in $CDCl_3$ and in addition in CD_2Cl_2 in order to gauge the hydrogen bond states of these compounds. As seen from Fig. 5 (**4am(t)**) and Fig. 6 (**10ap(t)**) bands due to NH stretching are broad and shifted strongly towards lower wave numbers (Table 2). For **5am(c)** two bands are observed due to an open (3377 cm^{-1}) and a hydrogen bonded case (~2800 cm^{-1}). For all other compounds this is not so.

4. Discussion

The discussion will be divided according to compounds and their hydrogen bond patterns, strength and solvent type. The hydrogen bonds are of intra or intermolecular type. The hydrogen bond strength is of course best given by the hydrogen bond energy, but as this is not known, the heavy atom distance can be used as a measure of hydrogen bond strength [29]. The heavy atom distances are in all cases calculated by the DFT method as given in Table 2. In a number of cases they have also been determined by X-ray [27]. The results not only show good correlation, but also that the calculated ones generally are 0.1 Å longer than those determined by X-ray.

The simple thioamides at so low concentration that even intermolecular hydrogen bonds are no longer important show small negative temperature coefficients in non-polar solvents. Examples are **11** and **15e(c** and **t)**. The temperature coefficients are of the order of −2 ppb/K. For simple amides the effects can be slightly larger, e.g. −5 ppb/K as seen for **14**, but in this case conformational effects of the methoxy group cannot be ruled out. The thioamides of N-substituted-3-piperidine or morpholine type studied in the present case show NH temperature coefficients more negative than −7.5 ppb/K and for compounds such as **4ap(t)**, **4am(t)**, **5ap(t)** and **4bep(t)** very negative temperature coefficients are found. The same is true for the corresponding amides **9amCl** and **10ap(t)**. All these compounds are characterised

Table 4
^{13}C chemical shifts (ppm) of all compounds, obtained at 300 K (upper) and 210 K (lower) in $CDCl_3$ solution unless stated otherwise

