Crystal Engineering of Primary Cubanecarboxamides. Repetitive Formation of an Unexpected N−H···O Hydrogen-Bonded Network

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The unusual N−H···O hydrogen bond pattern in a family of primary cubanecarboxamides is described. 4-Chloro-1-cubanecarboxamide, **1**, and the corresponding bromo and iodo derivatives, **2** and **3**, form the "shallow-glide" hydrogen-bonded motif instead of the usual 5.1 Å translated ribbon pattern, more characteristic of primary amides. This behavior is also seen, somewhat unexpectedly, for cubanecarboxamide, **4**, but more or less unsurprisingly for 1,4-cubanedicarboxamide, **5**. This repetitive occurrence of the same hydrogen bond pattern is of significance in crystal engineering wherein synthon robustness is measured in terms of such repetitivity. The cubyl group is directly responsible for the appearance of the shallow-glide motif in this family in preference to the 5.1 Å translation pattern for two reasons: (1) steric—it is too large to fit in a 5.1 Å translated structure and (2) electronic—its carbon acidity is sufficient to result in the appearance of C−H···O hydrogen bonds to the C═O group, disrupting any putative 5.1 Å translated structure. Such a molecule → supermolecule relationship is of value in crystal engineering strategies.

Introduction

An understanding of the relationship between molecular structure and crystal structure[1] is the cornerstone of the subject of crystal engineering.[2,3] Despite the difficulties in obtaining such understanding in a complete way, a strategy that has often proved successful is to consider smaller elements of the supramolecular structure and to identify combinations of molecular functionality that yield these structural elements regularly and consistently. These smaller units are the supramolecular synthons, and in many ways, they represent the key structural features of the crystal that need to be built up from molecular precursors. Simply put, they are the supramolecular synthetic targets.[4]

Hydrogen bonding is the most reliable design element in the noncovalent assembly of neutral molecules with donor and acceptor functionalities, and as such it is the most important interaction in crystal engineering.[5] Hydrogen bonds are primarily electrostatic and are formed with both strong and weak donors and acceptors.[6] It is in order to comment here about weak donors and acceptors. With the increasing number of crystal structures that are being analyzed, there is a growing awareness that the distinctions between strong (O−H···O, O−H···N, N−H···O) and weak (C−H···O, O−H···π, C−H···π) hydrogen bonds are more a matter of degree rather than arising from any fundamental differences in interaction type.[6,7]

N−H···O hydrogen bonds in amides have featured prominently in the design of a number of supramolecular nanoscale architectures, described variously as capsules, channels, helices, layers, ribbons, rosettes, rods, tapes, tubes, sheets, and spheres. The hydrogen bond formed by amide N−H donors and C═O acceptors is particularly strong and directional. Therefore, amides assemble predictably into large and complex structures.[8,9] A seminal article by Leiserowitz and Hagler provides a detailed classification of crystal structures of primary amides.[10] The most common pattern is the centrosymmetric dimer

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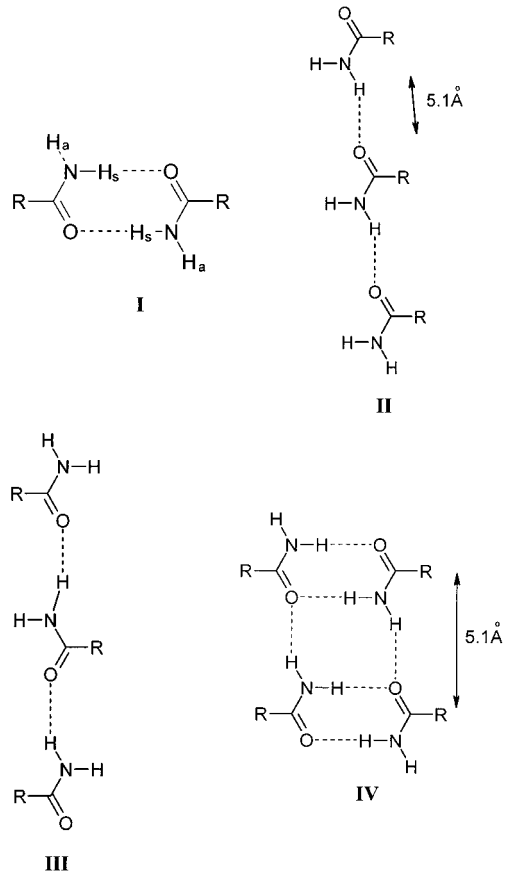
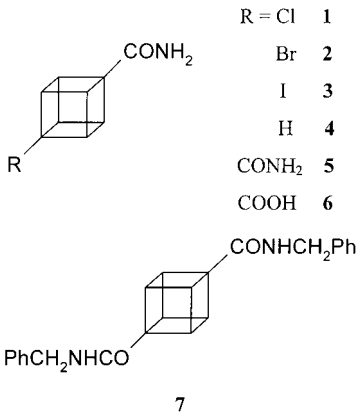
synthon **I** formed with the *syn*-oriented $N-H_s$ group of the amide group. This is analogous to the carboxylic acid dimer. The *anti*-oriented $N-H_a$ group forms hydrogen bonds according to one of two motifs: (a) a linear pattern **II** in which succeeding molecules are related by a ~5.1 Å translation, or (b) a linear pattern **III** where adjacent molecules are related by a glide plane or a 2_1 axis. The 5.1 Å translation is generally preferred over the glide/screw motif and, in combination with synthon **I**, leads to the commonly found translation ribbon synthon **IV**.



