Formation of *N*-acyl-*N,N'*-dicyclohexylureas from DCC and arenecarboxylic acids in the presence of hydroxybenzotriazole in CH_2Cl_2 at room temperature

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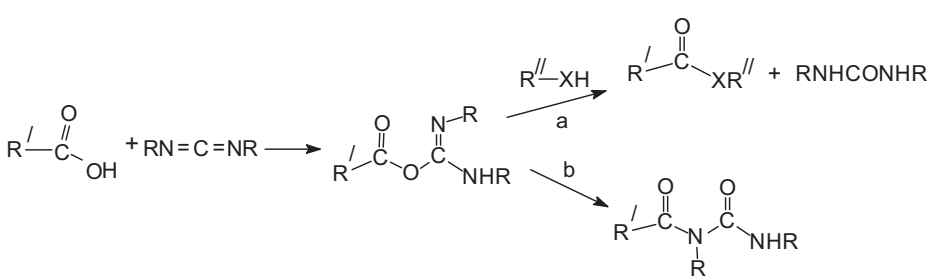
The syntheses of *N*-acyl-*N,N'*-dicyclohexylureas from 1,3-dicyclohexylcarbodiimide and arenecarboxylic acids [*p*-$XC_6H_4CO_2H$ (X = H or NO_2), 2-, 3- or 4-pyridinecarboxylic acid and pyrazinecarboxylic acid] in the presence of hydroxybenzotriazole in CH_2Cl_2 at room temperature are reported. The reactions proceed via the intermediacy of *O*-acyl-*N,N'*-dicyclohexylurea derivatives which undergo rapid *O*-acyl to *N*-acyl rearrangements. No acid anhydrides were detected. Under the same reaction conditions, the *O*-acyl derivative from the alkanecarboxylic acid, *N*-(benzyloxycarbonyl)-*DL*-pipecolic acid does not undergo rearrangement, as shown by the subsequent reaction with MeOH to give methyl *N*-(benzyloxycarbonyl)-*DL*-pipecolate. Characterisations were generally achieved by spectroscopic means, and specifically for *N*-(*p*-nitrobenzenecarbonyl)-*N,N'*-dicyclohexylurea by X-ray crystallography.

Keywords: DCC, *N*-acyl-*N,N'*-dicyclohexylureas, X-ray crystallography, *O*-acyl-rearrangement

Carbodiimides are common reagents with the most used being 1,3-dicyclohexylcarbodiimide[1] (DCC). Carbodiimides have found great use as coupling agents for aminoacids[2] in peptide synthesis. Because carbodiimides are powerful dehydrating agents, they have other applications, including the preparation of esters,[3] anhydrides[4] and amides[5] (all from carboxylic acids), alcohol oxidation[6] (Moffatt oxidation), dehydration of hydroxy compounds[7] and the inversion of the configuration of secondary alcohols.[8]

The reactions of carboxylic acids with carbodiimides proceed *via* initial protonation of the carbodiimide, followed by attack of the carboxylate anion to give a reactive *O*-acylurea derivative. This was originally proposed by Khorana in 1953,[9,10] see Scheme 1. Subsequent reactions of the *O*-acyl derivative depends on reagents and conditions, but the two overall possibilities are (i) reaction with a nucleophile such as a carboxylate anion, an alcohol or an amine to form an acid anhydride, an ester or an amide, respectively, *pathway a* in Scheme 1, or (ii) to undergo a *O-N* rearrangement to give a, *pathway b* in Scheme 1.

