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Conformational studies on substituted ε-caprolactams by X-ray crystallography and NMR spectroscopy†‡

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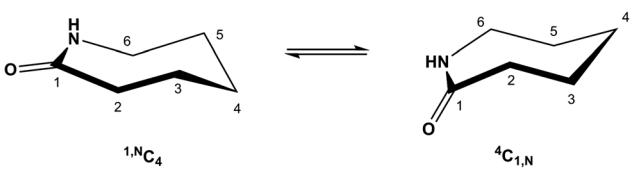
The synthesis and conformational analysis of ε-caprolactams containing a –COOMe group at the C-6 position is described. The influence of different C-2, C-6 and *N* substituents on ring conformation was studied using X-ray crystallography and NMR spectroscopy. The results provide evidence that all the analysed caprolactams adopt a chair type conformation with a planar lactam. In the 6-substituted caprolactam, the –COOMe residue prefers to reside in an equatorial position, but can be induced to occupy an axial orientation by the introduction of a bulky *tert*-butyloxycarbonyl (BOC) group on the lactam nitrogen or by C-2/C-3 ring desaturation. The BOC protected caprolactam was found to undergo exchange between two chair forms as detected by solution NMR, one with the C-6 ester equatorial (30%) and the other with it in the axial position (70%); the latter was observed by X-ray crystallography. For the C-2 dithiocarbamate substituted C-6 methyl ester seven-membered rings, a single chair form is observed for *cis*-isomers with both substituents equatorial. The analogous *trans*-isomers, however, exist as two chair forms in a 1 : 1 equilibrium ratio of $^{1,N}C_4$ and $^{4}C_{1,N}$ conformers, where either substituent can occupy axial or equatorial positions.

Introduction

ε-Caprolactam, or hexahydro-2-azepinone, is an important starting material in polymer chemistry; it is produced from cyclohexanone by Beckmann rearrangement.[1] ε-Caprolactam is used in nylon preparation,[2] and as such is the basis for the manufacturing of many useful products. Derivatives of ε-caprolactam are of interest for the production of modified nylons[3] and nanogels.[4] Azepinones and their unsaturated and saturated analogues play an important role in medicinal chemistry,[5] including in drugs (*e.g.* Benazepril,[6] Ivabradine,[7] Telcagepant[8]), antibiotic research (*e.g.* capuramycin[9]), and as simple models of cyclic peptides.[10] Despite the importance of caprolactams, reports on the influence of substituents on the conformations of caprolactam rings and the mutual influence of different substituents are rare[11] including with respect to the solid state behavior of single component caprolactams and respective co-crystals.[12]

Although the influence of various substituents on the conformation of cyclohexanes has been studied in detail, analogous reports on seven-membered rings are much less comprehensive. Based on studies of the conformation at the cycloheptene ring,[13] caprolactams are predicted to exist in (pseudo) 'chair', 'boat' or a transition 'twisted boat' or 'twisted chair' conformations. In the case of the 'chair' form, two energetically favoured chair conformations can be identified ($^{4}C_{1,N}$ and $^{1,N}C_4$), assuming the amide C–C(=O)–N–C segment is planar[14] (Scheme 1). Furthermore it is known, that axial substituents on caprolactams are higher in energy than the equatorial substituents as shown for methyl and *tert*-butyl substituents at C-2 and C-6.[15]



$^{1,N}C_4$ $^{4}C_{1,N}$

Scheme 1 The two energetically favoured (pseudo) chair conformations of ε-caprolactam: $^{1,N}C_4$ and $^{4}C_{1,N}$. (For consistency we apply here the reported numbering system.[14])

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† Dedicated to Dr Margit Gruner, an expert on NMR studies of complex natural products and supramolecular systems, on the occasion of her 65th birthday.

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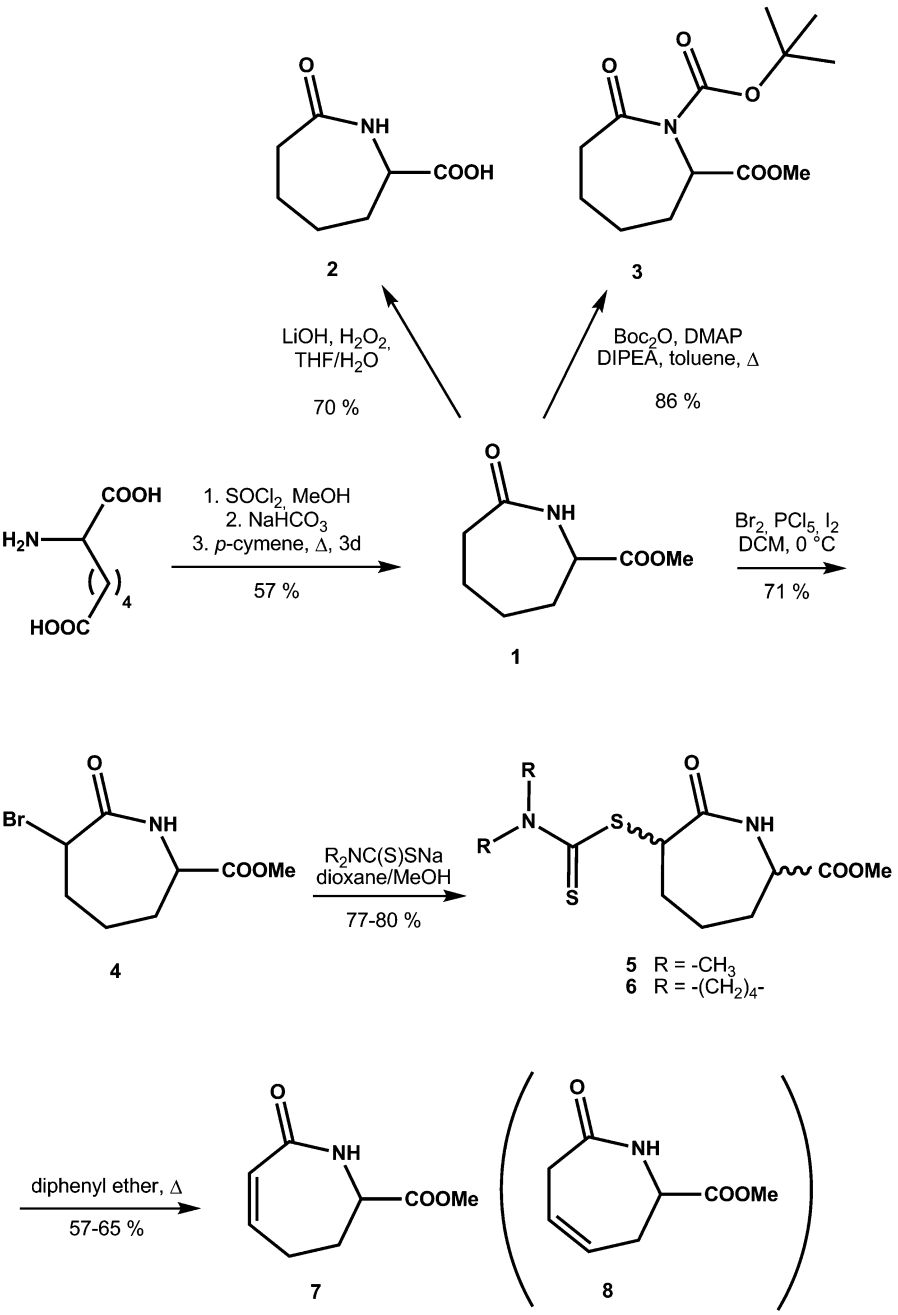
Arising from studies on β-lactam antibiotic biosynthesis and mode of action,[16] we were interested in a caprolactam functionalized at C-6 with a –COOMe group (**1**). For subsequent reactions concerning the caprolactam core we were keen to alter the conformation of the ring and position the methyl ester in an axial position. For this purpose, the effects of a C-2 substituent (adjacent to the rigid amide) and at the amide nitrogen on the conformations of the respective caprolactam derivatives were tested. Here we report solution NMR and crystallographic structural studies on the effects of substituents on caprolactam conformation.

Results and discussion

Synthesis

For the preparation of methyl ester **1** we investigated several different reactions. In contrast to the efficient γ- and δ-lactam preparation, analogous cyclization of the respective racemic aminopimelic acid with subsequent methylation had little success when using activating agents such as 3,4,5-trifluorobenzene boronic acid[17] (no reaction) or SiO_2[18] (10% yield). However, preparation of the dimethyl ester of aminopimelic acid followed by heating in refluxing *p*-cymene[19,20] gave **1** in reasonable yield (57%,



Scheme 2 Synthesis of caprolactam derivatives **1–8**.

unoptimised). The free caprolactam acid **2** was obtained after saponification of **1** (LiOH, aq. THF) (70%).

In order to introduce a sterically hindered *tert*-butyloxycarbonyl group at the amide nitrogen, **1** was reacted with $(^{t}BuO\text{-}CO)_2O$ under basic conditions in toluene to give **3**. For C-2 substitution, we first carried out bromination using molecular bromine[21] to yield an inseparable mixture of isomers (**4**). Subsequent treatment with two different dithiocarbamate salts yielded compounds **5** and **6**, which could be separated into *cis* and *trans* isomers, with a significantly higher amount of the *cis* isomer being formed. The dithiocarbamates were chosen as, in general, they allow versatile consecutive reactions.[22] After a Tschugaev-like pyrolysis,[23] we obtained the C-2/C-3 unsaturated caprolactam (**7**), together with the rearranged C3/C4 isomer (**8**) in a 1 : 1 ratio[24] (Scheme 2).