In this paper, we have explored the crystal chemistry of a family of primary cubanecarboxamides. This follows an earlier study of cubanecarboxylic acids where it was noted that an uncommon molecular structural element (cubyl group) led repeatedly to an uncommon supramolecular structural element (*syn-anti* catemer).[11] Specifically, the formation of the rare catemer could be attributed to the acidic nature of the cubyl C−H group. Structural repetitivity is a valuable attribute in crystal engineering, and so the most important reason for undertaking the present study was the following: Given the presence of the cubyl group, would the crystal structures of the primary cubanecarboxamides similarly follow an unexpected pattern, *and repetitively*? We report here the crystal structures of amides **1**−**5**. In these molecules, a controlled set of substitutional changes have been made in the 4-position. The aim of the study is to try to rationalize the observed crystal structures in terms of the molecular structural elements.



Results

Amides **1**−**5** were obtained from the corresponding carboxylic acids or esters prepared as described previously.[11] A variety of solvents (DMF, ethyl acetate, methanol, dichloromethane, formic acid, 1,4-dioxane, THF, and mixtures of these solvents) were used for crystallization, and X-ray quality crystals were obtained from the solvents listed in Table 1. The crystal structures of carboxamides **1**−**5** were then analyzed.

4-Halogenated Amides 1−3. Chloro amide **1**, bromo amide **2**, and iodo amide **3** are isostructural and crystallize in the monoclinic space group $P2_1/c$ with one molecule in the asymmetric unit (Table 1). In all of these structures, the dimer $N-H_s\cdots O$ synthon **I** is observed. Dimers are extended along [010] via C−H···O and C−H···X hydrogen bonds formed by the acidic ($pK_a \approx 38$) cubyl C−H groups (Figure 1a). Table 2 shows that these "weak" hydrogen bonds have metrics within the accepted ranges for these interactions.[6] As for the *anti* N−H groups, they

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Table 1. Table of Crystallographic Parameters for the Compounds in This Study

	1	2	3	4	5
empirical formula	C_9H_8NOCl	C_9H_8NOBr	C_9H_8NOI	C_9H_9NO	$C_{10}H_{10}N_2O_2$
crystallized from	EtOAc	EtOAc	DMF	CH_2Cl_2	HCOOH
space group	$P2_1/c$	$P2_1/c$	$P2_1/c$	$C2/c$	$P2_1/c$
a [Å]	12.862(3)	13.152(11)	13.788(5)	23.200(4)	7.0382(11)
b [Å]	6.670(2)	6.792(4)	7.115(3)	6.5702(10)	6.7624(4)
c [Å]	9.5304 (3)	9.551(6)	9.648(4)	9.6280(15)	9.4848(13)
β [deg]	101.69(1)	101.25(3)	101.364(7)	98.805(3)	101.537(6)
volume [Å^3]	800.6(3)	836.8(10)	927.9(6)	1450.3 (4)	442.31(9)
λ [Å]	0.71073	0.71073	0.71073	0.71073	1.5418
D_{calc} [g/cm^3]	1.507	1.795	1.955	1.348	1.43
$2\theta_{max.}$	55.0	60.0	57.16	56.64	70
range h	−16 to 17	−9 to 18	−15 to 17	−30 to 25	−8 to 8
range k	−7 to 8	−7 to 9	−8 to 8	−8 to 2	−8 to 0
range l	−12 to 12	−13 to 4	−12 to 2	−11 to 12	−11 to 0
reflns collected	12441	7892	5696	4929	890
unique reflns	1832	2114	1840	1564	835
R_1 [$I > 2\sigma(I)$][a]	0.042	0.038	0.055	0.078	0.042
T [K]	120(2)	123(2)	183(2)	123(2)	294(2)
diffractometer	Nonius CCD	Smart CCD	Smart CCD	Smart CCD	Enraf-Nonius CAD4
C_k * [%][b]	70.5	70.0	66.8	69.2	69.6