The rates of reaction of carbodiimides with carboxylic acids and the ratio of products by *pathway a* [an anhydride] and *b* [a *N*-acyl derivative] obtained are affected by a number of factors, including the solvent, temperature and the presence of acids or bases. Melman and coworkers[11] indicated that the initial *O*-acyl derivatives, formed from carboxylic acids with alpha hydrogens, *e.g.*, RR'$CHCO_2H$, are converted to ketenes, RR'C=C=O, which then react with nucleophiles. There are various examples in the older literature of formation of *N*-acyl derivatives from reaction of carbodiimides with carboxylic acids in the presence of bases.[12] More recently, reactions of substituted benzoic acids with DCC in THF, at 25 °C, in the presence of $[Bu_3NH][ClO_4]/[Bu_3N]$ buffer were shown just to give the *N*-acyl derivatives.[13] Complete formation of *N*-acyl derivatives were also reported in reactions of DCC with $CF_3(CF_2)_5C(CH_2)_9CO_2H$ and palmitic acid in CH_2Cl_2, in the presence of 4-(*N,N*-dimethylamino)pyridine, DMAP, and Et_3N at 0–25 °C.[14] In contrast, the aliphatic acid, *N*-methyl-*N*-(7-nitrobenx-2-oxa-1,3-diazol-4-yl)-6-aminohexanoic acid produced a little of the anhydride as well as the *N*-acyl derivative, the major product, on reaction with DCC in such solvents as MeCN, $PhNO_2$, $PrNO_2$, CH_2Cl_2 and Me_2CO.[15] The reaction of ferrocenecarboxylic acid with DCC in THF, initially at RT, but followed by refluxing in dioxane, [the refluxing was reported to bring about conversion of the *O*-acyl derivative to the *N*-acyl one] was reported to provide a little anhydride as well as the major *N*-acyl derivative.[16,17]



Scheme 1 Reactions of carboxylic acids with di-imines: R''-XH = R'-CO_2H, R''-OH, R''-NH_2, *etc.*

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The presence of an acid can inhibit the rearrangement of the *O*-acyl urea to the *N*-acyl urea and making it more available for reactions with added nucleophiles,[18,19] as shown by the formation of esters of naphthalenecarboxylic acids in reactions with alcohols in the presence of DCC and added *p*-toluenesulfonic acid.[18] However, Rauf and Parveen reported quantitative yields of esters from fatty acids and phenylalkanols using DCC at RT in the presence of DMAP.[20]

In our earlier efforts to prepare compounds with promising antituberculosis activities, we attempted the coupling of pyrazinecarboxylic acid with ethyl *L*-serinate using DCC as the coupling agent in the presence of hydroxybenzotriazole (HOBt) in CH_2Cl_2 at room temperature.[21] Rather than the desired ester formation, the major product (ca. 70%) was the *N*-acyl derivative, *N,N′*-dicyclohexyl-*N*-(pyrazinecarbonyl)-urea, that is the *O*-acyl to *N*-acyl rearrangement occurred even in the presence of the amine.

This has led us to further investigate the reactions of benzoic acids and pyridinecarboxylic acids with DCC in CH_2Cl_2 in the presence of HOBt and in the absence of any additional nucleophilic species, see Scheme 2. The reaction of the aliphatic acid, *N*-(benzyloxycarbonyl)-*DL*-pipecolic acid, under the same reaction conditions, Scheme 3, was carried out as a comparison.