Conformational analyses of monosubstituted caprolactams

Caprolactam derivatives **1**, **2**, **3**, **5** *cis*, **5** *trans* and **6** *cis* and **7** were characterized by single-crystal X-ray diffraction. For selected crystallographic and structural refinement parameters, molecular torsion angles, and information regarding hydrogen bond geometries see Tables 1 and 2 and Table S1 (ESI‡). The molecular overlay calculation data, rmsd (= root mean square of the atomic distances) and maxd (the maximal atomic distance difference of corresponding atoms) for the caprolactam moieties with respect to ε-caprolactam are listed in Table 3. Crystal structures of ε-caprolactam have been reported;[25,26] the most recently reported structure of caprolactam (published by Winkler and Dunitz in 1975), was used for comparison as it has the best reported agreement factors (Cambridge Structural Database REF CODE: CAPLAC).

Generally in monosubstituted caprolactams, axial substituents are anticipated to be higher in energy than the equatorial ones, a conclusion supported by molecular mechanics calculations carried out on the C6 methyl ester (**1**). The $^{4}C_{1,N}$ form with the carboxylate in the axial position is calculated to be 8 kcal mol^{-1} higher in energy than the $^{1,N}C_4$ with the methyl ester in the equatorial position (Fig. 1a). Indeed, the predicted lower energy form is observed in our crystal structure of **1** (Fig. 1b) which reveals the –COOMe moiety in an equatorial position and with the ester carbonyl group (N1–C6–C7–O2) being almost coplanar with respect to the amide (C6–N1–C1–C2) (Table 2). In the packing of **1**, two molecules form hydrogen-bonded dimers *via* N–H···O hydrogen bonds [d(N···O) = 3.056(3) Å] (Fig. 1c). The graph set descriptor is $R_2^2(8)$, which is also seen in the ε-caprolactam (CAPLAC)[26] and the C-2/C-6 dimethyl[27] and C-2 phosphinoxide derivatives.[28]

In contrast to **1**, in the solid state, caprolactam acid **2** has three crystallographically independent molecules in the asymmetric unit; these form a trimer arranged around an approximate non-crystallographic three fold axis. The molecules are connected *via* three sets of strong NH···O and OH···O contacts [d(N···O) = 2.970(4)–3.074(4) Å; d(O···O) = 2.543(4)–2.555(4) Å] from the $R_2^2(8)$-type (Table S1 (ESI‡), Fig. 2a). Careful examination of the three crystallographically unique molecules in **2** shows they have two different configurations at the chiral C6.

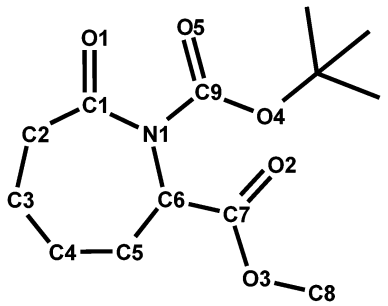
Table 1 Crystallographic and structure refinement data of the compounds studied

Compound	**1**	**2**	**3**	**5** *cis*	**5** *trans*	**6** *cis*	**7**
Empirical formula	$C_8H_{13}NO_3$	$C_7H_{11}N_1O_3$	$C_{13}H_{21}NO_5$	$C_{11}H_{18}N_2O_3S_2$	$C_{11}H_{18}N_2O_3S_2$	$C_{13}H_{20}N_2O_3S_2$	$C_8H_{11}NO_3$
Formula weight (g mol^{-1})	171.19	157.17	271.31	290.40	290.40	316.44	169.18
Crystal system	Triclinic	Triclinic	Monoclinic	Monoclinic	Triclinic	Monoclinic	Triclinic
Space group	$P\bar{1}$	$P\bar{1}$	$P2_1/n$	$P2_1/c$	$P\bar{1}$	$P2_1/n$	$P\bar{1}$
a (Å)	5.2735(2)	10.5713(8)	6.27304(11)	7.54965(8)	7.9432(6)	7.71325(7)	6.2079(4)
b (Å)	8.6164(4)	10.6265(5)	8.13334(11)	7.8511(1)	8.4258(6)	8.16076(7)	7.7139(7)
c (Å)	9.3766(4)	11.0705(7)	27.2810(5)	23.3724(3)	11.2990(8)	23.7540(2)	8.6278(8)
α (°)	97.6974(18)	72.339(5)	90	90	89.703(6)	90	82.686(8)
β (°)	93.5064(18)	78.005(6)	91.0045(16)	95.6507(11)	71.855(6)	94.6857(8)	88.718(7)
γ (°)	95.8677(19)	80.552(5)	90	90	73.959(6)	90	89.279(6)
V (Å^3)	418.80(3)	1152.29(13)	1391.68(4)	1378.62(3)	687.92(9)	1490.22(2)	409.68(6)
Z	2	6	4	4	2	4	2
D_c (Mg m^{-3})	1.358	1.359	1.295	1.399	1.402	1.410	1.371
μ (mm^{-1})	0.104	0.896	0.826	3.539	0.389	3.323	0.884
Data collection							
Temperature (K)	150	150	150	150	150	150	150
Wavelength (Å)	0.71073	1.54184	1.54184	1.54184	0.71073	1.54180	1.54184
No. of collected reflections	7659	10 066	13 198	11 617	6132	19 616	3072
θ_{max} (°)	27.408	76.407	76.124	76.330	30.707	76.356	75.764
Completeness to θ_{max} (%)	98.6	98.1	95.6	99.0	83.0	99.3	97.3
No. of unique reflections	1882	4752	2770	2866	3550	3107	1671
R(int)	0.028	0.023	0.028	0.025	0.037	0.021	0.011
No. of refined parameters	109	298	172	163	163	181	109
No. reflections [$I > 2\sigma(I)$]	918	3278	2364	2866	2530	2987	1592
Final R-indices							
R_1 [$I > 2\sigma(I)$] (%)	4.24	5.83	3.49	2.77	5.65	2.57	3.27
wR [$I > 2\sigma(I)$] (%)	10.79	15.18	8.54	7.18	9.53	10.49	8.83
S (= Goodness of fit on F^2)	0.9467	0.9925	0.9877	0.9588	1.0097	0.9997	1.0124
Final $\Delta\rho_{max}/\Delta\rho_{min}$ (e Å^{-3})	0.28, −0.28	1.03, −0.32	0.33, −0.23	0.30, −0.21	0.66, −0.67	0.29, −0.21	0.23, −0.18

Table 2 Torsion angles (°) for ring atoms in the caprolactam structures[a]

Atoms	1	2(1)	2(2)	2(3)	3	5 *cis*	5 *trans*	6 *cis*	7
C1–C2–C3–C4	82.8(3)	−80.8(3)	−79.3(3)	81.7(3)	84.34(17)	83.88(12)	−84.3(3)	84.96(10)	−2.1(2)
C2–C3–C4–C5	−61.4(3)	64.7(4)	59.4(3)	−64.1(4)	−60.79(17)	−67.42(14)	67.6(3)	−67.75(12)	1.29(18)
C3–C4–C5–C6	59.3(3)	−62.0(4)	−61.6(3)	61.9(3)	60.03(17)	63.95(15)	−60.0(3)	63.48(12)	−44.53(15)
C4–C5–C6–N1	−77.3(3)	75.9(3)	81.4(2)	−77.2(3)	−79.65(16)	−75.49(14)	69.1(3)	−75.44(12)	80.94(14)
C1–N1–C6–C5	66.5(3)	−66.1(3)	−65.1(3)	66.2(4)	65.01(15)	62.76(16)	−63.2(4)	62.63(14)	−54.82(15)
C6–N1–C1–C2	−0.4(3)	5.0(4)	−4.8(3)	−2.5(4)	−0.49(16)	0.93(18)	5.2(4)	1.65(15)	−2.02(15)
N1–C1–C2–C3	−68.0(3)	61.5(3)	70.3(3)	−63.9(4)	−67.95(16)	−66.95(14)	62.5(3)	−67.75(11)	25.22(18)
N1–C6–C7–O2	−7.3(3)	5.9(3)	0.3(3)	4.4(4)	14.50(16)	−11.24(14)	−9.6(4)	−10.46(14)	15.92(15)

[a] General numbering scheme for compound **3**:



Although this gives a ratio of 2 : 1 within the asymmetric unit, as the space group is centrosymmetric, the overall crystal is racemic,[29] *i.e.* the final ratio of the two (*S*) and (*R*) forms on C6 of the molecules is 1 : 1. Converting the three crystallographically independent molecules to the same configuration (*i.e.* inverting one) demonstrates that their molecular geometries are very similar. Hence, the loss of the methyl ester from **1** to **2**, does not substantially influence the conformation (Table 2). The carboxylic acid function of **2** is in the equatorial position as observed for the –COOMe ester in **1** (Fig. 2b).