[a] R_1, crystallographic reliability index. [b] C_k^*, packing fraction (calculated with the program PLATON).[16]

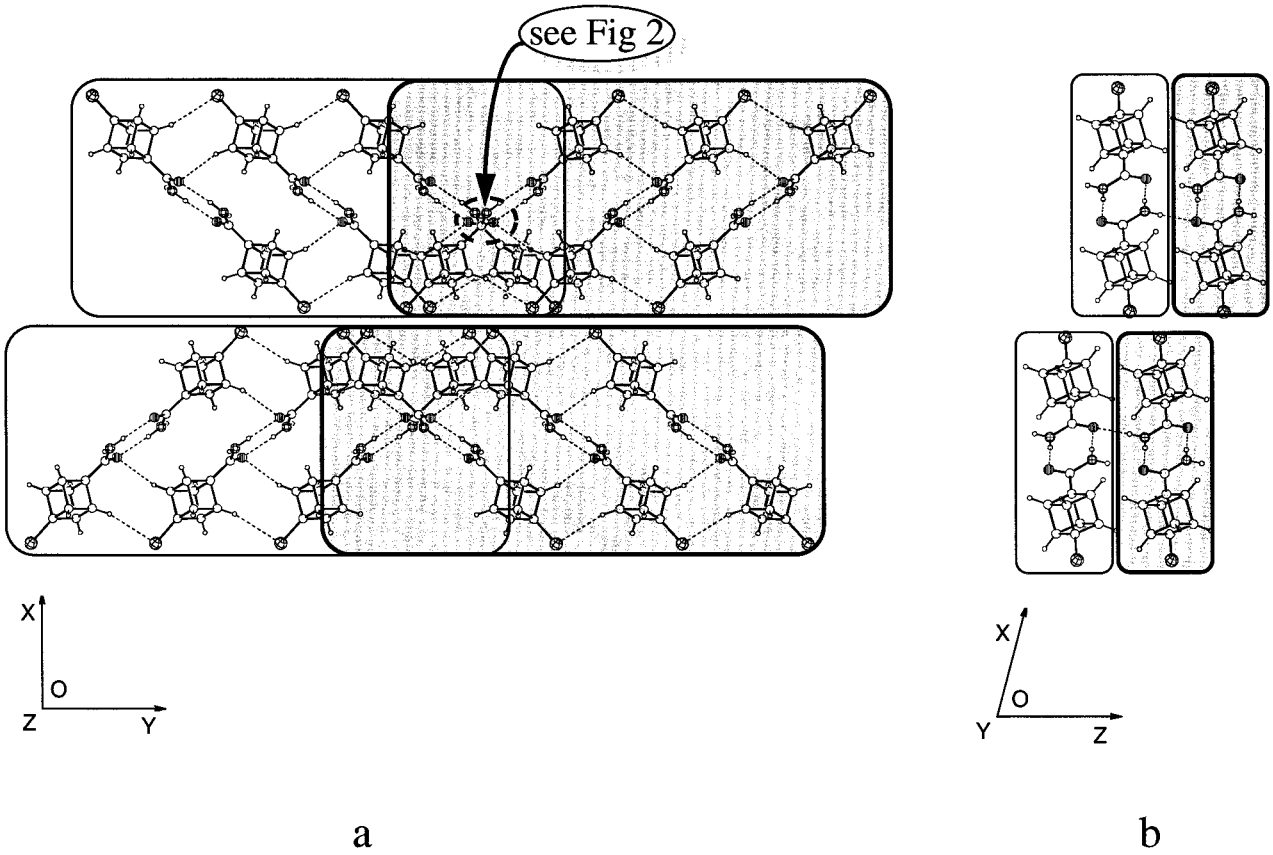


Figure 1. Crystal structure of 4-chloro-1-cubanecarboxamide (**1**). (a) View down [001] to show two (shaded differently) antiparallel layers. Notice the N−H_s···O hydrogen bonded dimer **I**, and the C−H···O and C−H···Cl interactions along [010]. (b) View down [010] to show the N−H_a···O hydrogen bond responsible for the shallow glide motif.