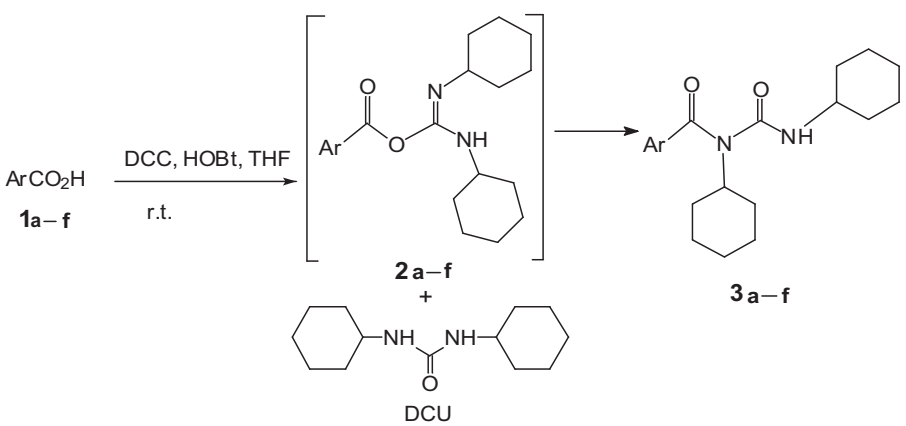
Results and Discussion

All the aromatic and heteroaromatic carboxylic acid reactions with DCC produced *N*-acyl derivatives, **3**, under our conditions in yields, after purification, of 60–70% except in the case of the $PhCO_2H$ reaction. In general, complete removal of the co-product, dicyclohexylurea, DCU, is difficult, but in the case of the $PhCO_2H$ reaction, it was particularly difficult to completely separate DCU from *N*-(benzenecarbonyl)-*N,N′*-dicyclohexylurea **3a**: a pure sample of **3a**, in low quantities, was obtained after successive recrystallisations from ethanol. Sufficiently good crystals however were obtained to confirm them to be **3a** by comparison of the cell parameters with those reported in the literature for the compound.[22] A report by Wei *et al*. had also reported that DCC/$PhCO_2H$ reactions gave "complicated product mixtures".[23]

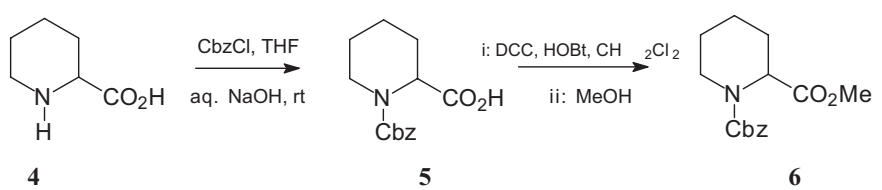
No anhydride product was detected prior to work up in any of the reactions. All the compounds were identified by their spectroscopic data, and in the case of the *p*-nitrobenzoic acid derivative, **3b,** *via* X-ray crystallography (see later). In general, the IR spectra of the *N*-acyl derivatives, **3**, exhibit ν(C=O) in the range 1650–1680 cm^{-1} and ν(N-H) in the range 1695–1710 cm^{-1}. The ^{1}H NMR spectra generally showed aromatic protons at 8.99–7.37 ppm, NH protons as a singlet in the range 6.33–5.94 ppm and cyclohexyl protons as multiplets between 0.8 and 2.0 ppm. The ^{13}C NMR spectra showed the ArCO signals at 166.7–168.6 and NCONH signal at 153.5–154.2 ppm.

In contrast to those of the aromatic acids, the reaction of the aliphatic acid, *N*-(benzyloxycarbonyl)-*DL*-pipecolic acid **5** with DCC, under the same conditions as were used for the arenecarboxylic acids, resulted in the formation of a stable *O*-acyl derivative. *O*-[*N*-(benzyloxycarbonyl)-*DL*-pipecolylcarbonyl-*N,N*-dicyclohexylurea survived two hours in the DCC/acid reaction mixture, before being trapped as the ester, methyl *N*-protected pipecolate, in 70% yield, by the addition of methanol, equation 1. The ^{1}H NMR spectrum of methyl *N*-(benzyloxycarbonyl)-*DL*-pipecolate **6** exhibited the Me signal at 3.73 ppm, while the ester carbonyl signal in the ^{13}C NMR spectrum was at 172.3 ppm. The ^{1}H NMR spectrum of **6** confirmed the presence of conformers, particularly from the two multiplet signals for H_2 [N-C*H*(CO_2Me) at 4.91 and 5.01 ppm:[24] all signals for the other piperidinyl protons are obtained as complex multiplets.