The introduction of a double bond between C2 and C3 of caprolactam ester **1** as in **7** ''flattens'' the seven membered ring chair conformation (Table 2 and Fig. 2c). However, the carbonyl group and the double bond are not fully coplanar, with a dihedral angle of 22.49(7)°. Notably, the placement of the –COOMe substituent on C6 has a different influence on the

Table 3 Overlay of the caprolactam moiety (*e.g.* N1, O1, C1, C2, C3, C4, C5 and C6) of the investigated structures. ''rmsD'': root mean square of the atomic distances, ''maxD'': the largest atomic distance difference of corresponding atoms

Compared structures		rmsD	maxD
CAPLAC	**1**	0.0391	0.0668
1	**2**(1)[a]	0.0856	0.1817
1	**2**(2)	0.0925	0.1907
1	**2**(3)[a]	0.0626	0.1150
1	**3**	0.0429	0.0786
1	**5** *cis*	0.0302	0.0489
1	**6** *cis*[a]	0.0290	0.0437
1	**7**[a]	0.2273	0.4423
2(1)[a]	**2**(2)	0.0734	0.1227
2(1)[a]	**2**(3)[a]	0.1223	0.2196
2(2)	**2**(3)[a]	0.0894	0.2149
5 cis	***6 cis***[a]	*0.0084*	*0.0136*

[a] Structure is inverted related to the received one or related to the other molecule present in the asymmetric unit.

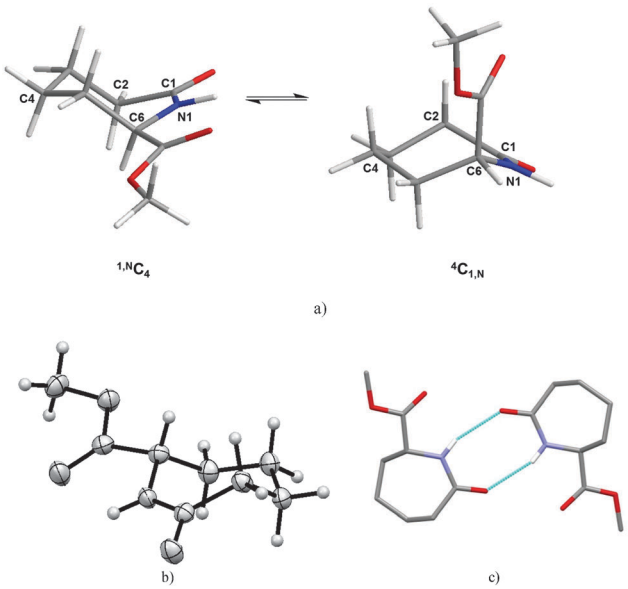


Fig. 1 (a) Caprolactam **1** in its two chair forms. $^{4}C_{1,N}$ is 8 kcal mol^{-1} higher in energy than $^{1,N}C_4$ as calculated by molecular modelling using Macro-Model. (b) Displacement ellipsoid plot of **1** from single crystal diffraction data and (c) dimer formation in **1** showing the $R_2^2(8)$ hydrogen bonding motif.

saturated and unsaturated compounds respectively *i.e.* it switches from an equatorial to an axial position, however, the dimer formation *via* $R_2^2(8)$ hydrogen bonds [*d*(N···O) = 2.8618(16) Å] of **7** is observed again.

Conformational analyses of disubstituted caprolactams

Crystallographic studies. On *N*-substitution at the amide of **1** with the *tert*-butyloxycarbonyl (BOC) group to give **3**, the caprolactam ring conformation is slightly changed (Table 2 and Fig. 2d). The carbonyl groups of –COOMe at C-6 and the

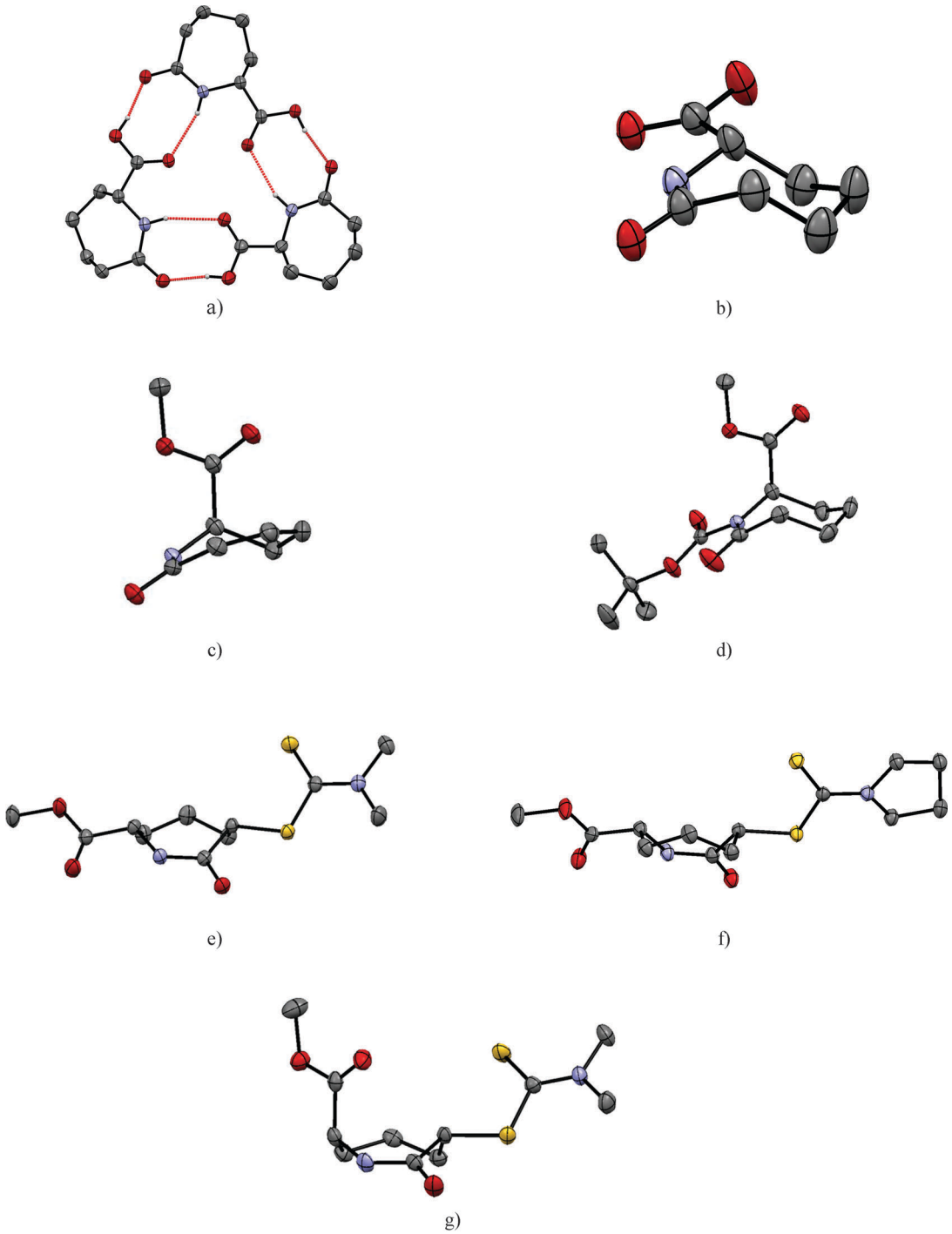


Fig. 2 The pseudo threefold symmetry of the three crystallographic independent molecules in the asymmetric unit of **2** (a) and the structures of caprolactam acid **2** (only one molecule of the asymmetric unit is displayed for clarity) (b), the desaturated lactam **7** (c), the *N*-functionalized lactam **3** (d) and the dithiocarbamates **5** *cis* (e), **6** *cis* (f) and **5** *trans* (g) from single crystal diffraction studies. Displacement ellipsoids are drawn at the 50% probability level and hydrogen atoms (except those illustrating hydrogen bonding interactions) are omitted for clarity.

$-COOC(CH_3)_3$ at N-1 are *trans* relative to each other, with the BOC carbonyl being approximately coplanar with the amide segment (C1–N1–C9–O4 = 8.38(17)°). Presumably due to the steric demand of the BOC group, the C-6 ester (which is in the equatorial position in the structures previously described), preferentially adopts the normally energetically disfavoured, axial position. As the amide proton is missing, no intramolecular dimer formation is observed. Instead, C6–H61···O2 weak intermolecular contacts apparently enable dimeric interactions.

The disubstituted lactams **5** and **6** were obtained as pairs of *cis*/*trans*-diastereomers. We were able to grow single crystals from the *cis* isomers of both **5** and **6** and the *trans* isomer of **5**.

Atoms C-2 and C-6 of the *cis*-dithiocarbamates (**5**, **6**) have the same configuration and crystallise in centrosymmetric space groups (making them racemic). In each case, both substituents adopt equatorial positions and neither the presence of the more flexible dimethyl group nor the preorganized pyrroldine dithiocarbamate group substantially influence the caprolactam ring conformation (Table 2 and Fig. 2e and f). The C2 substituent of **6** does not have a significant effect on the ring conformation as shown by the low cell similarity index (π)[30] of 0.03324 for **5** and **6**. Superimposing all 18 heavy atoms of **5** with the corresponding atoms of **6**, the root mean square of the atomic distances rmsd = 0.008, the largest atomic distance difference of corresponding atoms maxd = 0.014, which is lowest for all structures compared herein (Table 3).

