CrystEngComm

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Volume 13 | Number 19 | 7 October 2011 | Pages 5599–5964

RSC Publishing

COVER ARTICLE
Lemmerer *et al.*
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CrystEngComm

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Cite this: *CrystEngComm*, 2011, **13**, 5692

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PAPER

Covalent assistance in supramolecular synthesis: *in situ* modification and masking of the hydrogen bonding functionality of the supramolecular reagent isoniazid in co-crystals†

Andreas Lemmerer,*[a] Joel Bernstein‡*[b] and Volker Kahlenberg[c]

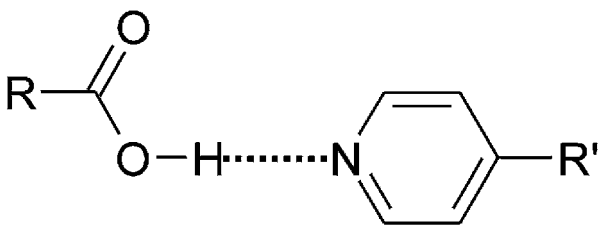
Received 31st January 2011, Accepted 14th March 2011
DOI: 10.1039/c1ce05152k

The supramolecular reagent isonicotinic acid hydrazide (isoniazid) is a promising molecule in the supramolecular synthesis of multi-component molecular complexes. Due to the covalent reaction of the carbohydrazide functional group with simple ketones and aldehydes, the hydrogen bonding functionality of isoniazid can be modified, where two of the hydrogen bond donors are replaced with hydrogen bonding "inert" hydrocarbons. The ketones used are propanone, 2-butanone, cyclopentanone, cyclohexanone, cycloheptanone, cyclooctanone, 4′-methylacetophenone and benzophenone and the aldehyde 4′-methylbenzaldehyde. The "modifiers" bonded to the isoniazid then give a measure of control of the outcome of the supramolecular synthesis with 3-hydroxybenzoic acid depending on the identity and steric size of the modifier used. The steric size itself can be used to shield or to "mask" the remaining hydrogen bonding functionality of isoniazid such that common homomeric and heteromeric interactions are prevented from taking place. This process of *covalent assistance to supramolecular synthesis* has been carried out in a one-pot covalent and supramolecular reaction to make six unhydrated co-crystals **2–7** and five hydrated co-crystals **8–12**.

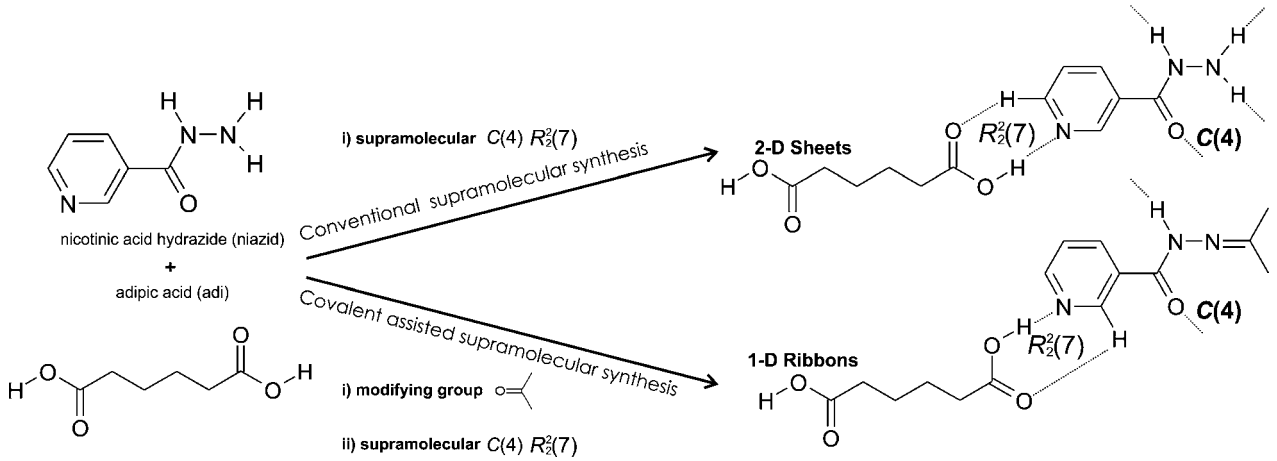
Introduction

How does one control and modify the self-assembly process of organic molecules towards a desired solid state? This question is one of the tenets of crystal engineering and the work done so far[1,2] has fallen under the umbrella of supramolecular synthesis, which looks at understanding and then (hopefully) controlling how the molecules crystallize. Work that has achieved some measure of success in unimolecular complexes is in carboxylic acids. Leiserowitz set the scene and described the two common hydrogen bonding arrangements of carboxylic acids, dimers and catmers.[3] Das *et al.* showed subsequently how the dimers, which are the dominant case, can be reduced to form catemers by altering the electronic and steric effects of the acid molecule as well as to generate a number of different types of catemeric arrangements.[4] Similar studies that try to rationalise the observed crystal structure through the molecular structure have been noted for the amides.[5]

