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

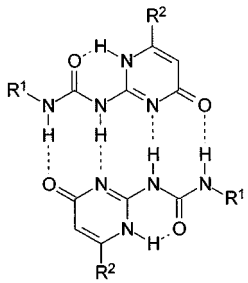
**Anthony P. Davis,*[a] Sylvia M. Draper,[a] Gavin Dunne[a] and Peter Ashton[b]**

[a] *Department of Chemistry, Trinity College, Dublin 2, Ireland. E-mail: adavis@tcd.ie*
[b] *School of Chemistry, University of Birmingham, Edgbaston, Birmingham, UK B15 2TT*

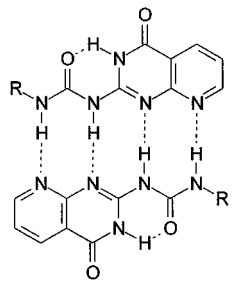
***Received (in Cambridge, UK) 6th September 1999, Accepted 1st October 1999***

**_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



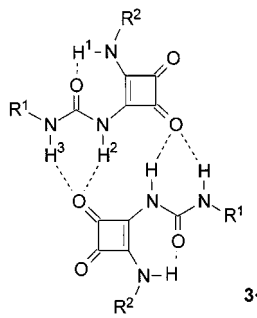
**1**



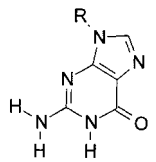
**2**

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.

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,



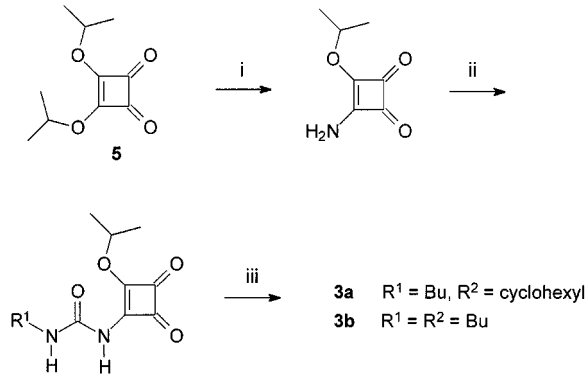
**3·3**



**4**

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**.

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.




**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.

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.

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

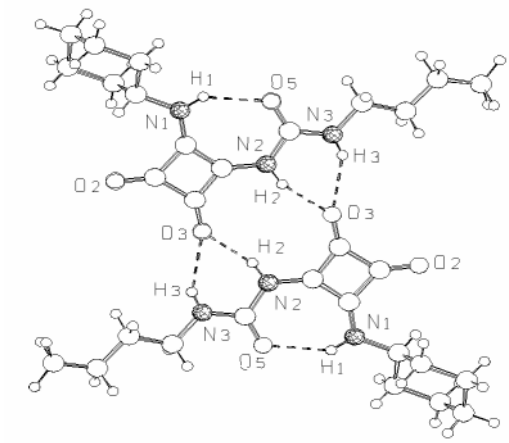



**Fig. 1** Crystal structure of **3a** showing the relationship between adjacent H-bonded molecules. Selected distances (Å) and angles (°) are H(1)···O(5) 2.120(2), H(2)···O(3) 1.936(1), H(3)···O(3) 2.204(6), H(1)–N(1) 0.869(6), H(2)–N(2) 0.900(3), H(3)–N(3) 0.832(2); N(1)–H(1)···O(5) 136.65(6), N(2)–H(2)···O(3)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

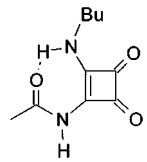
**Table 1** $^1$H NMR dilution studies for compounds **3** in $CDCl_3$–$CD_3CN$ (95 : 5)[a]

| Compound | $R^1$, $R^2$ | $K_d/M^{-1}$[b] | $\delta_{dimer} - \delta_{monomer}$ (ppm) 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 $\delta$ 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 $5 \times 10^3$ 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 $\delta$ ~6.5 for **3a**/**b** and $\delta$ ~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 ($\delta_{dimer}$–$\delta_{monomer}$) 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).




**6**

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.

Financial support for this work was provided by Enterprise Ireland, the Irish Health Research Board and the Wellcome Trust. We are grateful to Professor C. S. Wilcox for access to the HOSTEST binding analysis programme.

## 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, $\alpha$ = 89.694(6), $\beta$ = 81.471(5), $\gamma$ = 87.322(5)°, $U$ = 795.10(8) Å$^3$, $Z$ = 2, $D_c$ = 1.225 g cm$^{-3}$, $T$ = 293(2) K, $\mu$(Mo-K$\alpha$) = 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, $\omega$-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.

1 R. P. Sijbesma, F. H. Beijer, L. Brunsveld, B. J. B. Folmer, J. H. K. K. Hirschberg, R. F. M. Lange, J. K. L. Lowe and E. W. Meijer, *Science*, 1997, **278**, 1601; F. H. Beijer, R. P. Sijbesma, H. Kooijman, A. L. Spek and E. W. Meijer, *J. Am. Chem. Soc.*, 1998, **120**, 6761.
2 P. S. Corbin and S. C. Zimmerman, *J. Am. Chem. Soc.*, 1998, **120**, 9710.
3 U. Lüning and C. Kühl, *Tetrahedron Lett.*, 1998, **39**, 5735.
4 B. Gong, Y. F. Yan, H. Q. Zeng, E. Skrzypczak-Jankunn, Y. W. Kim, J. Zhu and H. Ickes, *J. Am. Chem. Soc.*, 1999, **121**, 5607.
5 R. Prohens, S. Tomàs, J. Morey, P. M. Deyà, P. Ballester and A. Costa, *Tetrahedron Lett.*, 1998, **39**, 1063.
6 S. Tomàs, R. Prohens, M. Vega, M. C. Rotger, P. M. Deyà, P. Ballester and A. Costa, *J. Org. Chem.*, 1996, **61**, 9394.
7 C. S. Wilcox, in *Frontiers in Supramolecular Chemistry and Photochemistry*, ed. H.-J. Schneider and H. Durr, VCH, Weinheim, 1990, p. 123.
8 G. M. Sheldrick, *Acta Crystallogr., Sect. A*, 1990, **46**, 467; SHELXL-93, University of Gottingen, Germany.

*Communication 9/07179B*