There appears to be a distinct difference between the reactions of aromatic and aliphatic acids under our reaction conditions. This could be linked to the differences in stabilities of arenecarbonyl [$ArCO^+$] and acyl [RCO^+] moieties. The greater stability of an aromatic $ArCO^+$ moiety, compared to that of an aliphatic RCO^+ one, would result in an *O*-acyl to *N*-acyl transformation to proceed more readily for aromatic compounds. In the case of the aliphatic acid, *N*-(benzyloxycarbonyl)-*DL*-pipecolic acid, which has an alpha hydrogen, reaction via a ketene intermediate is possible as suggested by Melman and coworkers.[11]



Scheme 2 Formation of **3**. Ar = (a) Ph; (b) p-$O_2NC_6H_4$; (c) pyridin-2-yl; (d) pyridin-3-yl; (e) pyridin-4-yl; (f) pyrazinyl.



Scheme 3 Formation of **6**.

Interestingly, if unexpected, isolations of *N,N′*-dicyclohexyl-*N*-(pyrazinoyl)urea **3f** [25] and *N,N′*-dicyclohexyl-*N*-nicotinoylurea **3d** [26] have been reported. Compound **3f** was obtained from DCC and pyrazinecarboxylic acid in DMF in the presence of $[H_3Ru_4(PhH)_4OH]Cl_2$.[25] The formation of **3f** was considerably slower in the absence of the ruthenium complex, but the role of the complex was not pursued. Compound **3d** was obtained from a mixture of the acid protected amine acid, *L*-phenylalanine-*L*-leucine ethyl ester, nicotinic acid, DCC and 1-hydroxybenzotriazole in CH_2Cl_2. Clearly here the aim was to prepare the amino acid amide of nicotinic acid, but the *O-N* rearrangement of the *O*-acyl derivative had proceeded to prevent the amide formation.[26]

Crystal structure and supramolecular arrangements in N,N′-dicyclohexyl-N-(4-nitrobenzenecarbonyl)urea (**3b**): The crystals used in the crystallographic determination were grown from ethanol solution. Data were collected at 120 K. The asymmetric unit is comprised of two independent molecules. The numbering scheme and atom arrangements are shown in Fig. 1, while Table 1 lists selected geometric parameters. Weak intramolecular H-bonds are present in both molecules: in molecule 1, there are two C–H---O hydrogen bonds, C8–H8---O3 and C15–H15---O5, while only one [C108–H108---O103] is indicated by PLATON [27] in molecule 2, see Table 1. The cyclohexyl rings adopt chair conformations, with their substituents in equatorial sites. The nitro group is near co-planar to its attached aryl ring with the angle between the best planes being only 1.40 (0.17)°.

Each type of independent molecule is linked into chains [C5] via hydrogen bonds, either N6–H6----O5^{ii} or N106–H106---O105^{i}, see Figure 2 and Table 2. Additionally there is a weak C15–H15---O3^{iii} interaction which links the chains of molecules 1: no equivalent interaction within the chains of molecule 2 was indicated by PLATON;[27] symmetry operations: $i = -1-x, 1/2+y, -1/2-z$; $ii = -x, 1/2+y, -1/2-z$; $iii = -x, 1/2+y, -1/2-z$.

Structure determinations of *N*-benzenecarbonyl-*N,N′*-dicyclohexylurea **3a**, at room temperature[22] and *N,N′*-dicyclohexyl-*N*-(pyrazinecarbonyl)urea **3f**, at 153 K[25] and at room temperature,[22] also indicated chains of molecules created by similar N–H---O hydrogen bonds. However, in each of these cases, only one molecular form was present. A different type of intermolecular interaction was however found for **3d**:[26] in this case, the intermolecular interactions linking each of the two types of independent molecules involved NH---N and C–H---O hydrogen bonds.

Experimental

Melting points were determined on a Buchi apparatus and are uncorrected. IR spectra were recorded on a Thermo Nicolet Nexus 670 spectrometer in potassium bromide pellets and frequencies are expressed in cm^{-1}. High resolution MS were obtained using a Micromass Q.Tof micro, mode: TOF MS ES + . NMR spectra were recorded on a Bruker Avance 500 spectrometer in Me_2SO-d_6 at room temperature. TLC was run on silica gel using ethyl acetate as eluent: products were detected with UV light.