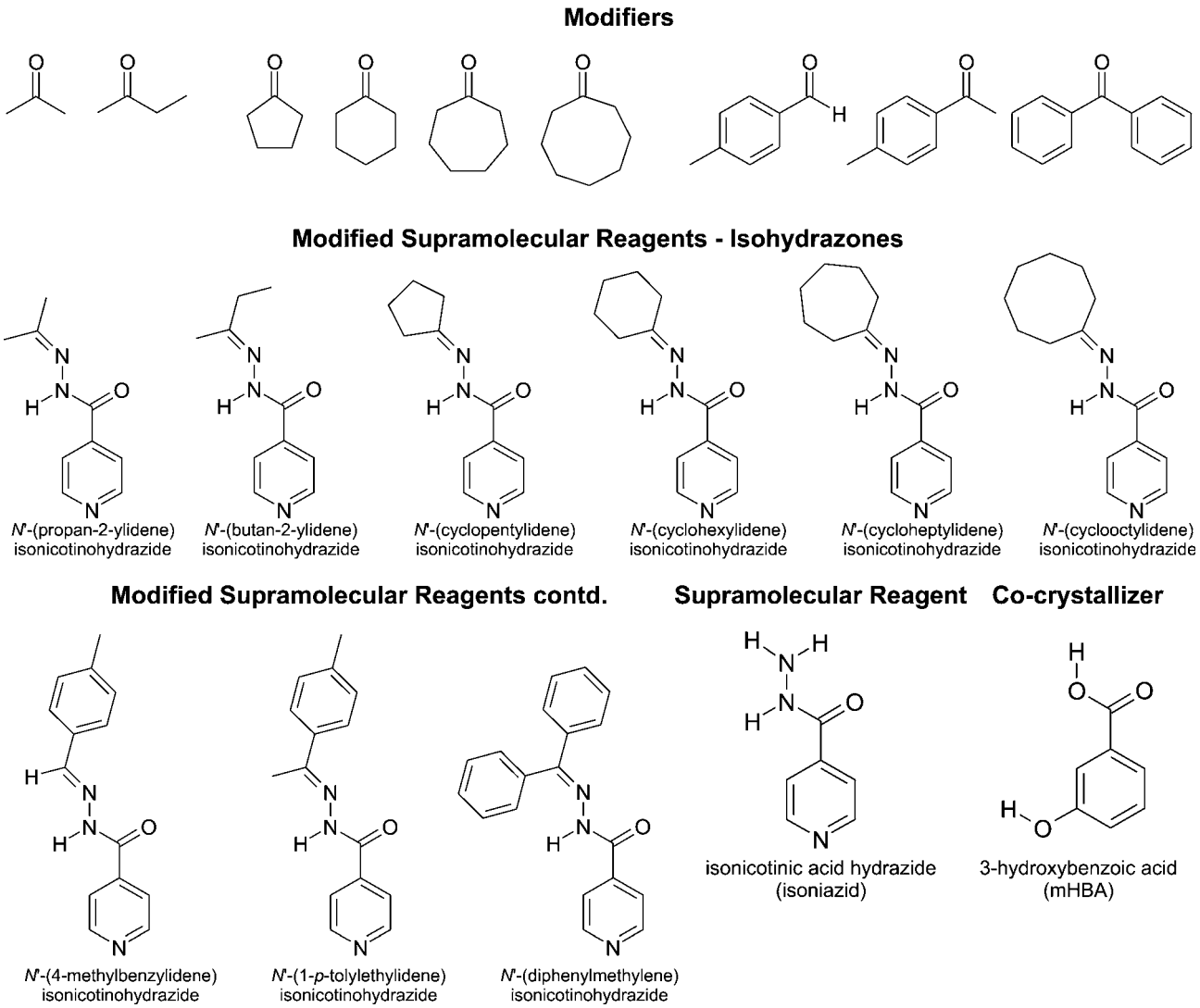
When assembling multimolecular complexes, or more accurately, a multi-component molecular complex,[6] the key is to identify the intermolecular interactions that will operate to bring together two or more different molecules. Predominant in terms of strength and directionality is the hydrogen bond.[7] Work in this field has benefitted from identifying first the heteromeric interactions[8] that are reliably doing this, and then identifying the molecules that contain these functionalities. The intermolecular interaction is then called a robust heterosynthon, which is defined as a supramolecular synthon between unlike but complementary functional groups,[9] and the molecule becomes a supramolecular reagent.[6b,10] The carboxylic acid···pyridine hydrogen bond is one of the leading candidates to date.[11] It has been shown by Shattock *el al.* that this hydrogen bond occurs very robustly, even in the presence of other hydrogen bonding functionalities.[12] The work by Aakeröy and co-workers has