too act as donors in N−H_a···O hydrogen bonds, but rather than form the 5.1 Å translated pattern **II**, they are hydrogen-bonded to glide-related molecules as shown in Figures 1b and 2. This pattern has been termed the "shallow glide motif" by Leiserowitz and Hagler and is not as common as the 5.1 Å translation motif.[10] The term "shallow" is justified in the present cases because the amide group is inclined at angles of, respectively, 55.6°, 59.9°, and 53.8° to the glide plane in amides **1**, **2**, and **3**. Halogen atoms seem to fulfill a space-filling role, though their geometry may nominally be described as type II.[12] Relevant intermolecular interactions are given in Table 2.

Cubanecarboxamide, 4. In the cubanecarboxylic acid family, the unsubstituted acid forms a dimer, in contrast to the 4-halogeno derivatives, which form *syn-anti* catemers.[10] In contrast, cubanecarboxamide, **4**, crystallizes just like the 4-halogenated amides **1**−**3**. Figure 3a shows the amide dimers, **I**, with the C−H···O and C−H···X

(12) The type-I and type-II nomenclature is based on the angles θ_1 and θ_2 in the C−X···X−C contact. When $\theta_1 \cong \theta_2$ the contact is denoted as type I and when $\theta_1 \cong 90°$ and $\theta_2 \cong 180°$, it is denoted as type II. See the following: (a) Desiraju, G. R.; Parthasarathy, R. *J. Am. Chem. Soc.* **1989**, *111*, 8725. (b) Pedireddi, V. R.; Reddy, D. S.; Goud, B. G.; Craig, D. C.; Rae, A. D.; Desiraju, G. R. *J. Chem. Soc., Perkin Trans. 2* **1994**, 2353. (c) Navon, O.; Bernstein, J.; Khodorkovsky, V. *Angew. Chem., Int. Ed. Eng.* **1997**, *36*, 601.

Table 2. Geometrical Parameters of Intermolecular Interactions

amide	interaction[a]	*d* (Å)	*D* (Å)	*θ* (deg)
1	N−H_s···O	1.881	2.888	174.9
	N−H_a···O	1.806	2.815	177.9
	C−H···O	2.446	3.501	164.1
	C−H···Cl	2.867	3.866	153.7
2	N−H_s···O	1.910	2.906	168.5
	N−H_a···O	1.854	2.834	162.8
	C−H···O	2.522	3.574	163.6
	C−H···Br	2.933	3.929	153.0
3	N−H_s···O	1.967	2.967	170.6
	N−H_a···O	1.911	2.893	163.6
	C−H···O	2.724	3.783	165.9
	C−H···I	3.136	4.124	152.0
4	N−H_s···O	1.881	2.881	170.8
	N−H_a···O	1.857	2.841	164.2
	C−H···O	2.490	3.538	162.4
5	N−H_s···O	1.913	2.896	164.2
	N−H_a···O	1.939	2.885	154.9
	C−H···O	2.617	3.625	154.5
	C−H···O	2.658	3.598	144.9

[a] The subscripts *s* and *a* refer to *syn* and *anti* N-H groups.

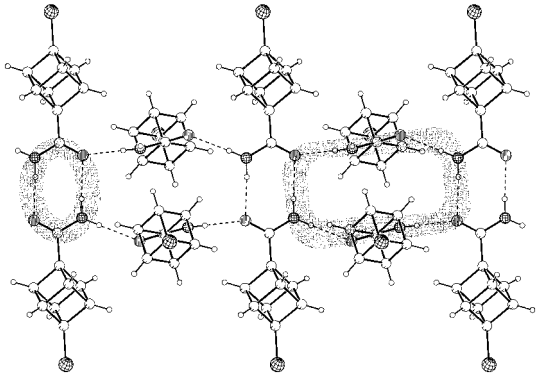


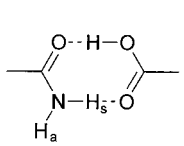
Figure 2. Shallow glide motif in amide **1**. The dimer and glide synthons are highlighted.

connections (compare with Figure 1), while Figures 3b and 4 show the shallow glide motif (compare with Figures 1b and 2). The interaction metrics are given in Table 2. There is a doubling of the *a*-cell edge (space group *C*2/*c*), but the *b* and *c* dimensions are nearly the same as in amides **1**−**3**, reflecting the near identity of the hydrogen-bonded motifs. It may be argued that the structural variety possible in the acids because of the switch of OH group conformation from *anti* to *syn* cannot occur in primary amides because the latter contain both *anti* and *syn* N−H groups.