In contrast to the literature structure of caprolactam,[25,26] and the structures of **1** and **7** herein, no stereotypical N–H···O amide dimers are seen for the *cis* diastereoisomers of the dithiocarbamate derivatives **5** and **6** in the crystalline state. This is interesting because the N–H of the amide of **5** and **6** do not form any hydrogen bonds at all. The strong N–H···O hydrogen bonds are apparently replaced by weaker C–H···O interactions to the amide oxygen O1 and short contacts between the ester oxygen and the dithiocarbamate. It is possible that, C–H···S,[31] N–H···S[32] and S···S[33] contacts are relevant (Fig. S1, ESI‡).

In the *trans*-diastereomer of **5** the chair is again the favoured conformation of the caprolactam core with one substituent adopting an axial orientation (C6) whilst the other (C-2) adopting an equatorial position (Fig. 2g). Likely for steric reasons, the C-2 dithiocarbamate residue is in the equatorial position forcing the C-6 methyl ester into the axial position. Consequently, this leads to a rather short intermolecular distance of 2.424(3) Å between

Table 4 Influence of one and two substituents on their relative position on the ring and the CO···NH bonding pattern in the solid state of the caprolactams investigated

	C(6) substituent		2nd substituent		H bonding pattern[34]
CAPLAC	—	—	—	—	$R_2^2(8)$
1	–COOMe	Equatorial	—	—	$R_2^2(8)$
2	–COOMe	Equatorial	—	—	$R_2^2(8)$
3	–COOMe	Axial	*N*-BOC	Lactam and *N*-BOC carbonyls coplanar	—
5 *cis*	–COOMe	Equatorial	C2–S(S)C–N(Me)$_2$	Equatorial	—
5 *trans*	–COOMe	Axial	C2–S(S)C–N(Me)$_2$	Equatorial	$R_2^2(8)$
6 *cis*	–COOMe	Equatorial	C2–S(S)C–N(CH$_2$)$_4$	Equatorial	—
7	–COOMe	Axial	—	—	$R_2^2(8)$

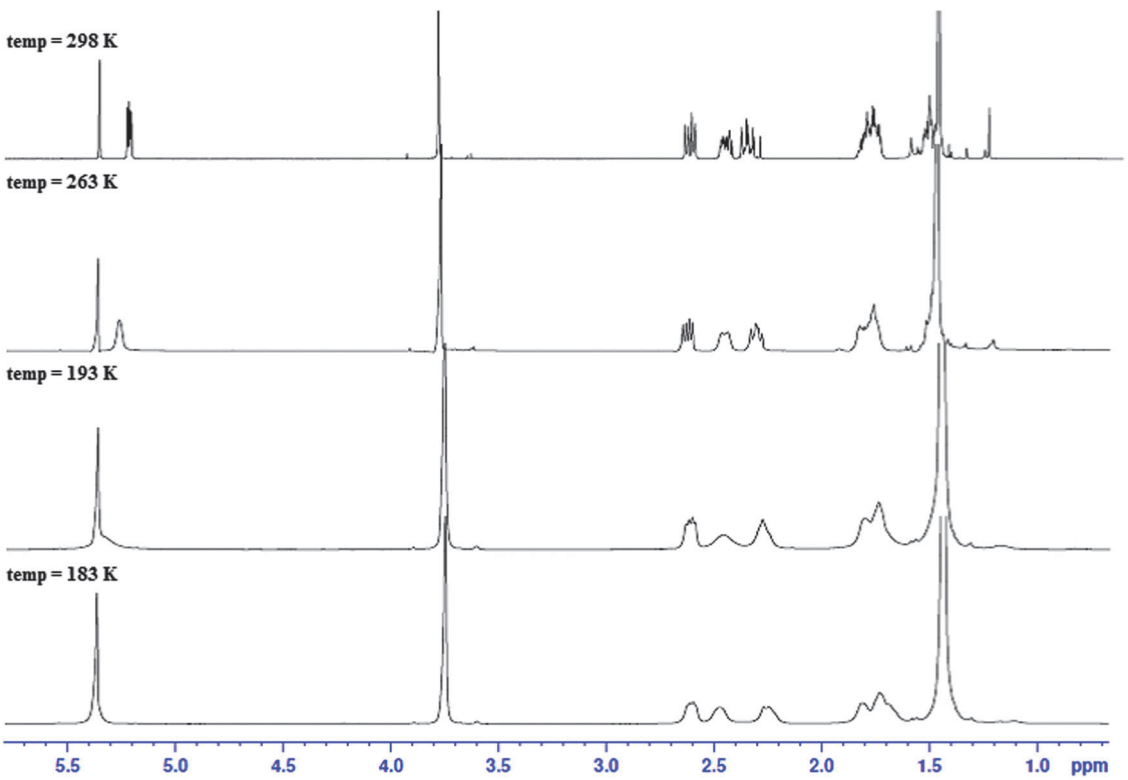


Fig. 3 ^{1}H NMR spectra of the *N*-Boc protected C-6 substituted methyl ester (**3**) at different temperatures (183–298 K) in CD_2Cl_2.

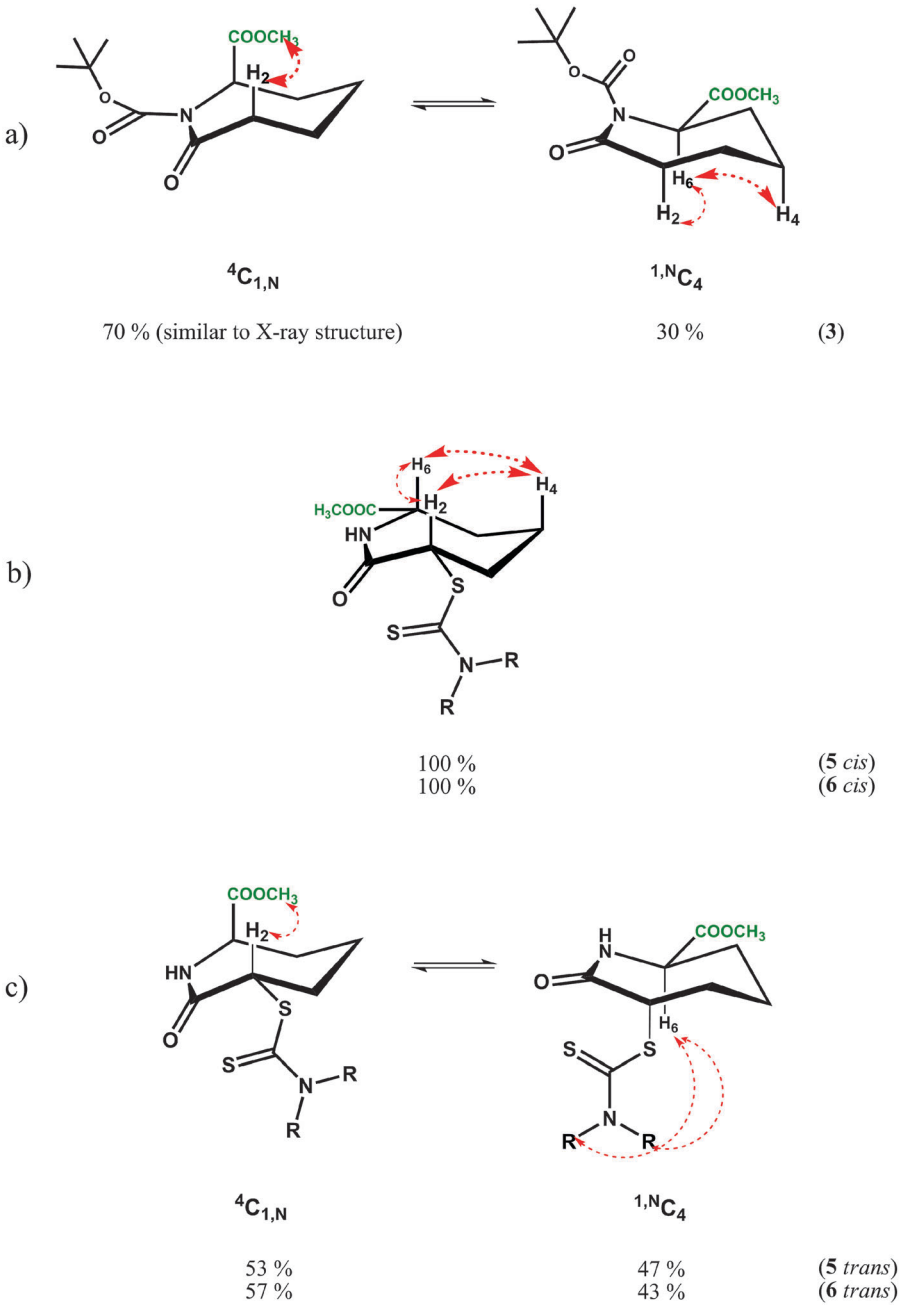


Fig. 4 Conformational isomers of the caprolactams **3** (a), **5** *cis*, **6** *cis* (b), **5** *trans* and **6** *trans* (c). Within caprolactam **3** and *trans* dithiocarbamates **5** and **6**, $^{1,N}C_4$ and $^{4}C_{1,N}$ are in fast conformational exchange at room temperature in either CD_2Cl_2 or C_6D_6. Observed NOEs, indicated by dotted red arrows, are consistent with both forms being present in solution (spectral overlap for H4′ negated its irradiation in either CD_2Cl_2 or C_6D_6).

the carbonyl of the methyl ester and the facing methylene hydrogen. In the packing of **5** *trans*, amide dimers featuring the $R_2^2(8)$ motif are the most striking feature (Table 4).