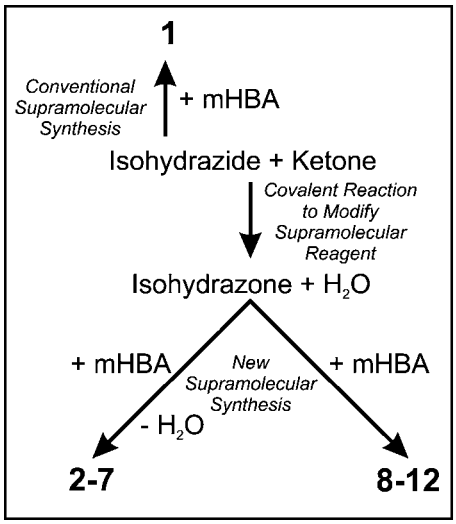
[a]*Molecular Sciences Institute, School of Chemistry, University of the Witwatersrand, Johannesburg, 2050, South Africa. E-mail: Andreas.lemmerer@wits.ac.za; Fax: +27 11 717 6749; Tel: +27 11 717 6711*
[b]*Department of Chemistry, Ben-Gurion University of the Negev, Beer-Sheva, Israel 84105. E-mail: yoel@bgu.ac.il; Fax: +972 8 647 2943; Tel: +972 8 647 2455*
[c]*Institute of Mineralogy and Petrography, University of Innsbruck, Innsbruck, Austria 6020. Fax: +43 512 507 2926; Tel: +43 512 507 5503*
† Electronic supplementary information (ESI) available: PXRD patterns of **4–12**. See DOI: 10.1039/c1ce05152k
‡ Present address: Faculty of Natural Sciences, New York University Abu Dhabi, P. O. Box 129188, Abu Dhabi, United Arab Emirates. E-mail: joel.bernstein@nyu.edu, Tel: 971 2 628 4190.



Scheme 1 The proof of concept carried out for covalent assistance to supramolecular synthesis using niazid: conventional supramolecular synthesis of co-crystal between niazid and adipic acid forms 2-D sheets, whereas the covalent-assisted supramolecular synthesis features a covalent reaction between niazid and the modifier acetone, and subsequent co-crystallization with adipic acid to form 1-D ribbons. See ref. 24.



Scheme 2 An overview of the different molecules used to demonstrate the covalent assisted supramolecular synthesis. There are nine modifiers used, eight ketones and one aldehyde, which are then reacted with the supramolecular reagent isoniazid to produce nine modified isoniazid supramolecular reagents.



Non-hydrated Co-crystals (2-7):
2: (*N*′-(propan-2-ylidene)isonicotinohydrazide)·(3-hydroxybenzoic acid)
3: (*N*′-(butan-2-ylidene)isonicotinohydrazide)·(3-hydroxybenzoic acid)
4: (*N*′-(cyclopentylidene)isonicotinohydrazide)·(3-hydroxybenzoic acid)
5: (*N*′-(cyclooctylidene)isonicotinohydrazide)·(3-hydroxybenzoic acid)
6: (*N*′-(1-*p*-tolylethylidene)isonicotinohydrazide)·(3-hydroxybenzoic acid)
7: (*N*′-(diphenylmethylene)isonicotinohydrazide)$_2$·(3-hydroxybenzoic acid)

Hydrated Co-crystals (8-12):
8: (*N*′-(propan-2-ylidene)isonicotinohydrazide)·(3-hydroxybenzoic acid)·(H_2O)
9: (*N*′-(butan-2-ylidene)isonicotinohydrazide)·(3-hydroxybenzoic acid)·(H_2O)
10: (*N*′-(cyclohexylidene)isonicotinohydrazide)·(3-hydroxybenzoic acid)·(H_2O)
11: (*N*′-(cycloheptylidene)isonicotinohydrazide)·(3-hydroxybenzoic acid)·(H_2O)
12: (*N*′-(4-methylbenzylidene)isonicotinohydrazide)·(3-hydroxybenzoic acid)·(H_2O)

Scheme 3 The nine modified reagents shown in Scheme 2 are then co-crystallized with the co-crystallizer mHBA to produce six unhydrated co-crystals and five hydrated co-crystals. The process of modification and co-crystallization all occurs in one pot. A conventional supramolecular synthesis not involving the modifying process is shown schematically and contrasted to the covalent assisted supramolecular reaction.

shown how this heterosynthon can be modified and controlled to design specific assemblies.[13] By increasing the basicity of the N atom, the strength of the resulting O–H···N hydrogen bond drives the co-crystallization with a number of different acids and increases the supramolecular yield.[14] The same principle can be used to bring together three different molecules and form