Compound	C-1	C-2	C-3	C-5	C-9	C-6	C-8	C-7	C-1′	C-2′	C-3′	C-4′	C-1″	C-2″	C-6″	C-3″	C-5″	C-4″	Other
1ap	201.8	56.3	42.2	53.5		26.1		24.1	139.6	122.3	128.7	125.9	–	–		–		–	–
	201.6	55.7	40.8	52.9		25.8		23.7	138.7	122.4	128.8	126.2	–	–		–		–	–
2ap	201.3	46.2	67.7	49.4[a]		26.4		24.1	139.6	122.7	128.8	126.1	134.8	128.6		128.1		128.0	–
	201.0	44.5	66.8	52.9	44.1	26.4	25.6	23.7	138.6	122.8	128.9[a]	126.4[a]	133.5	128.7[a]		128.0		128.0[a]	–
2am	200.9	46.6	67.1	48.7		67.7		–	139.3	122.7	128.4	126.3	134.6	128.6		128.9		128.3	–
	200.6	44.6	66.6	51.3	43.8	67.0[b]	66.8[b]	–	138.3	122.7	128.2[a]	126.5[a]	133.0	128.5[a]		129.0		128.3[a]	–
2apme	201.3	46.4	67.3	52.5[a]	44.6	35.0	34.4	30.6	139.6	122.7	128.8	126.1	134.9	128.6		128.1		128.0	21.7
C_6D_6	200.9	47.5	66.9	52.3[a]	44.5	35.1	34.6	21.8	140.9	122.2	129.0	125.8	135.4	128.9		128.1		127.9	
	201.1	44.7	66.4	52.4	43.6	34.7	33.9	30.4	138.6	122.8	128.9	126.3[a]	133.6	128.5[a]		128.0[a]		128.0[a]	22.1
2amCl	201.0	46.5	67.6	48.7		67.1		–	137.8	123.9	128.6[b]	131.3	134.4	128.5[b]		128.5[b]		129.0[b]	–
220 K	201.1	44.9	66.8	51.5	44.0	67.1	66.9	–	137.1	123.9	128.5	131.1	133.0	128.3		128.4		129.0	–
2apNO$_2$	203.2	46.7	67.5	49.1[a]		26.5		24.0	145.2	121.9	128.6	144.4	134.2	128.3		124.8		128.3	–
230 K	203.1	45.7	66.8	52.9	44.3	26.6	25.8	23.7	144.9	122.0	128.6	143.8	133.4	128.1		124.8		128.3	–
2bep	202.1	44.0	67.6	49.2		25.6		23.9	136.6	128.8[b]	128.9[b]	128.0[b]	135.0	128.5[b]		128.0[b]		128.0[b]	50.7
	201.0	42.3	66.7	52.7	43.9	24.9		23.4	135.5	129.0[b]	128.9[b]	128.3[b]	133.7	128.4[b]		128.3[b]		127.9[b]	51.0
2bem	201.7	44.5	67.7	44.7		66.5		–	136.5	128.7[b]	129.0[b]	128.5[b]	134.8	128.2[b]		128.3[b]		127.8[b]	50.7
	200.8	44.2	66.6	51.1	43.5	66.1	66.0	–	135.5	129.1[b]	129.1[b]	128.9[b]	132.9	128.5[b]		128.3[b]		128.2[b]	50.9
3ap	206.8	41.9	63.9	54.1		26.1		24.0	139.9	122.8	128.7	125.8	–	–		–		–	19.2
	206.7	39.7	63.2	55.3	51.3	26.1	25.5	23.6	139.0	123.1	128.8	126.1	–	–		–		–	18.9
3am	206.7	42.4	63.7	53.3		66.9		–	139.5	122.9	128.8	126.2	–	–		–		–	19.3
	206.5	40.1	63.0	54.1	51.0	66.9	66.7	–	138.8	123.1	128.9	126.3	–	–		–		–	19.0
5ap(t)	207.3	46.1	74.1	49.7[a]		26.3		24.0	139.9	123.7	128.8	126.3	134.4	129.2[a]		128.2		127.8[a]	21.6
	206.9	43.9	73.1	52.3	45.0	26.2	25.5	23.5	139.1	123.8	129.0	126.5	133.3	131.2[b]	126.6[b]	128.2[b]	128.1[b]	127.8	21.8
5am(c)	206.4	47.6	74.4	51.2		67.2		–	138.9	123.7	128.3	126.5	135.3	129.5		128.9		127.9	18.9
	206.5	46.3	74.9	51.9	48.9	67.1	66.9	–	138.2	123.8	128.2	126.8	134.4	br. ca 129.1		128.8		127.8	19.1
7ap	201.5	48.4	58.8	48.4[a]		26.4		24.4	139.6	122.7	128.8	126.0	–	–		–		–	12.8
	201.2	47.0	58.3	52.2	42.9	26.3	25.5	24.0	138.6	122.6	128.7	126.0	–	–		–		–	12.6
7bep	202.1	48.0	58.7	48.0		25.5		24.2	136.6	128.8[b]	128.7[b]	127.9	–	–		–		–	50.5
																			12.6
220 K	201.5	45.1	58.3	52.3	42.9	25.0	25.0	23.9	135.8	128.9	128.8	128.1		–		–		–	50.7
																			12.5
7bem	201.8	46.0	58.4	47.6		66.5		–	136.6	128.7[b]	129.0[b]	128.2	–	–		–		–	50.6
																			12.9
	201.0	44.6	58.0	50.9	42.9	66.2	66.0	–	135.7	128.9[b]	129.0[b]	128.5	–	–		–		–	50.7
																			12.7
9amCl	169.6	37.5	65.8	49.0		67.2		–	137.9	120.7	128.4[b]	128.7	–	129.0[b]		128.5b		128.3	–
220 K	170.0	36.1	65.0	51.6	44.2	67.2	67.1	–	136.7	120.4	128.4	128.4	–	129.0		128.3		128.3	–

Compound	C-1	C-2	C-3	C-5	C-9	C-6	C-8	C-7	C-10	C-11	C-12	C-13	C-1′	C-2′	C-3′	C-4′	Other
4ap(t)	207.0	50.4	67.6	48.3		26.4		24.4[b]	34.9	26.6[b]	25.6b	23.7	139.9	123.7	128.7	126.0	–
220 K	206.8	48.6	67.2	51.3	44.4	26.4	25.7	24.0[b]	34.5	26.3[b]	25.1b	23.3	139.9	123.8	128.9	126.3	–
4am(t)	207.1	52.5	67.0	47.8		67.3		–	35.0	26.4	25.4	23.8	139.4	123.9	128.9	126.4	–

