The *N*-carbamoyl squaramide dimer: a compact, strongly associated H-bonding motif

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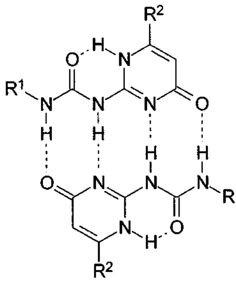
***N*-Carbamoyl squaramides 3, readily available from dialkyl squarate 5, form hydrogen-bonded dimers in solution and in non-polar organic solvents; in $CDCl_3$ they show no significant dissociation down to concentrations of ~ 0.5 mM.**

The continuing development of supramolecular self-assembly requires accessible subunits which can be relied upon to associate strongly and predictably through non-covalent interactions. Particular attention has recently been paid to systems capable of forming four intermolecular hydrogen bonds,[1–4] such as the self-complementary 'DDAA' units **1** and **2** studied by the groups of Meijer[1] and Zimmerman,[2] respectively. These units self-associate essentially completely in solvents such as $CDCl_3$, and are only disrupted by significant quantities of polar solvents such as DMSO.



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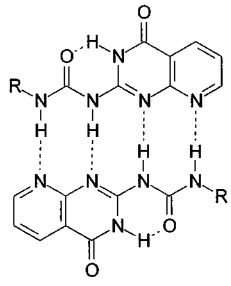

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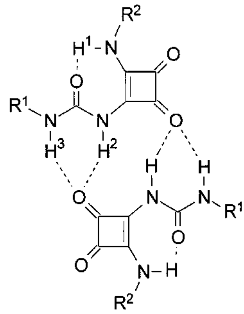
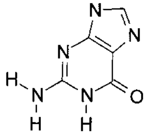
Herein we report a new homodimer which is related to **1** and **2** but with significant geometric differences. It is nearly as strongly bound, while being exceptionally compact and easy to construct. The new system **3·3** is based on the squaramide unit, previously shown by Ballester, Costa and co-workers to provide a distinctive array of H-bonding sites for molecular recognition.[5,6] Unlike the earlier squaramides, monomer **3** possesses a ureidyl substituent capable in principle of intramolecular hydrogen bonding to the neighbouring NH. The result should be a well-defined, roughly planar structure with an intriguing resemblance to guanine derivatives **4**.



3·3



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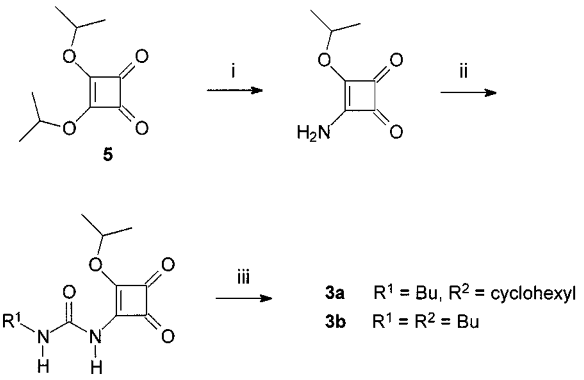
Planning to investigate the interaction of **3** with nucleobases, we synthesized examples **3a** and **3b** from diisopropyl squarate **5** as shown in Scheme 1. Preliminary ^1H NMR binding experiments in $CDCl_3$ gave unexpected results, leading us to suspect that the squaramides self-associated to some degree. However, dilution studies in this solvent showed no substantial changes in the spectra of **3a** or **3b** ($\Delta\delta < 0.1$ ppm) over a wide range of concentrations (~25–0.5 mM), suggesting either that association was not taking place or that it was very strong indeed.



Scheme 1 *Reagents and conditions*: i, NH_3, MeOH–CH_2Cl_2, room temp.; ii, R^1NCO, Et_3N, MeCN, room temp.; iii, R^2NH_2, CH_2Cl_2, room temp.

Suspecting the latter, we obtained crystals of **3a** from CH_2Cl_2–light petroleum and subjected them to X-ray crystallography.† As shown in Fig. 1, **3a** exists as a centrosymmetric dimer in the crystal, apparently maintained by four NH···O=C hydrogen bonds. The carbamoylsquaramide units are essentially planar, and exhibit the expected intramolecular hydrogen bond.

The hypothesis that **3** dimerises strongly in $CDCl_3$ was tested by NMR studies in the presence of 'competitive' co-solvents. Addition of CD_3CN (up to 40% v/v) to $CDCl_3$ solutions of **3a** resulted in *upfield* movements of all three N*H* signals. For H(1) and H(3) the motions were moderate ($\Delta\delta \sim -0.7$ ppm), while

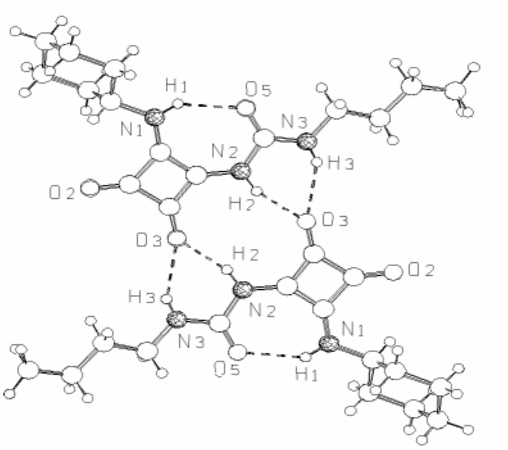


Fig. 1 Crystal structure of **3a** showing the relationship between adjacent H-bonded molecules. Selected distances (Å) and angles (°) are H(1)···O(5) 2.120(2), H(2)···O(3) 1.936(1), H(3)···O(3) 2.204(6), H(1)–N(1) 0.869(6), H(2)–N(2) 0.900(3), H(3)–N(3) 0.832(2); N(1)–H(1)···O(5) 136.65(6), N(2)–H(2)···O(3) 160.96(8), N(3)–H(3)···O(3) 149.03(9), H(2)···O(3)···H(3) 60.81(9).