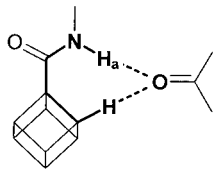
1,4-Cubanedicarboxamide, 5. At this stage, it was not hard to anticipate the crystal structure of 1,4-cubanedicarboxamide, **5**. Indeed, on the basis of the robustness of the amide hydrogen-bonded network in **1**−**4** it was possible to realize an instructed three-dimensionally networked structure by introducing the additional carboxamide group in the 4-position. Compound **5** crystallizes in space group $P2_1/c$ with a half molecule in the asymmetric unit. The one-dimensional ribbon is extended to the second dimension with C−H···O hydrogen bonds as shown in Figure 5a. The two-dimensional sheet is further extended with 2_1-related molecules in the third dimension with N−H_a···O hydrogen bonds formed by the *anti*-N−H groups and additional C−H···O bonds along [010]. This is shown in Figures 5b and 6 and in Table 2.

Discussion

All five primary amides **1**−**5** studied adopt the dimer synthon **I** and the shallow glide motif **III**. In other words, the 5.1 Å translation ribbon, **IV** (which is inclusive of translation synthon **II**), that is common in so many primary amides is absent here. What drives the cubane amides to adopt the shallow glide packing? To rationalize this observation, it was noted that the cubyl group with an average sectional distance of 5.4 Å is too large to fit into the 5.1 Å translation motif **IV**, without making the N−H···O hydrogen bonds unacceptably long. Therefore, one of the reasons why primary cubanecarboxamides are unable to form the 5.1 Å ribbon is a steric one. Indeed it has already been stated that, in a general sense, the shallow glide motif is sterically less demanding than the 5.1 Å translation motif.[8c]



V



VI

There are other precedents in cubane chemistry for the *anti* N−H group to form an N−H_a···O hydrogen bond with a glide-related neighbor rather than with a translation-related one. In 4-(carboxamido)-1-cubanecarboxylic acid, **6**, the *syn* N−H group forms a hetero acid−amide mixed dimer, **V**, but the *anti* N−H group forms a hydrogen bond with a glide-related neighbor via synthon **VI**.[11] In the symmetrical N,N′-dibenzyl-1,4-cubanedicarboxamide, **7**, synthon **VI** is again observed; the single N−H group is *anti* in this case.[13] Synthon **VI** depends for its robustness on C−H donor acidity, which in turn follows from the fact that it is part of a cubyl moiety. Therefore fortification by both types of C−H···O hydrogen bonds in structures **1**−**5**, the [010] translation interaction shown in Figures 1, 3, and 5 and the synthon **VI** forming interaction, is another good reason for the adoption of the shallow glide motif. The observed crystal structures **1**−**5** contain as many N−H···O hydrogen bonds as would be possible if they had adopted the 5.1 Å translation structure, but in addition they also contain C−H···O hydrogen bonds formed by the acidic cubyl C−H groups. An alternative pattern seen in amide crystal structures is the "steep" glide motif. This is observed in formamide and the diamides, succindiamide, acetylenedicarbonamide, and fumaramide. For monoamides $RCONH_2$, R should be no larger than H to form the steep glide motif, and so this is not a viable option here. For diamides, the motif can form if there is a matching of the dimensions of certain molecular and supramolecular synthons. The distance between the two amide functionalities within the same molecule should be the same as the size of the amide dimer supramolecular synthon.[10] The steep glide motif is not possible for diamide **5**, because the intramolecular amide···amide distance (5.4 Å) is a mismatch to the size of the dimer synthon **I** (∼4 Å).