NMR solution studies. To investigate the influence of a substitution on caprolactam conformation in solution, NMR studies were carried out initially on the *N*-BOC protected C-6 substituted methyl ester **3** at different temperatures (183–298 K) in CD_2Cl_2 (Fig. 3). The ^{1}H NMR spectrum of **3** was sharp and well resolved at 298 K, but exhibited broadening as the temperature was lowered, suggesting dynamic conformational exchange. At 183 K, the signals were too broad to obtain meaningful *J*-coupling or NOE information.

NOE experiments on **3** at room temperature, however, were consistent with both $^{1,N}C_4$ and $^{4}C_{1,N}$ forms being present in solution due to the presence of a medium strength NOE between the methyl ester and H2′ in $^{4}C_{1,N}$ and strong-medium NOEs between H6 and H2 and H6 and H4 in $^{1,N}C_4$. These two groups of mutually exclusive NOEs can only be observed if the two chair forms $^{1,N}C_4$ and $^{4}C_{1,N}$ are present in fast exchange (Fig. 4a) at room temperature.

Conformational averaging is also reflected in the vicinal *J*-couplings at room temperature, for example ^3J(H6,H5) = 6.3 Hz, ^3J(H6,H5′) = 3.0 Hz (values for $^3J(H_{ax},H_{ax})$ = ∼11.0 Hz, $^3J(H_{ax},H_{eq})$ = 2–5 Hz and $^3J(H_{eq}H_{eq})$ = 2–4 Hz[35] in conformationally 'frozen' forms; see later section on *cis*-isomer of dithiocarbamates **5** and **6**). Assuming for **3** the existence of the two chair conformers in dynamic exchange at room temperature, it is possible to calculate the conformer populations of $^{1,N}C_4$ and $^4C_{1,N}$ from the averaged vicinal coupling constants[36,37] and the literature values of ^3J couplings in conformers with distinct conformations in similar systems.[38] For the BOC protected methylester **3**, a ratio of 70 : 30 was calculated with the higher populated chair form having the ester substituent in an axial position, thus minimising the steric bulk of the BOC group; the latter is as observed in the X-ray structure, see Fig. 2d. The NMR observations are consistent with the molecular dynamics calculations, where simulations commencing with the equatorial methyl ester $^{1,N}C_4$, proceed to yield twisted chairs, boat and finally the more stable axial methyl ester $^4C_{1,N}$ conformation (by energy difference ∼8 kcal mol^{-1} in favour of $^4C_{1,N}$). The less populated conformer of **3** is less favoured energetically due to steric clash between the equatorial ester function being in close proximity to the BOC substituent.

The NMR results for *cis* isomers of dithiocarbamates **5** and **6** are apparently unambiguous and irrespective of solvent (*e.g.* CD_2Cl_2 or C_6D_6). The proton resonances are sharp indicating a predominant conformer with both *J*-couplings and the NOEs consistent with a chair $^4C_{1,N}$ species containing both 6- and 2-substituents in equatorial positions, see Fig. 4b below. The solution analyses are thus consistent with both X-ray structures. An unusual feature of the spectra for **5** and **6** (both *cis*) is the low coupling constant for ^3J(H2,H3) which approaches zero (1.0–1.8 Hz), see Table 5, suggesting a close to 90° dihedral angle for $H2_{ax}$–C2–C3–$H3_{eq}$ this angle is 79° in the X-ray structure and the energy minimised structure predicts an angle of 81°, also consistent with the observed vicinal coupling constant. The other vicinal coupling constant for the corresponding protons on the other side of the seven-membered ring, ^3J(H6,H5) is 'normal' for $^3J(H_{ax},H_{eq})$ of 4.5–5.2 Hz corresponding to a smaller dihedral angle; in this case the X-ray structure reveals this angle is 68.5° as does the calculated value. An explanation for the unusual small coupling constant for $^3J(H2_{ax},H3_{eq})$ and 80° dihedral angle may reside in the bulky partially delocalised dithiocarbamate group, sterically forcing the dihedral angle containing the equatorial proton H_3, to twist in order to accommodate it.

The flipping of the ring of the $^4C_{1,N}$ to the $^{1,N}C_4$ chair of **5** *cis* and **6** *cis* would mean both C-2 and C-6 substituents are in the axial position, which is not favoured energetically. Molecular dynamics simulations suggest the energy difference between the favoured di-equatorial $^4C_{1,N}$ species and the di-axial $^{1,N}C_4$ conformation is ∼20 kcal mol^{-1}, which is presumably why the later form is not observed in solution by NMR.

In the case of the *trans* dithiocarbamates caprolactams *trans*-**5** and *trans*-**6**, the NMR studies reveal that at room temperature there is fast conformational exchange between the two chair forms, $^{1,N}C_4$ and $^4C_{1,N}$, irrespective of the type of dithiocarbamate substituent. The ^3J(H2,H3), ^3J(H2,H3′), ^3J(H6,H5) and ^3J(H6,H5′) values (Table 4) represent conformationally averaged ensembles of the two forms, although the conformer distribution may be more biased towards $^4C_{1,N}$ in C_6D_6 since ^3J(H2,H3′) tends towards values for axial H_2 compared to CD_2Cl_2 solutions (compare ^3J(H2,H3′) of 9.8 to 10 Hz in C_6D_6 *versus* 8.0 to 8.3 Hz in CD_2Cl_2). The observed NOEs are also consistent with both forms being present from the NOEs between H2 and the Me ester ($^4C_{1,N}$) and H6 and the dithiocarbamate *N*Me or *N*CH_2 substituent ($^{1,N}C_4$). In this situation, where either substituent can occupy an axial orientation, the steric clash between them is minimised. The energy differences between $^{1,N}C_4$ and $^4C_{1,N}$ conformers is predicted to be low 5–8 kcal mol^{-1} in favour of $^4C_{1,N}$, unlike the *cis* isomer, where only one species is observed in solution.

For *trans* **5** and **6**, at 198 K–229 K in CD_2Cl_2, both $^4C_{1,N}$ and $^{1,N}C_4$ forms are clearly observed in the proton spectra, in a ratio of 1 : 0.9, a slight excess of $^4C_{1,N}$. The NOESY spectrum of **5** *trans*

Table 5 Observed ^3J-coupling constants ($^3J_{H,H}$ in Hz) for caprolactams **3**, **5** and **6**

Coupling atoms	CD_2Cl_2 298 K	C_6D_6 298 K
3[a]		
H2–H3	7.0	—
H2–H3′	2.7	—
H6–H5	6.3	—
H6–H5′	3.2	—
5 (*cis*)		
H2–H3′	11.6	11.4
H2–H3	<1.0	1.7
H6–H5	10.8	10.8
H6–H5′	5.2	4.9
6 (*cis*)		
H2–H3′	11.4	11.2
H2–H3	1.8	1.8
H6–H5′	10.9	11.0
H6–H5	4.5	5.2

Coupling atoms	CD_2Cl_2			C_6D_6
		229 K		
	298 K[b]	$^{1,N}C_4$	$^4C_{1,N}$	298 K[a]
5 (*trans*)				
H2–H3′	8.3	10.5	[c]	9.8
H2–H3	2.5	0	[c]	2.0
H6–H5	5.9	[c]	10.4	[a]
H6–H5′	2.9	[c]	[c]	[a]

Coupling atoms	CD_2Cl_2			C_6D_6
		198 K		
	298 K[b]	$^{1,N}C_4$	$^4C_{1,N}$	298 K[a]
6 (*trans*)				
H2–H3′	8.0	10.2	[c]	10.1
H2–H3	2.5	0	[c]	2.0
H6–H5	7.0	[c]	10.8	[a]
H6–H5′	2.4	[c]	3.9	[a]

[a] Signals broadened by dynamic conformational averaging. [b] Sharp signal, fast conformational exchange. [c] *J*-coupling indiscernible due to line broadening from conformational exchange or signal overlap.