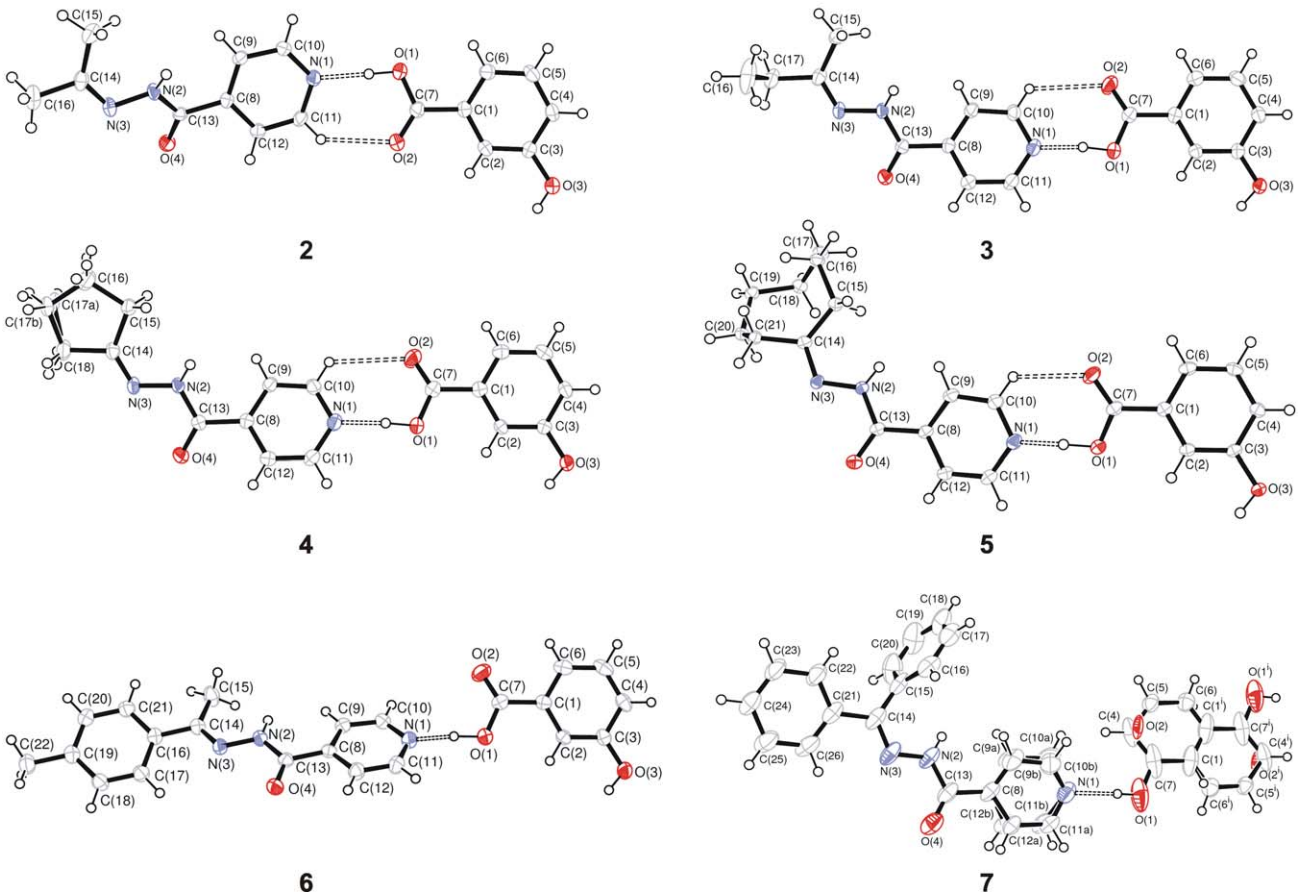


Fig. 1 The contents of the asymmetric unit for unhydrated co-crystals **2–7**, showing the atomic numbering scheme. Displacement ellipsoids are shown at the 50% probability level. The disorder in the cyclopentane ring of **4** is discussed in the text. Atoms with superscript *i* are at the symmetry position [$-x + 3$, $-y + 1$, $-z + 1$].