Figure 7 is a schematic drawing of translation-related molecules in the observed crystal structures. The *syn*-dimers **1** are extended by C−H···O hydrogen bonds. Were they to be extended by N−H_a···O hydrogen bonds, the 5.1 Å structure would have resulted. The N−H_a groups

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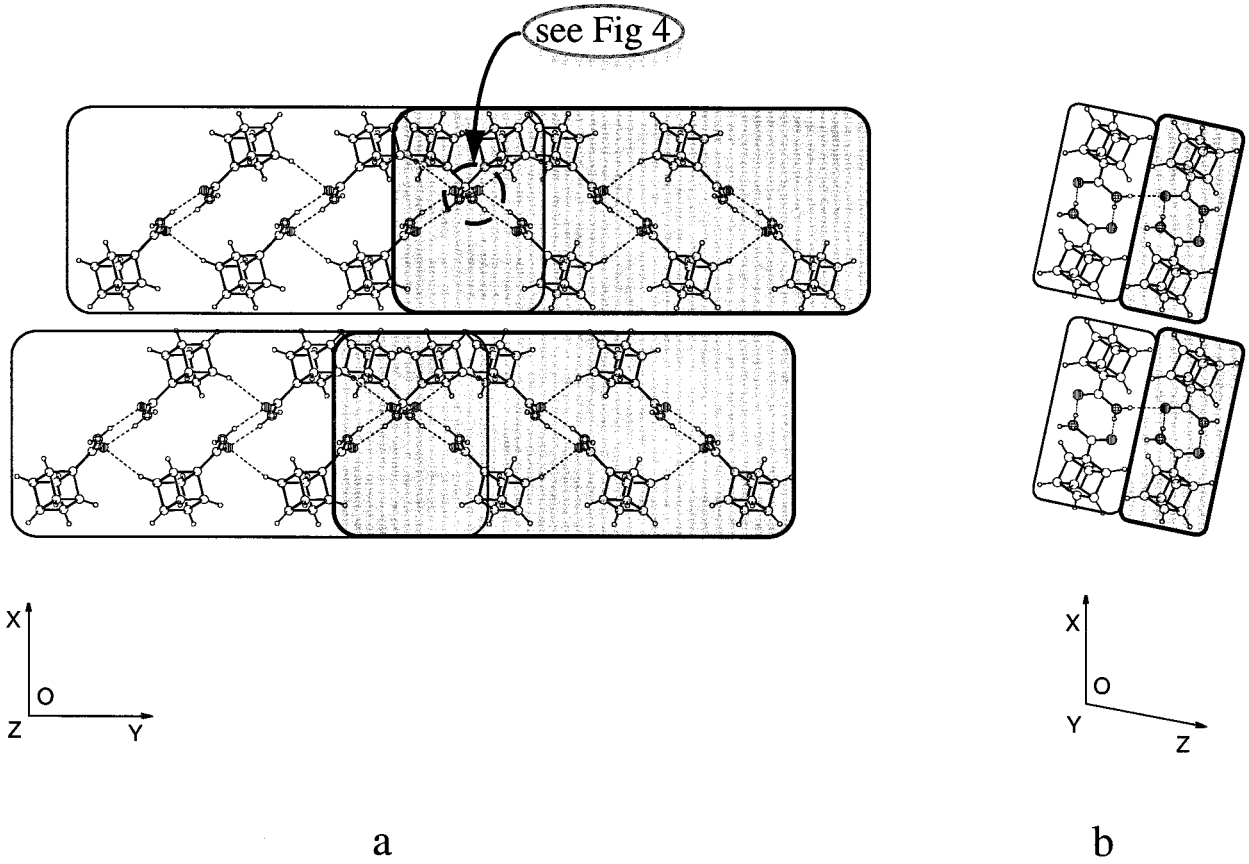

Figure 3. Crystal structure of cubanecarboxamide (**4**). (a) View down [001] to show two (shaded differently) antiparallel layers. Notice the N−H_s···O hydrogen bonded dimer **I**, and the C−H···O interaction along [010]. (b) View down [010] to show the N−H_a···O hydrogen bond responsible for the shallow glide motif. Notice the inclination of the tapes.

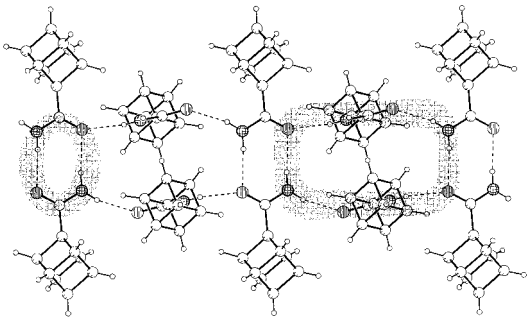

Figure 4. Shallow glide motif in amide **4**. The dimer and glide synthons are highlighted. Compare with Figure 2.

do not donate hydrogen bonds to the C=O groups shown in the sketch. They form N−H···O hydrogen bonds to other C=O groups, according to the so-called shallow glide pattern, after suitable tilting. These latter C=O groups are not shown in the sketch.