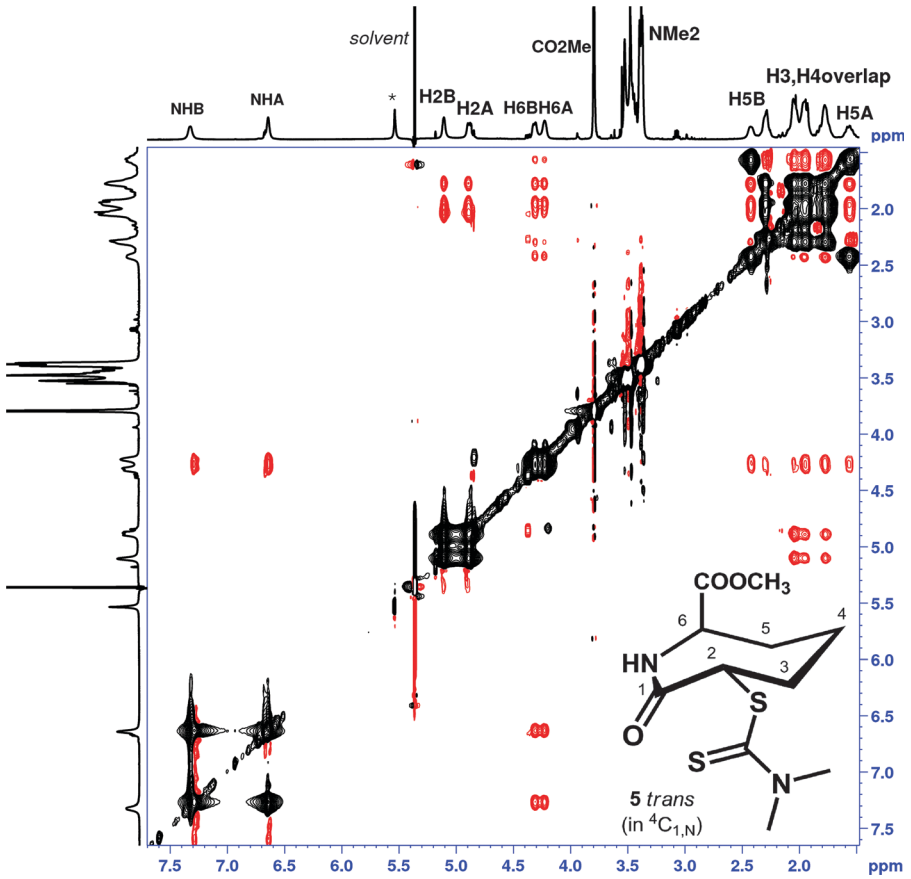


Fig. 5 ^{1}H NMR NOESY spectrum of **5** *trans* (CD_2Cl_2, 500 MHz, mixing time 800 ms, 224 K); resonance labelling follows Scheme 1. Black cross peaks indicate dynamic exchange peaks between conformers $^{4}C_{1,N}$ and $^{1,N}C_{4}$, red cross peaks indicated inter-proton NOEs. Note the NOE between H6 and the NMe_2 is not visible in the figure shown, but is present at higher contour levels, modelling suggests inter-proton distances >3.2 Å.

(Fig. 5), reveals conformational exchange is evident even at 198 K, as shown from the exchange cross peaks which are of opposite phase to those of the NOEs. The NOEs, however, were also consistent with both $^{4}C_{1,N}$ and $^{1,N}C_{4}$ forms present in dynamic exchange.

Conclusions

Overall, the conformational analyses reveal that the investigated caprolactams prefer to adopt a chair conformation featuring a planar arrangement of the lactam group (C2–C1–N1–C6). The positions of the attached substituents relative to the ring are summarized in Table 5. Bond lengths and torsion angles of the caprolactam ring differ only slightly with C2-, C6- or *N*-substitution as shown by the X-ray data. Formation of amide 'dimers' were observed crystallographically in four of the six possible cases. The introduction of unsaturation, *i.e.* a C-2/C-3 alkene, has a considerable effect resulting in the seven membered ring chair conformation being partially flat along the –C1–C2═C3–C4– portion of the molecule. There is no residual solvent accessible void in any of the structures of the presented ε-caprolactams, which is promoted by weak C–H···O contacts. Interestingly, in almost all structures, the slightly acidic proton at C-6 may be involved in these interactions. For the caprolactams **1**, **5** (*cis*) and **6** (*cis*), the –COOMe residue occupies an equatorial position, but is forced into the axial position by the introduction of a BOC group at a neighbouring atom (**3**) or by ring desaturation (**7**).

The NMR studies are consistent with the chair conformations dominating in solution. Caprolactam **3** was found to undergo dynamic exchange between two chair forms, one with the ester equatorial (30%) and the other with the ester axial (70%), the latter observed in the X-ray structure. For the C2-substituted seven-membered rings **5** and **6**, we observed one chair form for both *cis* isomers with both ester and dithiocarbamate groups occupying equatorial positions. The respective *trans* isomers exist in equilibrium between two chair forms in an 1 : 1 ratio where either substituent can occupy axial or equatorial positions. In all cases, solvent *e.g.* benzene or chloroform had only negligible influence on the conformational properties of the caprolactams.

Experimental section

Materials and methods

All reactions involving moisture sensitive reagents were carried out under a nitrogen atmosphere. Cooling was performed in

ice-water baths (0 °C) or dry ice–acetone baths (−78 °C). Anhydrous solvents were obtained from solvent stills and were activated by passing over a short column of activated alumina. Reagents were obtained from Acros or Aldrich fine chemical suppliers and used as supplied. Thin layer chromatography (TLC) was performed on Merck DC-Kieselgel 60 F 254 0.2 mm precoated plates with fluorescence indicator. Visualization of spots was achieved using UV light (254 nm) and by developing in a basic solution of $KMnO_4$ followed by heating. Chromatography was performed using a Biotage SP4 chromatography system, using prepacked Biotage KP-SIL SNAP columns.

Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded using a Bruker AV400 (400 MHz) and AVII 500 (500 MHz) spectrometers. Proton decoupled carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded on a Bruker AV400 (100 MHz) and AVII 500 (125.6 MHz) with sample temperatures regulated at 298 K, unless otherwise stated. Spectra were assigned using COSY, DEPT-135, HMQC, edited-HSQC, and HMBC. All chemical shifts are quoted on the scale in ppm and referenced to residual solvent peaks; CD_2Cl_2 at 5.32 ppm and C_6D_6 at 7.2 ppm and calculated internally by the spectrometer. Resonances are described as s (singlet), d (doublet), t (triplet), m (multiplet), and br s (broad singlet). 1-D NOE experiments were performed using DPFGSE-NOE pulse sequence employing two 180 degree pulses and a mixing time of 800 ms.[39]

Single crystals suitable for single crystal X-ray diffraction studies were obtained from cyclohexane for compound **1** and from a mixture of dichloromethane/methanol (1 : 1) for **5**, **6** and **7**. Compound **3** was recovered as a colourless oil, that produced suitable crystals after some weeks. Single crystal X-ray diffraction data were collected using a Nonius Kappa CCD diffractometer (**1**) or Oxford Diffraction (Agilent) SuperNova diffractometer (**2–7**) fitted with an Oxford Cryosystems Cryostream open-flow nitrogen cooling device. Data collection and reduction were carried out using HKL COLLECT/DENZO-SCALEPACK[40] or CrysAlisPro as appropriate. Structures were solved using SIR92[41] within the CRYSTALS suite[42] and optimized by full-matrix least squares on F^2. Hydrogen atoms were not generally provided by the initial solution, however they were usually clearly visible in the difference Fourier map. Hydrogen atoms were positioned at geometrically sensible positions and refined using soft restraints prior to inclusion in the final refinement using a riding model.[43] The rmsD and maxD data were calculated with the program Mercury[44] and torsion angles were calculated using PLATON.[45] CCDC numbers: 1018875–1018881.

IR spectra were recorded using a Bruker Tensor 27 ATR-FT-IR spectrophotometer. Selected absorption maxima (ν_{max}) are given in wavenumbers (cm^{-1}) and are uncorrected. Mass spectra were recorded on a Waters LCT premier. Melting points were recorded on a Leica VMTG heated-stage microscope melting point apparatus.

All molecular modelling work was carried out using the Schrödinger's Maestro modelling package employing MacroModel with the Schrödinger's implementation of the OPLS_2005 molecular mechanics force field.[46] Conformational searches were performed as follows. Initial molecular models for each compound were energy minimised (convergence criterion: RMS energy gradient < 0.001 kcal mol^{-1} $Å^{-1}$) using constant dielectric constant with chloroform as the solvent and used as starting points for molecular dynamics simulations at an effective temperature of 1000 K. A total of 50 samples were extracted from each dynamics trajectory with a time interval of 1 ps between samples. The sampled structures were then energy minimised, and structural duplicates removed (match criterion: heavy atom RMSD < 0.2 Å). The final set of unique minimum-energy conformers was then sorted according to calculated energy.