(*continued on next page*)

Table 4 (*continued*)

Compound	C-1	C-2	C-3	C-5	C-9	C-6	C-8	C-7	C-10	C-11	C-12	C-13	C-1′	C-2′	C-3′	C-4′	Other
220 K	207.0	50.2	66.5	50.0	44.1	67.3	67.0	–	34.7	26.1	25.0	23.3	138.7	123.9	129.0	126.7	–
4bep(t)	205.8	47.2	66.6	48.0		24.4		23.2[b]	33.4	25.5[b]	24.6[b]	22.6[b]	135.8	127.9[b]	127.7[b]	126.8	51.0
220 K	204.5	46.1	66.2	50.3	43.2	23.8	23.6	23.2[b]	32.7	25.2[b]	24.2[b]	22.2[b]	134.8	128.2[b]	127.7[b]	127.0	50.3
4bep(c)	204.3	44.8	66.9	50.4		ca 25.6		25.3[b]	30.9	21.4[b]	24.0[b]	25.6[b]	136.9	128.7[b]	128.7[b]	127.7	50.9
220 K	203.7	43.8	66.7	50.9	49.3	25.6	25.4	25.2[b]	30.6	21.3[b]	23.9[b]	25.4[b]	136.4	129.1[b]	129.0[b]	128.2	51.5
6ap(t)	205.6	50.9	70.7	49.4		26.6		24.5	29.3	20.8	22.0	–	139.8	122.6	128.7	125.7	–
220 K	205.2	49.5	69.77	54.2	43.7	26.6	25.8	24.1	28.7	19.9	21.4	–	138.9	122.6	128.7	125.9	–
6am(t)	205.4	51.2	70.4	48.8		67.4		–	29.7	21.2	22.5	–	139.6	122.6	128.9	126.0	–
220 K	201.2	50.3	69.8	53.2	43.8	67.7	67.3	–	29.6	20.9	22.3	–	138.9	123.1	129.3	126.6	–
6bep(t)	206.3	49.2	70.6	49.4		25.8		24.3	29.2	20.6	21.8	–	136.7	128.7[b]	127.6[b]	127.8	50.3
220 K	205.3	48.0	69.9	54.0	43.7	25.4	25.2	23.9	28.6	19.7	21.3	–	135.8	128.7[b]	128.8[b]	128.0	50.6
6bem(t)	206.2	49.8	70.5	48.6		66.8		–	29.7	21.1	22.5	–	136.7	128.9[b]	128.6[b]	128.2	50.4
220 K	205.1	48.1	69.5	52.6	43.3	66.5	66.4	–	28.9	20.0	21.7	–	135.7	128.9[b]	128.8[b]	128.3	50.6
10ap(t)	172.8	43.6	65.6	48.8		26.6		24.6[b]	29.2	26.0[b]	25.7[b]	23.9	139.3	119.8	128.9	123.3	–
220 K	173.1	42.6	65.0	51.9	44.6	26.6	25.8	24.3[b]	28.8	25.7[b]	25.3[b]	23.4	138.8	119.4	128.9	123.2	–

[a] Broad signal.
[b] Could be interchanged.

by strong intramolecular hydrogen bonding judged from a N···N distance as found in Table 2, by the fact that the acceptor is a sp^3 hybridised nitrogen with a non-planar S=C–N–H bond.

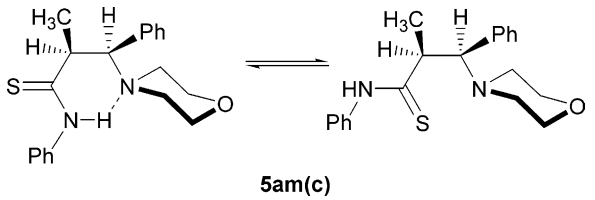
For thioamides with intramolecular hydrogen bonds in which the acceptor is oxygen, the picture is akin to that described for intermolecular hydrogen bonds to a polar solvent (see later). The shorter the N···N distance the less negative the temperature coefficients as seen from the series of thioamides **16**–**18** and for the amides **19**–**21** something similar is seen.