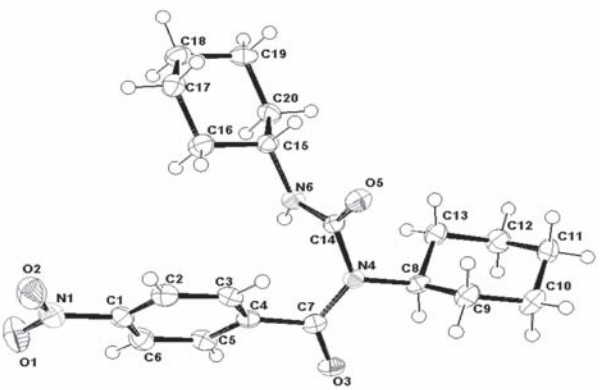


Fig. 1 Atom arrangements and numbering scheme for molecule 1 of **3b**: ellipsoids are drawn at the 50% probability level, hydrogen atoms are drawn as spheres of arbitrary radius. Molecule 2 has a very similar arrangement: changes in the numbering scheme for molecule 2 are atoms X(1–9) and X(10–20) in mole 1 → X(101–109) and X(110–120) in molecule 2, *e.g.,* N6 → N106 and C20 → C120.

Synthesis

General procedure. To a stirred solution of the appropriate carboxylic acid (4.1 mmol) in anhydrous DCM (25 ml) were added DCC (3.15 mmol) and HOBt (catalytic quantity). After 2 hours at room temperature, the precipitate of *1,3*-dicyclohexylurea was removed by filtration, the filtrate was added to a saturated aqueous $NaHCO_3$ (20 ml) and extracted with EtOAc (3 × 20 ml). The combined organic layers were dried over $MgSO_4$ and rotary evaporated. The residue was columned chromatographed on silica gel using a gradient 10 to 50% EtOAc in hexane. The product was recrystallised from EtOH.

1,3-Dicyclohexyl-1-(4-nitrophenylcarbonyl)-urea (**3b**): (73%), m.p. 196–197 °C. lit.[27] 195–196 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.26 (2H, d, J = 8.7, H_2 and H_6), 7.70 (2H, d, J = 8.7, H_3 and H_5), 6.10 (1H, m, J = 5.4, NH), 4.03 (1H, m, NCH), 3.50 (1H, m, NHC<u>H</u>), 2.0–1.1 (20H, m, cyclohexyl) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.8, 153.5, 148.8, 142.7, 127.7, 123.8, 57.6, 49.9, 32.4, 30.8, 26.1, 25.3, 25.2, 24.5 ppm. IR: ν_{max} 1696 (CONH), 1650 (CON) cm^{-1}.

MS: 374 [(M + H)$^+$]. Found: C, 64.5; H, 7.1; N, 11.1. Calc. for $C_{20}H_{27}N_3O_4$: C, 64.3; H, 7.3; N, 11.25%.

1,3-Dicyclohexyl-1-(pyridine-2-carbonyl)-urea (**3c**): (60%), m.p. 142.0 °C. lit.value:[28] 144–145 °C.^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.57 (1H, d, J = 3.6 Hz, H_6), 7.78 (1H, m, H_4), 7.68 (1H, d, J = 7.6 Hz, H_3), 7.37 (1H, m, H_5), 6.09 (1H, s, NH), 4.20 (1H, m, NCH), 3.51 (1H, m, NHC<u>H</u>), 0.8–2.0 (20H, m, cyclohexyl) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.1, 154.0, 153.9, 148.5, 137.0, 125.1, 122.9, 56.4, 49.8, 33.9, 32.4, 30.7, 26.2, 25.6, 25.4, 25.3, 24.9, 24.6 ppm.