Conclusions

In summary, the shallow glide motif is seen repetitively in primary cubanecarboxamides for two reasons: (1) a misfit of size of the cubyl group in the 5.1 Å ribbon structure and (2) fortification of this motif by a C−H···O hydrogen bond from an acidic cubyl C−H group. The main hypothesis underlying this study, namely, that an uncommon molecular structural feature (cubyl group) can repetitively lead to an unexpected supramolecular structural feature (shallow glide motif), stands established for a family of primary 4-substituted carboxamides. The reason for structural repetitivity is largely the same as it is for the corresponding acids, namely, the presence of activated C−H groups in the cubyl moiety. With this study, one may be reasonably sure that the cubyl fragment is supramolecularly active. It is able to perturb, and consistently so, traditional hydrogen bond patterns, the O−H···O dimer in carboxylic acids and the 5.1 Å translation N−H_a···O ribbon in primary carboxamides. This kind of structural interference accompanied by synthon robustness is an especially valuable attribute in crystal design. We conclude then that the cubyl group may be confidently included in the toolkit of the crystal engineer.

Experimental Section

Amides **1**−**5** were prepared from the corresponding carboxylic acids or from the corresponding esters using standard procedures. In all reaction workups, the solvent was first removed completely under vacuum and the mixture was washed well with distilled water. The crude residue was dissolved in the appropriate solvents, filtered, and concentrated in vacuo to yield the final product. ^{1}H NMR spectra were recorded at 200 MHz on a Bruker ACF instrument. IR spectra was recorded on a Jasco 5300 spectrometer. **1**:^{1}H NMR ($CDCl_3$) δ 4.1−4.25 (m, 6H); IR (cm^{-1}) 3301, 3129, 2922, 1716. **2**:^{1}H NMR (DMSO-d_6) δ 4.3 (s, 6H); IR (cm^{-1}) 3293, 3142, 3000, 1668. **3**:^{1}H NMR (DMSO-d_6) δ 4.15−4.45 (s, 6H); IR (cm^{-1}) 3292, 3153, 2995, 1670. **4**: ^{1}H NMR ($CDCl_3$) δ 4.05 (s, 4H), 4.25 (s, 3H); IR (cm^{-1}) 3374, 3202, 2988, 1680. **5**: ^{1}H NMR (DMSO-d_6) δ 4.10 (s, 6H); IR (cm^{-1}) 3322, 3142, 3000, 1667. Single crystals of **1**−**5** were obtained by slow evaporation from various solvents and pertinent X-ray crystallographic details are given in Table 1. The structure solutions and refinements of **1** were performed with the SIR92 and the RAELS pro-