In polar solvents like DMF, compounds that form only moderately strong hydrogen bonds to the solvent give temperature coefficients of −6 to −8 ppb/K (examples are **12**, **13** and **15e**(**c** and **t**). For the compounds **2bep**, **2bem** and **4ap**(**t**) the temperature coefficients are however only −4, −4 and −2 ppb/K, respectively. We will return to this point.

4.1. Structural features

One possibility to be considered with strongly hydrogen bonded thioamides is the possibility of tautomerism. This has been observed in a couple of cases [11,23]. This can be ruled out judging from the very small changes in the C-1 and C-2 carbon chemical shifts (Table 4). Another possibility has been pointed out by Muller and Reiter [30] that very low frequency vibrations may be important in strongly hydrogen bonded systems. This could lead to a high frequency shift. However, frequency calculations using the DFT ab initio calculations do not suggest that the present compounds have strong low frequency vibrations.

Conformational changes have been pointed out as a potential source of the temperature coefficients [5,14–18]. The thioamides are clearly flexible. However, the overall conformational changes are very moderate as seen from the small changes in the H–H coupling constant with temperature (Fig. 4). Compounds like **4ap**(**t**), **4am**(**t**), **5ap**(**t**), **4bep**(**t**) and **10ap**(**t**) do not show changes at all and furthermore, for the remaining compounds these changes stop as the temperature is reaching a temperature typical for each compound. This indicates that these small changes are not the origin of the temperature coefficients as these vary uniformly throughout the temperature interval with exception of **5am**(**c**). In this case the drop in the temperature coefficient (see Table 2) is due to the compound being an equilibrating mixture of hydrogen bonded and an open form (Scheme 1). This is, judging from the ^{1}H chemical shifts, not the case for the remaining compounds. For some of the compounds the phenyl ring rotation is slowed down at very low temperatures [31] but this is not reflected in the temperature coefficient either, as the temperature coefficients vary uniformly. The IR spectra reveal that all intramolecularly hydrogen bonded compounds **1**–**7**, **9** and **10**, except **5am**(**c**), do not exist in the open form (Scheme 1). Overall structural changes can thus



Scheme 1. H bonded (closed) and non-H bonded opened form of **5am**(**c**).

in almost all cases be excluded for the group of N-substituted-3-piperidinethiopropionamides.

An interesting feature is that for some of the present thioamides **4ap**(**t**), **4am**(**t**), **5ap**(**t**) and **4bep**(**t**) the S=C–N–H dihedral angle is considerably smaller than 180° (Table 2). It can be seen that the more negative temperature coefficients are found in compounds with large deviations from planarity. A plot is shown in Fig. 7. From this plot it is also seen that the temperature coefficients are more negative for morpholine than for piperidine derivatives. A possible mechanism could then be a change in the S=C–N–H dihedral angle upon temperature change. If this is the case, one would expect a change in some of the chemical shifts of the neighbour carbons. For the C=S carbon the changes with temperature are close to null (Table 4). For C-2 small changes with temperature are seen and they correlate weakly for thioamides with substituents at C-2 with the NH temperature coefficients (Fig. 8). The twist of the S=C–N–H bond has effects on the N–H bond lengths. The larger the twist the shorter the N–H bond length. However, no direct correlation is seen between N–H bond lengths and the temperature coefficients. A comparison of data for the four compounds: **2ap**, **4bep**(**t**), **5ap**(**t**) and **4ap**(**t**) all with similar R_{NH} bond length show again a dramatic increase in the temperature coefficient with non-planarity (see Table 2). Another interesting pair of compounds is **4bep**(**t**) and **4bep**(**c**) as they have very different temperature coefficients but the NH and N···N distances are fairly similar. The main difference lies in the S=C–N–H dihedral angles, which is much smaller for **4bep**(**t**) than for **4bep**(**c**) corroborating