Syntheses

Methyl 7-oxoazepane-2-carboxylate (1). Methanol (30 ml) was cooled to −10 °C and thionylchloride (2.5 ml, 34.46 mmol) was dropped in with stirring. Subsequently, (±)-2-aminopimelic acid (3.0 g, 17.13 mmol) was added, the reaction mixture allowed to warm to room temperature and was stirred overnight. The solvents were removed *in vacuo*, to yield the hydrochloride of the amino acid, which was used without purification. The intermediate was neutralized by addition of a small amount of water containing sodium bicarbonate (1 eq.), before extracting this solution with ethyl acetate. The organic phase was dried ($MgSO_4$), filtered and concentrated to afford the free base. After addition of *p*-cymene (80 ml), the mixture was stirred at reflux for 72 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (SiO_2; eluent: ethyl acetate). White solid. Yield: 1.68 g (57%, 9.81 mmol). Mp. 75–76 °C. R_f = 0.35 (SiO_2; ethyl acetate).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.2 (*C*OOCH$_3$), 171.9 (*C*ONH) 55.7, 52.9 (COO*C*H$_3$, NH*C*H), 37.0 (*C*H$_2$), 33.7 (*C*H$_2$), 29.5 (*C*H$_2$), 23.0 (*C*H$_2$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.45 (br s, 1H, N*H*), 4.07–4.03 (m, 1H, NHC*H*), 3.74 (s, 3H, COOC*H*$_3$), 2.47–2.33 (m, 2H, C*H*$_2$), 2.19–2.15 (m, 1H, C*H*$_2$), 2.03–1.96 (m, 1H, C*H*$_2$), 1.86–1.77 (m, 1H, C*H*$_2$), 1.65–1.51 (m, 3H, C*H*$_2$). IR: 3270, 2949, 2919, 2865, 1740, 1645, 1557, 1513, 1468, 1437, 1404, 1343, 1312, 1298, 1261, 1241, 1214, 1196, 1183, 1136, 1107, 1089, 1062, 1012, 965, 933, 873, 850, 801, 733. *m*/*z* = 172.11 [M + H$^+$], calc. 172.09.

7-Oxoazepane-2-carboxylic acid (2). Methyl 7-oxoazepane-2-carboxylate (**1**) (1.08 g, 6.33 mmol) was dissolved in tetrahydrofuran (35 ml). Lithium hydroxide monohydrate (1.06 g, 25.27 mmol) in water (50 ml) and 6.2 ml hydrogen peroxide solution (30%) were added and the solution stirred overnight. The pH of the aqueous layer was adjusted to three with hydrochloric acid (2 M) and extracted three times with ethyl acetate. The organic layers were combined and washed with water (3×) and with brine (1×). The solution was dried (Na_2SO_4) and the solvent removed *in vacuo* to yield 693 mg (70%), 4.41 mmol of a white solid. Mp. 161–162 °C (Lit.:[47] 160–162 °C).

^{13}C NMR (100 MHz, CD_3OD): δ = 178.9 (*C*OOH), 173.8 (*C*ONH), 55.9 (NH*C*H), 36.6 (*C*H$_2$), 33.4 (*C*H$_2$), 29.2 (*C*H$_2$), 23.1 (*C*H$_2$). ^{1}H NMR (400 MHz, CD_3OD): δ = 4.18–4.13 (m, 1H, NHC*H*), 2.59–2.40 (m, 1H, C*H*$_2$), 2.50–2.48 (m, 1H, C*H*$_2$), 2.25–2.17 (m, 1H, C*H*$_2$), 2.03–1.96 (m, 1H, C*H*$_2$), 1.89–1.81 (m, 1H, C*H*$_2$), 1.78–1.67 (m, 1H, C*H*$_2$). IR: 3234, 2922, 2850, 1703, 1612, 1443, 1413, 1358, 1343, 1327, 1265, 1250, 1229, 1220, 1203,

1191, 1152, 1086, 1026, 942, 878, 853, 834, 807, 755, 728. m/z = 156.07 [M − H^+], calc. 156.17.

1-*tert*-Butyl 2-methyl 7-oxoazepane-1,2-dicarboxylate (3). Under a nitrogen atmosphere methyl ester **1** (481 mg, 1.77 mmol) was dissolved in dry toluene (50 ml). Subsequently, Hunig's base (603 μl, 3.54 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (43 mg, 0.35 mmol) were added at room temperature. To this mixture, a solution of di(*tert*-butyl)dicarbonate (1.93 g, 8.86 mmol) in dry toluene (10 ml) was added and the resulting mixture stirred overnight under reflux. After cooling down, water (40 ml) was added and the mixture stirred at room temperature for 30 min. The organic layer was separated and dried over Na_2SO_4. Evaporation of the solvent and column chromatography yielded the respective compound. The crude products were purified by column chromatography (SiO_2; *n*-hexane/ethyl acetate = 1 : 1). 86% (481 mg, 1.77 mmol) of a colourless oil, which slowly crystallizes. Mp. 48–49 °C. R_f = 0.80 (SiO_2; *n*-hexane/ethyl acetate = 1 : 1).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.3 (*C*OOCH$_3$), 170.9 (*C*ONH), 153.3 (NCOO^{t}Bu), 83.2 (*C*(CH$_3$)$_3$), 56.5 (NH*C*H), 52.4 (COO*C*H$_3$), 39.5 (*C*H$_2$), 29.8 (*C*H$_2$), 27.9 (C(*C*H$_3$)$_3$), 25.6 (*C*H$_2$), 22.6 (*C*H$_2$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.16–5.12 (m, 1H), 3.71 (s, 3H), 2.63–2.58 (m, 1H, C*H*$_2$), 2.46–2.40 (m, 1H, C*H*$_2$), 2.36–2.29 (m, 1H, C*H*$_2$), 1.79–1.73 (m, 3H, C*H*$_2$), 1.51–1.46 (m, 2H, C*H*$_2$), 1.43 (s, 9H). IR: 2983, 2961, 2933, 2869, 1715, 1701, 1454, 1434, 1380, 1368, 1295, 1285, 1251, 1235, 1204, 1144, 1127, 1083, 1050, 1022, 986, 956, 929, 912, 875, 842, 819, 806, 779, 745, 727, 704. m/z = 272.17 [M + H^+], calc. 272.14.

Methyl 6-bromo-7-oxoazepane-2-carboxylate (4). Methyl 7-oxoazepane-2-carboxylate (**1**) (342 mg, 2.00 mmol) was dissolved in dry dichloromethane (15 ml) and cooled to 0 °C. PCl_5 (458 mg, 2.20 mmol) and I_2 (9 mg, 0.034 mmol) were added. The reaction mixture was stirred for 15 min at 0 °C. Then, bromine (354 mg, 2.22 mmol) in dichloromethane (2 ml) was added, and the reaction was stirred at 0 °C for 4 h. The reaction was quenched by adding aqueous sodium sulfite solution and extracted several times with dichloromethane. The combined organic phases were dried (Na_2SO_4), and the solvent was evaporated to yield a dark a red oil, which was column chromatographed (SiO_2, ethyl acetate). Flesh-coloured oil (357 mg, 1.43 mmol, 71% yield) as a mixture of *cis* and *trans* isomers, which were inseparable by chromatographic techniques. R_f = 0.70 (SiO_2; ethyl acetate).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.7, 170.2, 54.5 (COO*C*H$_3$), 53.2 (*C*HCOO), 51.1 (*C*HBr), 33.5 (*C*H$_2$), 30.0 (*C*H$_2$), 24.3 (*C*H$_2$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.67 (br s, 1H, N*H*), 4.63 (m, 1H, C*H*Br), 4.55 (dd, ^3J = 11.0 Hz, ^2J = 3.5 Hz, 1H, NHC*H*), 3.79 (s, 3H, COOC*H*$_3$), 2.38–2.31 (m, 1H), 2.24–2.12 (m, 1H, C*H*$_2$), 2.09–1.91 (m, 3H, C*H*$_2$), 1.57–1.46 (m, 1H, C*H*$_2$). IR: 3347, 2952, 2933, 1734, 1672, 1434, 1379, 1360, 1337, 1303, 1269, 1240, 1223, 1177, 1147, 1107, 1076, 1061, 1011, 939. m/z = 250.02, 251.98 [M + H^+], calc. 250.00, 252.00.

Preparation of dithiocarbamates 5 and 6. Methyl 6-bromo-7-oxoazepane-2-carboxylate (**4**) (mixture of diastereomers) (1 eq.) was dissolved in dioxane (15 ml) and the mixture was heated to 60 °C. Subsequently, a solution of the respective sodium dithiocarbamate (1.2 eq.) dissolved in methanol (15 ml), is added dropwise. After stirring is continued at 60 °C for 90 min, the solvent is removed under reduced pressure. The raw material was purified by column chromatography (SiO_2; *n*-hexane/ethyl acetate = 1 : 1 → ethyl acetate) to yield in both cases two separable diastereomers.