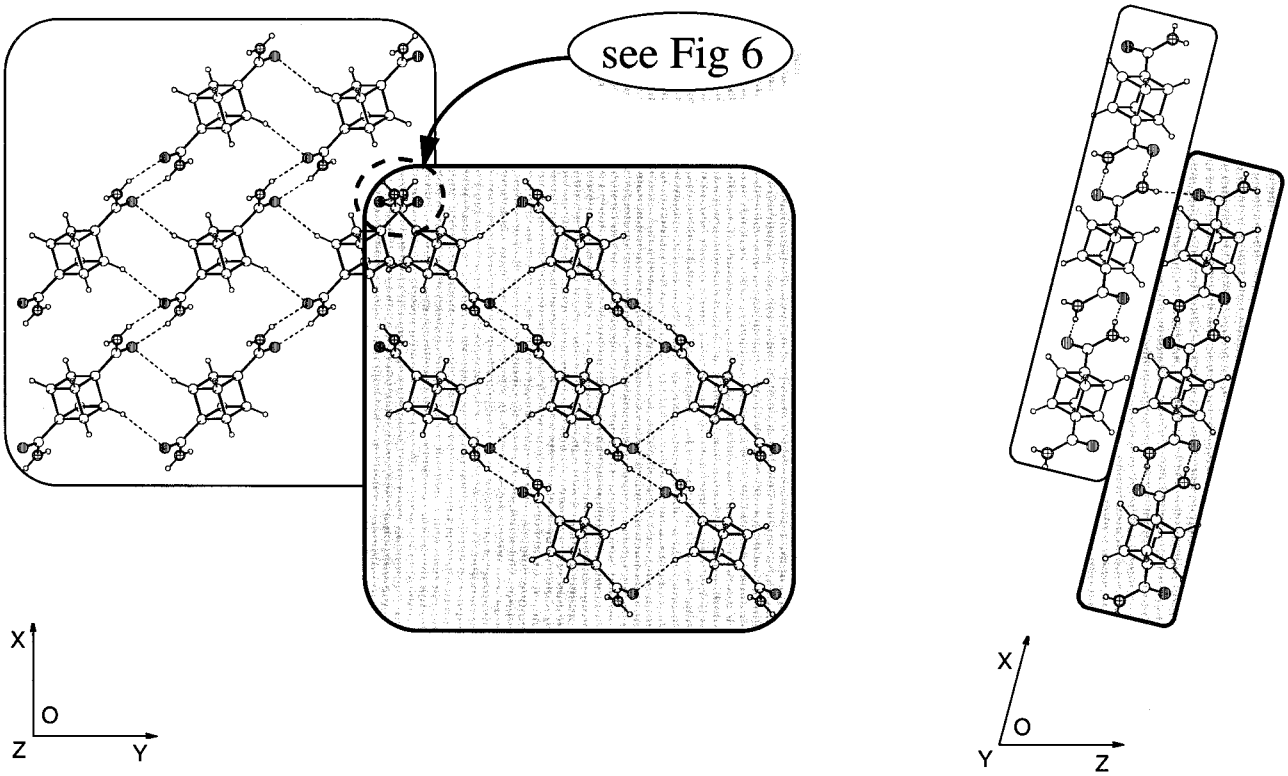

Figure 5. Crystal structure of 1,4-cubanedicarboxamide (**5**). (a) Two-dimensional layer mediated with $N-H_s\cdots O$ and $C-H\cdots O$ hydrogen bonds. Antiparallel layers are shaded differently. (b) Successive arrangement of $N-H_a\cdots O$ glide-related layers viewed down [010].

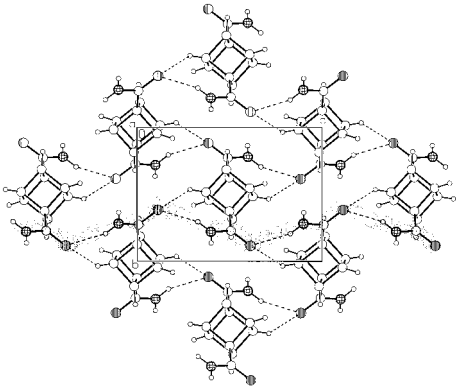

Figure 6. View of the structure of **5** down [100] showing the $N-H_a\cdots O$ hydrogen bond responsible for the shallow glide motif along with the $C-H\cdots O$ hydrogen bond. The glide $N-H_a\cdots O$ hydrogen bond is highlighted. Notice synthon **VI**.

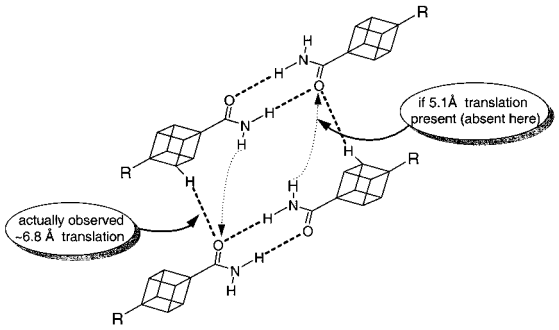

Figure 7. Schematic view of alternative hydrogen bond arrangements for primary cubanecarboxamides. Centrosymmetric dimers are formed via $N-H_s\cdots O$ bonds. The C═O groups accept hydrogen bonds from cubyl C−H groups (shallow glide motif), rather than from $N-H_a$ groups (5.1 Å translation motif).

grams[14] and of **2**−**5** with the program SHELX97.[15] All the geometrical analysis were carried out with PLATON[16] on Indigo Solid Impact and Indy workstations from Silicon Graphics.

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Supporting Information Available: Details of X-ray structural analyses of **1**−**5**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0013453

(14) (a) *SIR92*: Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Polidori, G. *J. Appl. Crystallogr.* **1994**, *27*, 435. (b) *RAELS*: Rae, A. D. A Comprehensive Constrained Least Squares Refinement Program, University of New South Wales, 1989.

(15) Sheldrick, G. M. *SHELX97*: Program for the Solution and Refinement of Crystal Structures; University of Göttingen: Germany, 1997.

(16) *PLATON*: Spek, A. L. Bijvoet Center for Biomolecular Research, Vakgroep Kristal-en Structure-chemie, University of Utrecht.