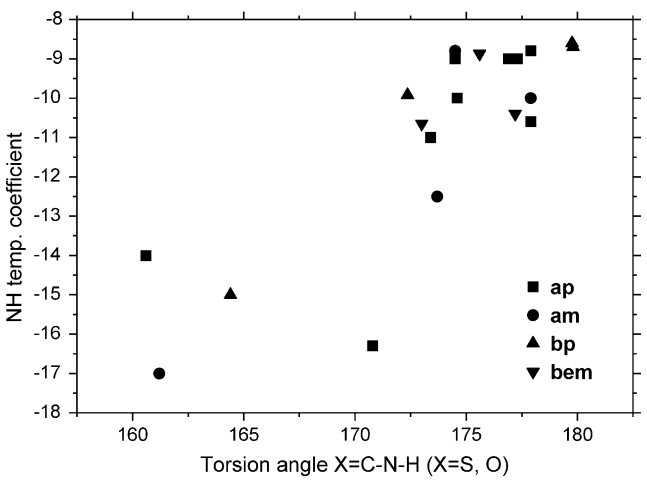


Fig. 7. Plot of NH temperature coefficients vs. torsion angle X=C–N–H (X = S, O).

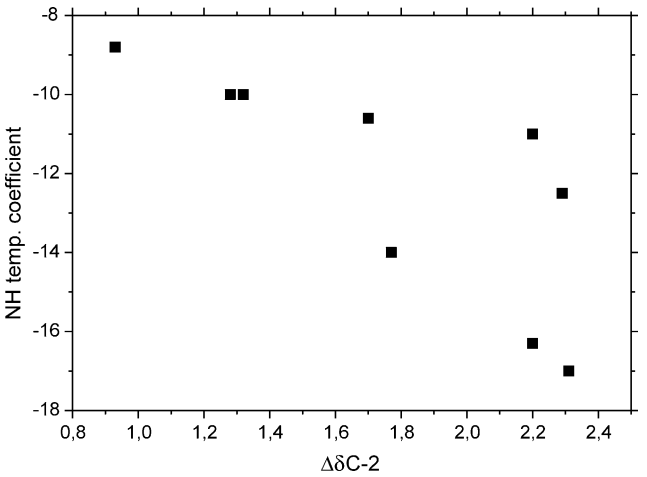


Fig. 8. Plot of NH temperature coefficients vs. $\Delta\delta$C-2.

the suggestion that this is an important factor for the NH chemical shift temperature coefficients.

The temperature coefficients for corresponding benzyl and aniline derivatives are not significantly different (see Table 2), whereas for **2ap** and **2am** the coefficients increase in this order although the $R_{N\cdots N}$ distances and twist angles are similar. In this case the electric field effects from the hetero atom are different.

Also interesting is that the amides **9amCl** and **10ap**(**t**) (oxygen analogues of **2amCl** and **4ap**(**t**)) show large negative temperature coefficients and have O=C–N–H dihedral angels smaller than 180° (Table 2).

Much of the current thinking regarding temperature coefficients is based on solvent interactions as the cause of negative temperature coefficient and also recently that conformational effects may play a role [5,14–18]. Llinas and Klein [3] studied temperature coefficients in a broad range of solvents, trifluoroacetic acid, chloroform, water, dimethylsulfoxide, dimethylformamide and pyridine and stated "the temperature coefficient affords an excellent criterion to determine the extent of exposure of the NH group, whatever the solvent". In the present study tetrahydrofuran, methylene chloride and toluene have been included. This will of course explain the close to zero effects seen for simple thioamides in non-polar solvents as no interaction with solvent takes place.

The temperature coefficients found for thioamides with intramolecular hydrogen bonds to a sp^2 hybridised oxygen represented by **15k**, **16k**, **17k** and **18** give a different picture than the thioamides and amides in which the acceptor is a nitrogen. Basically the stronger the hydrogen bond the less negative the temperature coefficient and the magnitudes are apparently not related to the non-planarity of the S=C–N–H group (Table 2). The results of Gellman et al. [14–18] that intramolecularly hydrogen bonded peptides show a temperature coefficient of −5 ppb/K in non-polar solvents is on the high side.