*Methyl 6-[(dimethylcarbamothioyl)thio]-7-oxoazepane-2-carboxylate (**5**).* Yield 80% (202 mg, 0.70 mmol) as a mixture of 178 mg (88%) *cis* and 24 mg (12%) *trans* isomer.

cis-Methyl 6-[(dimethylcarbamothioyl)thio]-7-oxoazepane-2-carboxylate (**5** *cis*). Mp. 136–137 °C. R_f = 0.70 (SiO_2; ethyl acetate). ^{13}C NMR (100 MHz, DMSO/CD_3OD): δ = 195.5, 172.5, 171.2, 57.6, 55.5, 51.1, 45.3, 41.7, 33.6 (*C*H$_2$), 32.3 (*C*H$_2$), 24.3 (*C*H$_2$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.60 (br s, 1H, N*H*), 4.96 (dd, 1H, C*H*SC═S), 4.35 (dd, 1H, NHC*H*), 3.80 (s, 3H, COOC*H*$_3$), 3.51, 3.39 (s, NC*H*$_3$, 6H), 2.30–2.20 (m, 1H), 2.12–2.03 (m, 2H, C*H*$_2$), 1.96–1.84 (m, 2H, C*H*$_2$), 1.59–1.49 (m, 1H, C*H*$_2$). IR: 3369, 3308, 2950, 2859, 1738, 1654, 1490, 1433, 1395, 1367, 1353, 1329, 1305, 1216, 1135, 1081, 1034, 1007, 983, 943, 873, 854, 817, 786, 742, 718. m/z = 291.11 [M + H^+], calc. 291.08.

trans-Methyl 6-[(dimethylcarbamothioyl)thio]-7-oxoazepane-2-carboxylate (**5** *trans*). Mp. 111–113 °C. R_f = 0.65 (SiO_2; ethyl acetate). ^{1}H NMR (400 MHz, dichloromethane): δ = 6.54 (br s, 1H, N*H*), 5.07 (d, 1H, ^3J = 8.0 Hz, C*H*SC═S), 4.59 (dd, ^3J = 10 Hz, ^2J = 4 Hz, 1H, NHC*H*), 3.89 (t, ^3J = 10 Hz, NC*H*$_2$CH$_2$), 3.83 (s, 3H, COOC*H*$_3$), 3.71 (t, ^3J = 10 Hz, NC*H*$_2$CH$_2$), 2.45–2.37 (m, 1H), 2.33–2.21 (m, 1H, C*H*$_2$), 2.14–2.07, 2.02–1.97 (m, NCH$_2$C*H*$_2$, 4H), 1.93–1.84 (m, 3H, C*H*$_2$), 1.61–1.54 (m, 1H, C*H*$_2$). ^{13}C NMR (100 MHz, DMSO/CD_3OD): δ = 195.1, 172.8, 171.3, 56.7, 54.7, 53.1, 45.7, 41.6, 33.0 (*C*H$_2$), 32.5 (*C*H$_2$), 25.2 (*C*H$_2$). IR: 3364, 3245, 3089, 3038, 2984, 2946, 2937, 1747, 1708, 1655, 1478, 1455, 1440, 1408, 1376, 1363, 1348, 1325, 1307, 1288, 1274, 1250, 1205, 1177, 1157, 1126, 1105, 1084, 1030, 1012, 984, 945, 896, 879, 869, 841, 800, 774. m/z = 291.11 [M + H^+], calc. 291.08.

*Methyl 6-[(pyrrolidine-1-carbonothioyl)thio]-7-oxoazepane-2-carboxylate (**6**).* Yield 77% (296 mg, 0.94 mmol) of a mixture consisting of 213 mg (72%) *cis* and 83 mg (28%) *trans* isomer.

cis-Methyl 6-[(pyrrolidine-1-carbonothioyl)thio]-7-oxoazepane-2-carboxylate (**6** *cis*). Mp. 129–131 °C. R_f = 0.70 (SiO_2; ethyl acetate). ^{1}H NMR (400 MHz, dichloromethane): δ = 6.54 (br s, 1H, N*H*), 5.07 (d, 1H, ^3J = 8.0 Hz, C*H*SC═S), 4.59 (dd, 1H, NHC*H*), 3.89 (t, ^3J = 10 Hz, NC*H*$_2$CH$_2$), 3.82 (s, 3H, COOC*H*$_3$), 3.71 (t, ^3J = 10 Hz, NC*H*$_2$CH$_2$), 2.45–2.37 (m, 1H), 2.33–2.21 (m, 1H, C*H*$_2$), 2.14–2.07, 2.02–1.97 (m, NCH$_2$C*H*$_2$, 4H), 1.93–1.84 (m, 3H, C*H*$_2$), 1.61–1.54 (m, 1H, C*H*$_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.0, 172.5, 171.6, 56.5, 55.2, 54.5, 53.2, 51.1, 32.8 (*C*H$_2$), 32.7 (*C*H$_2$), 28.9 (*C*H$_2$), 26.7 (*C*H$_2$), 24.3 (*C*H$_2$). IR: 3369, 3303, 2950, 1736, 1657, 1431, 1396, 1353, 1307, 1221, 1161, 1083, 1066, 1035, 1008, 946, 873, 855, 821, 787, 739, 716. m/z = 317.08 [M + H^+], calc. 317.09.

trans-Methyl 6-[(pyrrolidine-1-carbonothioyl)thio]-7-oxoazepane-2-carboxylate (**6** *trans*). Mp. 119–121 °C. R_f = 0.59 (SiO_2; ethyl acetate). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.8, 173.4, 171.4, 55.4, 55.3, 54.2, 53.1, 50.7, 33.9 (*C*H$_2$), 32.5 (*C*H$_2$), 26.1 (*C*H$_2$), 25.2 (*C*H$_2$), 24.2 (*C*H$_2$). ^{1}H NMR (400 MHz, dichloromethane): δ = 6.60 (br s, 1H, N*H*), 5.15 (d, 1H, C*H*SC═S), 4.24 (m, 1H, NHC*H*), 3.88

(t, ^3J = 10 Hz, NCH_2CH$_2$), 3.83, 3.82 (s, 3H, COOCH_3), 3.68 (t, ^3J = 10 Hz, NCH_2CH$_2$), 2.48–2.38 (m, 1H), 2.31–2.23 (m, 1H, CH_2), 2.13–1.99 (m, NCH$_2$CH_2, 4H), 1.93–1.84 (m, 3H, CH_2), 1.63–1.55 (m, 1H, CH_2). IR: 3304, 3213, 3096, 2954, 2872, 1727, 1655, 1432, 1363, 1332, 1316, 1287, 1253, 1215, 1185, 1164, 1124, 1106, 1081, 1031, 1002, 957, 945, 889, 868, 846, 822, 794, 774. m/z = 317.08 [M + H$^+$], calc. 317.09.

Pyrolysis of dithiocarbamates. A solution of the respective thiocarbamate (**5** or **6**, resp.) (mixture of diastereomers) (1 eq.) in diphenylether (6.0 g) was heated to reflux for 10 h. The dark brown reaction mixture was allowed to cool to room temperature, then purified by column chromatography (SiO$_2$, ethyl acetate → ethyl acetate/MeOH = 9 : 1). In both cases, the pyrolysis of the respective dithiocarbamate yielded a mixture of two different desaturation products (**7** and **8**). Pyrolysis of **5** yielded 32% (66 mg, 0.39 mmol) of **7** and 33% (67 mg 0.40 mmol) of **8**. Pyrolysis of **6** yielded 30% (10 mg, 0.059 mmol) of **7** and 27% (9 mg, 0.053 mmol) of **8**.

*Methyl 7-oxo-2,3,4,7-tetrahydro-1H-azepine-2-carboxylate (Δ^2) (**7**).* Mp. 101–102 °C. R_f = 0.20 (SiO$_2$; ethyl acetate).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 171.5 (*C*OOCH$_3$), 168.4 (*C*ONH), 140.2 (COCH=*C*), 126.0 (CO*C*H=C), 53.8, 53.0 (COO*C*H$_3$, NH*C*H), 32.5 (*C*H$_2$), 28.7 (*C*H$_2$). ^{1}H NMR (400 MHz, CDCl$_3$): δ = 6.67 (br s, 1H, N*H*), 6.37–6.28 (m, 1H, COCH=CH), 5.94 (dd, ^3J = 12.5 Hz, ^2J = 2 Hz, 1H, COCH=C), 4.51–3.98 (m, 1H), 3.81 (s, 3H), 2.58–2.47 (m, 2H, CH_2), 2.37–2.43 (m, 1H, CH_2), 2.04–2.14 (m, 1H, CH_2). IR: 3277, 3238, 3182, 3132, 3031, 2956, 2923, 1720, 1667, 1619, 1487, 1435, 1390, 1368, 1351, 1331, 1279, 1243, 1216, 1197, 1183, 1146, 1085, 1044, 1009, 989, 932, 913, 874, 862, 836, 816, 784, 731. m/z = 170.11 [M + H$^+$], calc. 170.07.

*Methyl 7-oxo-2,3,6,7-tetrahydro-1H-azepine-2-carboxylate (Δ^3) (**8**).* Mp. 155–156 °C. R_f = 0.38 (SiO$_2$; ethyl acetate).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 173.2 (*C*OOCH$_3$), 171.1 (*C*ONH), 127.2, 120.5 (COCH=*C*, CO*C*H=C), 53.1, 52.8 (COO*C*H$_3$, NH*C*H), 35.4 (*C*H$_2$), 33.8 (*C*H$_2$). ^{1}H NMR (400 MHz, CDCl$_3$): δ = 6.52 (br s, 1H), 5.60–5.49 (m, 2H), 4.61–4.54 (m, 1H), 3.80 (s, 3H), 3.52–3.36 (m, 1H, CH_2), 2.91–2.80 (m, 1H, CH_2), 2.71–2.59 (m, 1H, CH_2), 2.49–2.35 (m, 1H, CH_2). IR: 3284, 3028, 2953, 1735, 1647, 1550, 1436, 1365, 1296, 1266, 1225, 1204, 1158, 1064, 1030, 998, 966, 931, 904, 860, 808, 743, 669, 610. m/z = 170.11 [M + H$^+$], calc. 170.07.

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