Table 1 Selected geometric parameters, (Å, °) for **3b**

(a) Bond lengths				
C(8)–N(4)	1.486(3)	C(108)–N(104)	1.479(3)	
C(7)–N(4)	1.372(3)	C(107)–N(104)	1.372(3)	
C(14)–N(6)	1.321(3)	C(114)–N(106)	1.327(3)	
C(15)–N(6)	1.467(3)	C(115)–N(106)	1.471(3)	
C(14)–N(4)	1.440(3)	C(114)–N(104)	1.447(3)	
(b) Hydrogen bonding parameters)				
D–H---A	D–H	H---A	D---A	D–H---A
N(106)–HN(106)---O(105) [i]	0.86(3)	2.09(3)	2.920(2)	164(2)
N(6)–HN(6)---O(5)[ii]	0.87(3)	1.99(3)	2.854(2)	176(3)
C(15)–H(15)---O(3)[iii]	1.00	2.37	3.322(3)	159
C(8)–H(8)---O(3)	1.00	2.32	2.757(3)	105
C(108)–H(108)---O(103)	1.00	2.37	2.804(3)	105
C(15)–H(15)---O(5)	1.00	2.44	2.833(3)	103

[i] $-1-x, 1/2+y, -1/2-z$; [ii] $= -x, 1/2+y, -1/2-z$; [iii] $= -x, 1/2+y, -1/2-z$

Table 2 Crystal data and structure refinement for **3b**

Empirical formula	$C_{20}H_{27}N_3O_4$
Formula weight	372.94
Temperature, K	120(2)
Wavelength, Å	0.71073
Crystal system, space group	Monoclinic, P21/c
Unit cell dimensions	*a* = 24.9660(8)Å *b* = 9.4872(2) Å, β = 105.6980(10)d° *c* = 16.7156(6) Å
Volume	3811.5(2) Å^3
Z	4
Density (calculated)	1.300 Mg/m^3
Absorption coefficient	0.091 mm^{-1}
F(000)	1596
Crystal size	0.58 × 0.12 × 0.10 mm
Theta range for data collection	3.06 to 27.48 deg.
Index ranges	–32< = *h* < = 21; –12< = *k* < = 12; –21< = *l* < = 21
Reflections collected	39958
Independent reflections	8679 [R(int) = 0.0977]
Reflections observed (>2σ)	4691
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	8679/0/494
Goodness-of-fit on F^2	1.008
Final R indices [*I*>2σ(*I*)]	R_1 = 0.0717 wR_2 = 0.1556
R indices (all data)	R_1 = 0.1477 wR_2 = 0.1899
Largest diff. peak and hole	0.864 and –0.628 e. Å^{-3}

IR: ν_{max} 1710 (CONH), 1680 (COM) cm^{-1}. Found: C, 69.1; H, 8.1; N, 12.6. Calc. for $C_{19}H_{27}N_3O_2$: C, 69.3; H, 8.3; N, 12.75%.

1,3-Dicyclohexyl-1-(pyridine-3-carbonyl)-urea: (**3d**): (65%), m.p. 171.5 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.81 (1H, s, H_2), 8.69 (d, *J* = 5.0 Hz, 1H, H_6), 7.91 (1H, d, *J* = 8.0 Hz, H_4), 7.37 (1H, dd, *J* = 8.0 Hz and 5.0 Hz, H_5), 6.33 (1H, s, NH), 4.14 (1H, m, NCH), 3.48 (1H, m, NHC<u>H</u>), 0.8–2 (20H, m, cyclohexyl) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.9, 153.6, 150.8, 147.5, 134.8, 133.1, 123.3, 56.9, 49.9, 33.9, 32.3, 30.8, 26.1, 25.6, 25.2, 25.1, 24.9, 24.6 ppm.

IR: ν_{max} 1695 (CONH), 1655 (CON) cm^{-1}. Found: C, 69.1; H, 8.3; N, 12.6 $C_{19}H_{27}N_3O_2$ requires C, 69.3; H, 8.3; N, 12.75%.