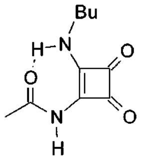
Table 1 ^{1}H NMR dilution studies for compounds **3** in $CDCl_3$–CD_3CN (95 : 5)[a]

			$\delta_{dimer} - \delta_{monomer}$ (ppm)	
Compound	R^1, R^2	K_d/M^{-1} [b]	H(2)	H(3)
3a	Bu, cyclohexyl	5800 ± 1100	2.32	0.59
3b	Bu, Bu	6100 ± 1300	2.42	[c]
3c	2,6-difluorophenyl, Bu	9800 ± 900	2.99	0.62

[a] Experiments performed at 303 K. Concentrations of **3** were varied between ~25 and ~0.2 mM. [b] Dimerisation constants K_d and error limits (standard deviations) were estimated from the movements of the signal due to H(2) using HOSTEST version 5.0 (ref. 7). [c] Not calculated, due to signal broadening.

for H(2) a substantial $\Delta\delta$ of -2.2 ppm was recorded. In the absence of self-association, downfield motions would have been expected due to the formation of NH···N≡C hydrogen bonds.‡ The observed upfield movements presumably result from the break-up of the aggregate, with the loss or weakening of the stronger NH···O=C hydrogen bonding.

The solvent system $CDCl_3$–CD_3CN (95:5) proved suitable for quantitative ^{1}H NMR dilution studies. Results are summarised in Table 1. In addition to **3a** and **3b**, the difluorophenyl-substituted example **3c** was synthesized (*cf.* Scheme 1) and studied under these conditions.§ In each case the signal due to H(2), which appeared between δ 10.3 and 10.9 at high concentrations, moved upfield upon dilution. The data were consistent with simple 1 : 1 dimerisations, yielding dimerisation constants (K_d) in the range 5×10^3 to 10^4 M^{-1}, and limiting chemical shift differences ($\delta_{dimer} - \delta_{monomer}$) in the range 2.3–3 ppm. The signals due to H(3), starting at δ ~6.5 for **3a**/**b** and δ ~8.1 for **3c**, also moved upfield during the experiments. Their motions were smaller and difficult to follow accurately due to broadening, but generally supported the analyses of H(2). A study of **3a** in $CDCl_3$–$(CD_3)_2SO$ (99 : 1) also suggested dimerisation, but with the lower K_d of ~180 M^{-1}. A re-examination of **3a** in $CDCl_3$ gave data consistent with K_d ~10^6 M^{-1}, on the assumption that (δ_{dimer}–$\delta_{monomer}$) is likely to be between 3 and 4 ppm in this solvent. The rôle of H(3) in maintaining the dimer was confirmed by a study of *N*-acetylsquaramide **6**, for which a K_d of just 120 M^{-1} was measured in $CDCl_3$–CD_3CN (95 : 5).



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The tendency of **3** to dimerise was also revealed in the FAB$^+$ mass spectrum of **3b**. In addition to the monomer at *m/z* 268 (MH^+), there was a significant (~30%) signal for the dimer at *m/z* 535 (M_2H^+). Signals for higher aggregates M_nH^+ (n = 3-5) appeared at <1.5%. Interestingly the addition of AcONa promoted not only the M_nNa^+ signals as expected, but also a series of general formula $[M_n - mH + (m + 1)Na]^+$ ($1 < m < n$). These ions presumably arise from substitution of the relatively acidic H(2) by Na, followed by clustering in various combinations with **3b** itself.

When compared with **1** and **2**, the present system **3·3** would seem to be somewhat less strongly associated. For example, K_d values of *ca.* 10^3 M^{-1} are reported for both **1** and **2** in $CDCl_3$–$(CD_3)_2SO$ (95 : 5).[1,2] However, **3·3** is more tightly bound than other systems joined by four hydrogen bonds,[3,4] being maintained down to very low concentrations in $CDCl_3$. Given the accessibility, variability and compact size of **3**, this moiety should be capable of playing a distinctive rôle in the design of self-assembling systems.

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Notes and references

† *Crystal data* for **3a**: $C_{15}H_{23}N_3O$, M = 293.36, triclinic, space group $P\bar{1}$, a = 5.9800(4), b = 9.5090(5), c = 14.1543(8) Å, α = 89.694(6), β = 81.471(5), γ = 87.322(5)°, U = 795.10(8) Å^3, Z = 2, D_c = 1.225 g cm^{-3}, T = 293(2) K, μ(Mo-Kα) = 0.086 mm^{-1}, wR_2 = 0.1250 (3009 reflections collected, 2726 unique), R = 0.0510 [$I > 2\sigma(I)$], ENRAF NONIUS CAD4 diffractometer with graphite monochromator, ω-scans, structure solved by automatic direct methods using SHELXS-86 and refined using full-matrix least-squares on F^2 using SHELXL-93 (ref. 8). All the non-hydrogen atoms were refined anisotropically and the hydrogen atoms were located from subsequent difference Fourier maps. CCDC 182/1435. See http://www.rsc.org/suppdata/cc/1999/2265/ for crystallographic data in .cif format.

‡ The N*H* signal for *N,N'*-dibutylurea in $CDCl_3$ moves downfield by ~0.13 ppm on addition of 5% CD_3CN.

§ A number of other aryl-substituted *N*-carbamoylsquaramides were prepared but found unsuitable for study, mainly due to solubility problems.

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