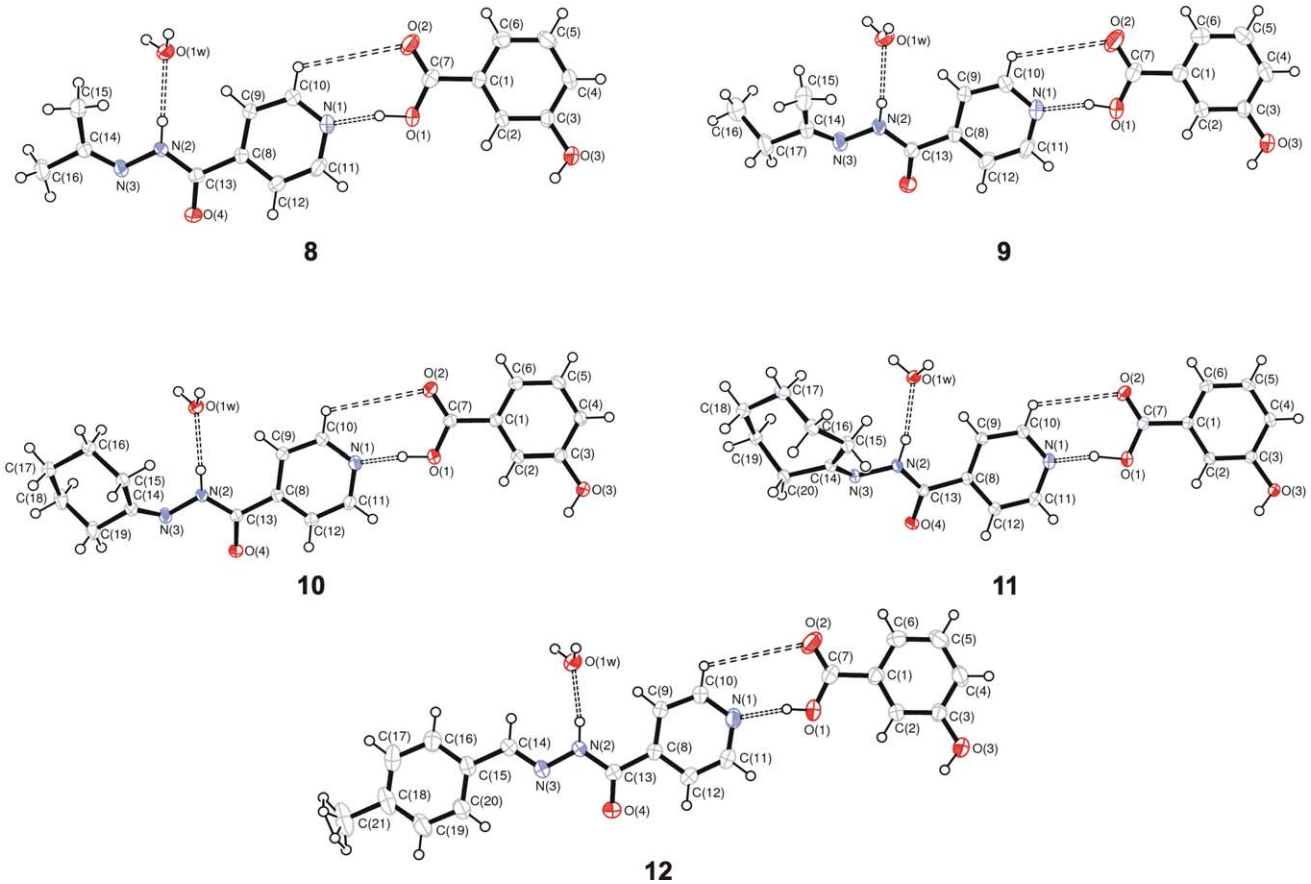


Fig. 2 The contents of the asymmetric unit for hydrated co-crystals **8–12**, showing the atomic numbering scheme. Displacement ellipsoids are shown at the 50% probability level. The disorder in the methyl ring of **12** is discussed in the text.

a ternary co-crystal. For example, by synthesizing a molecule with two different basic N atoms, two carboxylic acids with different acidities in principle can interact with the two different N atoms,[15] on the principle of best acceptor/best donor hierarchies.[16]

Further examples, and by no means an exhaustive list, of steering the crystal structure by modifying the molecular structure in both unimolecular and multimolecular complexes include changing the identity of the substituents,[17] the charge on the functional groups,[18] the spacers between functional groups,[19] the steric size adjacent to the functional group,[20] by removing hydrogen bonding sites through coordination chemistry,[21] and the relative position of the hydrogen bonding groups on the molecule.[22] Most of these examples require the synthesis of the potential reagents or selection of available moieties, and then carrying out the supramolecular reaction in a subsequent sequential step. The reagent preparation/modification and co-crystallization are often two distinct and physically separated events.

The molecule we have chosen to modify is isonicotinic acid hydrazide (isoniazid). Isoniazid is a versatile molecule. It is an active pharmaceutical ingredient that helped cure tuberculosis as part of a triple therapy cocktail, it co-crystallizes with carboxylic acids to form pharmaceutical co-crystals, and is also a versatile supramolecular reagent as it has multiple donor and accepting groups to interact with different functional groups.[23] From a Cambridge Structural Database (CSD) analysis, and limited work with acids, this supramolecular reagent was found to form seven types of homosynthons with itself, and five heterosynthons with acids.[23] In addition, it is also a molecule that allows one to modify its hydrogen bonding functionality *in situ* during the co-crystallization process, by adding simple ketones to the co-crystallizing solution. This process of modifying was demonstrated in a proof of concept experiment with its isomer nicotinic acid hydrazide (niazid) (Scheme 1).[24] Co-crystallization of niazid with adipic acid resulted in the utilization of the $C(4)$ homosynthon of the O=C–N–H– group to connect the niazid molecules and the $R_2^2(7)$ heterosynthon to connect the acid molecules to the niazid to form a hydrogen bonded sheet. These sheets are connected by the hydrogen bonding interactions of the amine group $-NH_2$ to the amide C=O and acid C–OH using N–H···O hydrogen bonds. However, if one adds acetone to the crystallization (by changing the solvent from methanol to acetone), then the NH_2 group is replaced by the acetone carbons and the N–H···O hydrogen bonds between the sheets are not able to form. This changes the crystal structure of the co-crystal to a ribbon arrangement, while the $C(4)$ and $R_2^2(7)$ synthons are retained. In summary, we have removed the hydrogen bonding functionality by replacing the two hydrogens by "inert hydrogen bonding" hydrocarbons, and subsequently altered the overall