1,3-Dicyclohexyl-1-(pyridine-4-carbonyl)-urea (**3e**): (70%), m.p.161.5 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.68 (2H, d, *J* = 6.0, H_5 and H_6), 7.40 (2H, d, *J* = 6.0, H_2 and H_3), 6.33 (1H, s, NH), 4.02 (1H, m, NCH), 3.48 (1H, m, 1NHC<u>H</u>), 0.8–2.0 (20H, m, cyclohexyl) ppm. ^{13} C NMR (100 MHz, $CDCl_3$) δ: 168.6, 153.5, 150.1, 144.7, 120.9, 57.4, 50.0, 34.1, 32.3, 30.8, 26.3, 25.8, 25.4, 25.3, 25.1, 24.7 ppm. IR: ν_{max} 1698 (CONH) and 1677 (CON) cm^{-1}. Found: C, 69.2; H, 8.1; N, 12.7 $C_{19}H_{27}N_3O_2$ requires C, 69.3; H, 8.3; N, 12.75%.

1,3-Dicyclohexyl-1-(pyrazinecarbonyl)-urea (**3f**): (68%), m.p.164.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.99 (1H, d, *J* = 1.6 Hz, H_3), 8.65 (1H, d, *J* = 2.4 Hz, H_6), 8.51 (1H, dd, *J* = 2.4 Hz and 1.6 Hz, H_5), 5.94 (1H, s, NH), 4.22 (1H, m, NCH), 3.56 (1H, m, NHC<u>H</u>),1.0–2.0 (20H, m, cyclohexyl) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.7, 154.2, 149.6, 146.6, 145.4, 143.2, 57.2, 50.6, 33.1, 31.4, 26.8, 26.0, 25.9, 25.3 ppm. IR: ν_{max} 1702 (CONH), 1650 (CON) cm^{-1}. Found: C, 65.3; H, 8.0; N, 16.8. $C_{18}H_{26}N_4O_2$ requires C, 65.4; H, 7.9; N, 16.9%.

N-(Benzyloxycarbonyl)-DL-pipecolic acid (**5**): A solution of benzyl chloroformate (0.84 ml, 6 mmol) in THF (20 ml) was slowly added to a solution of *DL*-pipecolic acid **4** (516 mg, 4 mmol) in 10% NaOH (20 ml) at 0 °C. After the addition of the reagent was complete, the mixture was allowed to warm to room temperature, and kept for 2 hours. The reaction mixture was washed with Et_2O (20 ml), and the aqueous layer was acidified with 2.5N HCl until pH 2 and then extracted with EtOAc (3 × 50 ml). The combined organic extracts were washed with water, and dried over $MgSO_4$. The solvent was removed using a rotary evaporator to give the desired product as a colourless solid (84%), m.p. 110 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.13 (1H, s, OH), 7.36–7.26 (5H, m, Ph), 5.16 (2H, s, CH_2Ph), 5.00(br) + 4.91(br) [1H, H_2], 4.09 (1H, m, H_{6eq}), 3.03 (1H, m, H_{6ax}), 2.30–1.25 (6H, m, H_{3ax}, H_{3eq}, H_{4ax}, H_{4eq}, H_{5ax}, H_{5eq}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 177.4, 156.9, 136.7, 128.7, 128.2, 128.0, 67.7, 54.6, 42.1, 26.9, 24.8, 20.8 ppm. Found: C, 64.0; H, 6.5; N, 5.5. $C_{14}H_{17}NO_4$ requires C, 63.9; H, 6.5; N, 5.3%.

Methyl N-(benzyloxycarbonyl)-DL-pipecolate (**6**): DCC (177 mg, 0.86 mmol) and HOBt (catalytic amount) were added to a stirred solution of **5** (205 mg, 0.78 mmol) in dry CH_2Cl_2 (20 ml). After 2 hours, anhydrous methanol (2 ml) was added and after 24 hours at room temperature the reaction mixture was extracted with EtOAc (3 × 20 ml). The combined organic extracts were washed with water and dried over $MgSO_4$, The solvent was removed using a rotary evaporator. The residue was purified by chromatography, providing the compound **6**, as an oil Yield: 70%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.36–7.26 (5H, m, Ph), 5.12 (2H, s, CH_2Ph), 4.91(br) + 5.00(br) [1H, H_2], 4.08 (1H, m, H_{6eq}), 3.73 (3H, s, CH_3), 3.01 (1H, m, H_{6ax}), 2.26–1.20 (6H, m, H_{3ax}, H_{3eq}, H_{4ax}, H_{4eq}, H_{5ax}, H_{5eq}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.3, 156.7, 136.8, 128.7, 128.2, 128.0, 67.5, 54.6, 52.4, 42.1, 26.9, 24.9, 20.9 ppm. Found: C, 64.8; H, 7.1; N, 4.9. $C_{15}H_{19}NO_4$ requires C, 65.0; H, 6.9; N, 5.05%.