4.2. Other effects

The results obtained for **4ap(t)**, **2bep** and **2bem** in DMF deserve discussion. The very small temperature coefficients −2 to −4 ppb/K are unusual as these compounds do not form intramolecular hydrogen bonds in DMF according to their NH chemical shifts (Table 2). Small values were also obtained by Martinez-Martinez et al. [12] for *N*,*N*′-bis[(2-hydroxy)phenyl]oxamides. These authors ascribe the small temperature coefficients to intramolecular hydrogen bonding. However, this is difficult to envisage as both possible hydrogen bonds only involve five-membered rings. We would like to suggest that repulsive protection from solvent is at play. The two oxygens at each end prevent the S=O end of the DMSO to get close due to simple electrostatic repulsion.

For the present compounds a similar mechanism could be at play assuming that the change in the hydrogen bond pattern and the following NH chemical shifts arise solely from the change in the solvent dielectric constant and not from specific interactions with the solvent.

4.3. Non-linearity of NH chemical shifts with temperature

Non-linearity is strongly seen for **5am(c)**. The IR spectrum as well as the ^3J(H-2,H-3) couplings show unambiguously that the compound exists as a mixture of a hydrogen bonded and an open form (Scheme 1).

The strong non-linearity of the temperature coefficient of **11** at high concentrations points to extensive dimer formation. The C=S group is involved in a reasonably strong hydrogen bond with the OH group. This then suggests that the dimer formation occurs as a N–H···N hydrogen bond. As none of the other chemical shifts are very temperature sensitive we can rule out aggregation in general.

At high concentration also the NH chemical shifts of **15** are non-linear in $CDCl_3$ and toluene. This is especially true for the NH proton of **15e(t)**, whereas the NH proton of **15e(c)** is much more linear. Such studies can in a simple manner tell about the tendency for dimer formation, but also give structural details of how this is occurring.

The intramolecularly hydrogen bonded compounds show much less tendency to non-linearity (Fig. 2).

As mentioned, the temperature coefficients are more negative for morpholines than for piperidines. This indicates that the potential also plays a role. The finding that temperature coefficients are different for **12** and **13** also shows that substitution to a smaller degree plays a role. This was less obvious for **2ap** and **2apNO$_2$** (Table 2).

5. Conclusions

From the present set of data no obvious differences are seen between amides and thioamides. The discussion of amides and thioamides without intramolecular hydrogen bonds is based on data obtained at sufficiently low concentration to avoid dimerisation seen as non-linearity of the δNH vs. T plot. A very distinct case in which an equilibrium exists between a closed and an open form is that of **5am(c)**. In non-polar solvents simple amides and thioamides give small temperature coefficients. This can be understood as no interactions take place. In solvents that can form hydrogen bonds such as water, DMF or DMSO the interaction may increase in strength at lower temperature thus leading to a high frequency shift. For intramolecularly hydrogen bonded compounds with a rigid structure and an optimal hydrogen bond geometry cooling will not modify the hydrogen bond to any great extent and the temperature coefficient will be small (see **18** and **19**). For compounds with intramolecular hydrogen bonds but of a flexible nature such as the small peptides described by Gellman et al. [13–18] the situation is similar to that found for intermolecular interactions.

For intramolecularly hydrogen bonded compounds with steric constraints leading, e.g. to non-planar amide or thioamide moieties and a nitrogen as acceptor such as **1–10** and hence with less than optimal hydrogen bond geometry a lowering of the temperature may cause the formation of a stronger hydrogen bond through geometry optimisation and therefore a strong high frequency shift. This situation is akin to *ortho*-hydroxy acyl aromatics in which steric perturbation prevents full conjugation of the acyl moiety with the aromatic ring. For those cases deuteriation of e.g. the acetyl group leads to optimisation of the hydrogen bond and to a high frequency shift of the OH proton [32]. For those compounds in which the acceptor is an sp^2 hybridised oxygen, such as **15k–17k**, **19** and **21** the temperature coefficients are not so negative despite the fact that the S=C–N–H or O=C–N–H angles are quite far from 180° in some cases. This can possibly be related to a combination of less rearrangement at low temperature and to the finding that the NH nuclear shielding tensor is much less asymmetric in these cases (Table 3).

Observation of NH temperature coefficients in non-polar solvents can be categorized as follows. Small coefficients point either to strong intramolecular hydrogen bonding or to intermolecular hydrogen bonding. In the latter case an increase in concentration most likely will lead to non-linearity.

Large negative temperature coefficients point to strong intramolecular hydrogen bonding in which the hydrogen bond is distorted.

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