Table 1 Crystallographic data for unhydrated co-crystals **4–7**

	4	**5**	**6**	**7**
Formula	$(C_{12}H_{13}N_3O)\cdot(C_7H_6O_3)$	$(C_{14}H_{19}N_3O)\cdot(C_7H_6O_3)$	$(C_{15}H_{15}N_3O)\cdot(C_7H_6O_3)$	$(C_{19}H_{15}N_3O)_2\cdot(C_7H_6O_3)$
M_r	341.36	383.44	391.42	740.80
Temperature/K	173(2)	100(2)	173(2)	173(2)
Wavelength/Å	0.71073	1.5418	1.5418	1.5418
Crystal size/mm^3	0.50 × 0.40 × 0.10	0.40 × 0.40 × 0.20	0.36 × 0.32 × 0.10	0.42 × 0.33 × 0.20
Crystal system	Monoclinic	Monoclinic	Monoclinic	Triclinic
Space group	$P2_1/c$	$P2_1/c$	$P2_1/c$	$P\bar{1}$
a/Å	19.7268(4)	21.3902(15)	24.4670(16)	9.8338(9)
b/Å	8.3772(2)	7.8621(5)	7.3712(5)	10.2475(9)
c/Å	10.1372(2)	11.2995(7)	10.8211(6)	10.8863(10)
α/°	90	90	90	104.295(8)
β/°	98.644(2)	97.986(3)	99.666(6)	112.784(8)
γ/°	90	90	90	103.370(8)
V/Å^3	1656.20(6)	1881.8(2)	1923.9(2)	912.17(18)
Z	4	4	4	1
ρ (calcd)/Mg m^{-3}	1.369	1.353	1.351	1.350
μ/mm^{-1}	0.098	0.744	0.775	0.727
F(000)	720	816	824	389
θ Range for data collection/°	3.17 to 25.50	4.17 to 67.40	3.67 to 67.49	4.75 to 62.65
Reflections collected	10 130	11 997	11 105	4365
No. of unique data [R(int)]	3073 [0.0235]	3383 [0.0366]	3452 [0.0425]	2793 [0.0202]
No. of data with $I > 2\sigma(I)$	2285	2940	2909	2516
Final $R(I > 2\sigma(I))$	0.0333	0.0459	0.0527	0.0568
Final wR_2 (all data)	0.0855	0.1329	0.1631	0.1618

architecture in what we describe as a *covalent assisted supramolecular synthesis*. What makes this concept work is that we are modifying the molecular structure of the supramolecular reagent, yet still achieving our goal of making a co-crystal with control on the co-crystal architecture.

We report here the systematic investigation of the modification of the supramolecular reagent isoniazid with specific modifiers (eight ketones and one aldehyde, Scheme 2), which primarily removes the $-NH_2$ functionality, and also the utilization of the steric size of the modifiers to further control the supramolecular architecture of co-crystals formed with 3-hydroxybenzoic acid (mHBA) (Scheme 3).

Experimental

Compounds. All reagents were purchased from commercial sources and used without further purification. Melting points were determined on a hot stage microscope.

(Isonicotinic acid hydrazide)·(3-hydroxybenzoic acid), 1

0.370 g of isonicotinic acid hydrazide (2.70 mmol) and 0.380 g of 3-hydroxybenzoic acid (2.75 mmol) were added into a sample vial. The solid was dissolved in AP-grade hot methanol (5 ml) and left to stand at room temperature. Colourless needles were afforded after 3 days. Mp 172–173 °C, corresponding to the literature value of isoniazid.

(*N*′-(Propan-2-ylidene)isonicotinohydrazide)·(3-hydroxybenzoic acid), 2

See ref. 23 for synthesis. Colourless plates. Mp 133–134 °C.

(*N*′-(Butan-2-ylidene)isonicotinohydrazide)·(3-hydroxybenzoic acid), 3

See ref. 23 for synthesis. Colourless plates. Mp 133–135 °C.

(*N*′-(Cyclopentylidene)isonicotinohydrazide)·(3-hydroxybenzoic acid), 4

0.200 g of isonicotinic acid hydrazide (1.46 mmol) and 0.213 g of 3-hydroxybenzoic acid (1.54 mmol) were added into a sample vial. The solids were dissolved in AP-grade hot cyclopentanone (6 ml), refluxed in a closed vial for six hours, and left to stand at room temperature open to the atmosphere. Colourless plates were afforded after 10 days. Mp 163–164 °C.

(*N*′-(Cyclooctylidene)isonicotinohydrazide)·(3-hydroxybenzoic acid), 5

0.150 g of isonicotinic acid hydrazide (1.09 mmol), 0.155 g of 3-hydroxybenzoic acid (1.12 mmol) and 0.142 g of cyclooctanone (1.12 mmol) were added into a sample vial. The solids were dissolved in AP-grade hot methanol (5 ml), refluxed for four hours in a closed vial, and left to stand at room temperature open to the atmosphere. Colourless plates were afforded after 5 days. Mp 118–120 °C.