Crystallography

The sample was recrystallised from EtOH. Data were obtained at 120 K with Mo-Kα radiation by means of the Enraf Nonius KappaCCD area detector diffractometer of the EPSRC crystallographic service, based at the University of Southampton. Data collection was carried out under the control of the program COLLECT[30] and data reduction and unit cell refinement were achieved with the COLLECT[30] and DENZO programs.[31] Correction for absorption, by comparison of the intensities of equivalent reflections, was applied using the program SADABS.[32] The progam ORTEP-3 for Windows[33] was used in the preparation of the Figure and SHELXL-97[34] and PLATON[27] in the calculation of molecular geometry. The structure was solved by direct methods using SHELXS-97[35] and fully refined by means of the program SHELXL-97.[32] In the final stages of refinement hydrogen atoms were introduced in calculated positions and refined with a riding model. Crystal data and structure

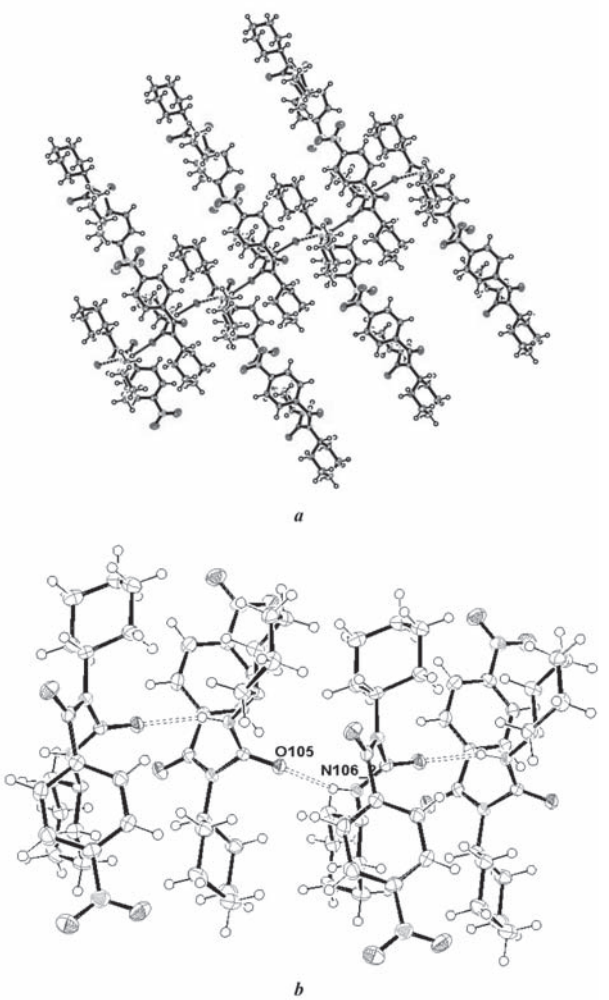


Fig. 2 Chains of molecules of **3b**. (a) molecule 1, generated by N6–H6---O5^{ii} (b) molecule 2, generated by N106–H106---O105^{i}: symmetry operations: *i* = –1 – *x*, 1/2 + *y*, –1/2 – *z*; *ii* = –*x*, 1/2 + *y*, –1/2 – *z*.

refinement details are listed in Table 1. "CCDC 676180 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif".

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