(*N*′-(1-*p*-Tolylethylidene)isonicotinohydrazide)·(3-hydroxybenzoic acid), 6

0.200 g of isonicotinic acid hydrazide (1.46 mmol), 0.213 g of 3-hydroxybenzoic acid (1.54 mmol) and 0.21 g of 4′-methylacetophenone (1.59 mmol) were added into a sample vial. The solids were dissolved in AP-grade hot methanol (5 ml), refluxed for 3 hours in a closed vial, and left to stand at room temperature open to the atmosphere. Colourless plates were afforded after 4 days. Mp 151–152 °C.

Table 2 Crystallographic data for hydrated co-crystals **8–12**

	8	**9**	**10**	**11**	**12**
Formula	$(C_9H_{11}N_3O)\cdot(C_7H_6O_3)\cdot(H_2O)$	$(C_{10}H_{13}N_3O)\cdot(C_7H_6O_3)\cdot(H_2O)$	$(C_{12}H_{15}N_3O)\cdot(C_7H_6O_3)\cdot(H_2O)$	$(C_{13}H_{17}N_3O)\cdot(C_7H_6O_3)\cdot(H_2O)$	$(C_{14}H_{13}N_3O)\cdot(C_7H_6O_3)\cdot(H_2O)$
M_r	333.34	347.37	373.40	387.43	395.41
Temperature/K	173(2)	173(2)	100(2)	100(2)	173(2)
Wavelength/Å	0.71073	0.71073	1.5418	1.5418	1.5418
Crystal size/mm^3	0.40 × 0.24 × 0.12	0.35 × 0.20 × 0.15	0.24 × 0.24 × 0.2	0.40 × 0.36 × 0.1	0.44 × 0.24 × 0.20
Crystal system	Triclinic	Triclinic	Triclinic	Monoclinic	Triclinic
Space group	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$	$P2_1/n$	$P\bar{1}$
a/Å	6.3511(6)	6.3699(2)	6.3632(6)	6.3127(4)	6.1506(5)
b/Å	10.5853(8)	10.9498(3)	10.8918(10)	11.4293(6)	10.5426(6)
c/Å	12.8026(12)	12.8120(3)	13.3842(12)	26.1598(15)	16.2041(12)
α/°	75.694(7)	81.009(1)	87.434(7)	90	73.603(6)
β/°	78.613(8)	80.566(1)	80.241(8)	91.109(5)	90.403(6)
γ/°	81.087(7)	83.859(1)	83.083(8)	90	79.320(6)
V/Å^3	812.47(12)	867.67(4)	907.26(14)	1887.07(19)	988.57(12)
Z	2	2	2	4	3
ρ (calcd)/Mg m^{-3}	1.363	1.330	1.367	1.364	1.328
μ(Mo-K$_\alpha$)/mm^{-1}	0.103	0.099	0.829	0.817	0.797
F(000)	352	368	396	824	416
θ Range for data collection/°	3.29 to 25.50	1.63 to 25.50	3.35 to 67.45	3.38 to 67.36	2.85 to 67.28
Reflections collected	5230	14 210	8274	11 880	9145
No. of unique data [R (int)]	2990 [0.0242]	3232 [0.0256]	3240 [0.0326]	3403 [0.0381]	3545 [0.0374]
No. of data with $I > 2\sigma(I)$	1906	2702	2666	2858	2833
Final $R(I > 2\sigma(I))$	0.0335	0.0408	0.0487	0.0453	0.0501
Final wR_2 (all data)	0.0741	0.1144	0.1338	0.1257	0.1430

(*N*′-(Diphenylmethylene)isonicotinohydrazide)$_2$·(3-hydroxybenzoic acid), 7

0.200 g of isonicotinic acid hydrazide (1.46 mmol), 0.213 g of 3-hydroxybenzoic acid (1.54 mmol) and 0.266 g of benzophenone (1.46 mmol) were added into a sample vial. The solids were dissolved in AP-grade hot methanol (5 ml), refluxed for 3 hours in a closed vial, and left to stand at room temperature open to the atmosphere. Colourless plates were afforded after 7 days. Mp 167–168 °C.

(*N*′-(Propan-2-ylidene)isonicotinohydrazide)·(3-hydroxybenzoic acid)·(H$_2$O), 8

0.200 g of isonicotinic acid hydrazide (1.46 mmol), 0.213 g of 3-hydroxybenzoic acid (1.54 mmol) and 1 ml of acetone were added into a sample vial. The solids were dissolved in AP-grade methanol (6 ml) and stirred with no heating for 12 hours. Thereafter, the crystals were allowed to grow by slow evaporation at room temperature. Colourless plates were afforded after 2 days. Mp 113–115 °C.

(*N*′-(Butan-2-ylidene)isonicotinohydrazide)·(3-hydroxybenzoic acid)·(H$_2$O), 9

0.200 g of isonicotinic acid hydrazide (1.46 mmol), 0.213 g of 3-hydroxybenzoic acid (1.54 mmol) and 1 ml of 2-butanone were added into a sample vial. The solids were dissolved in AP-grade methanol (6 ml) and stirred with no heating for 12 hours. Thereafter, the crystals were allowed to grow by slow evaporation at room temperature. Colourless plates were afforded after 2 days. Mp 113–115 °C.

(*N*′-(Cyclohexylidene)isonicotinohydrazide)·(3-hydroxybenzoic acid)·(H$_2$O), 10

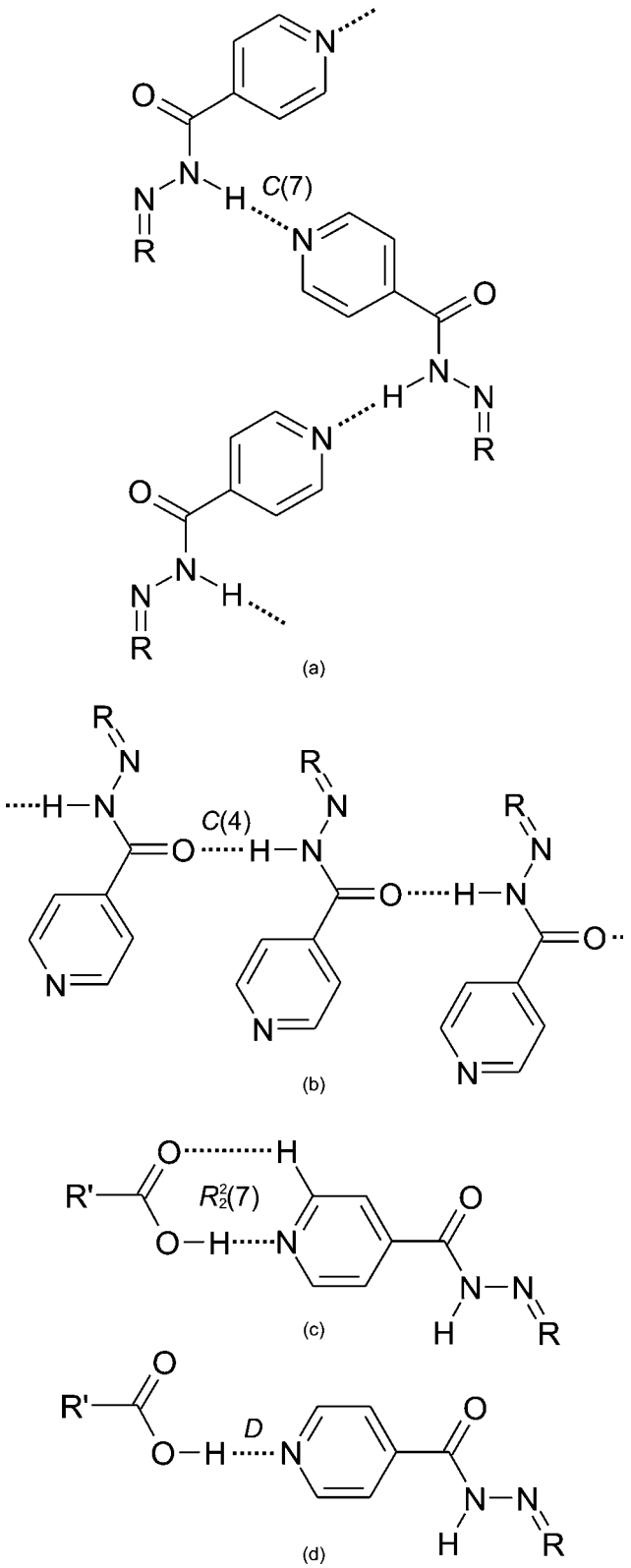
0.190 g of isonicotinic acid hydrazide (1.39 mmol), 0.190 g of 3-hydroxybenzoic acid (1.38 mmol) and 1 ml of cyclohexanone were added into a sample vial. The solids were dissolved in AP-grade hot methanol (5 ml), refluxed for 30 minutes in a closed vial, and left to stand at room temperature open to the atmosphere. Colourless plates were afforded after 7 days. Mp 145–146 °C.

(*N*′-(Cycloheptylidene)isonicotinohydrazide)·(3-hydroxybenzoic acid)·(H$_2$O), 11

0.150 g of isonicotinic acid hydrazide (1.09 mmol), 0.150 g of 3-hydroxybenzoic acid (1.09 mmol) and 1 ml of cycloheptanone were added into a sample vial. The solids were dissolved in AP-grade hot methanol (5 ml), refluxed for 2 hours in a closed vial, and left to stand at room temperature open to the atmosphere. Colourless plates were afforded after 6 days. Mp 139–140 °C.

(*N*′-(4-Methylbenzylidene)isonicotinohydrazide)·(3-hydroxybenzoic acid)·(H$_2$O), 12

0.200 g of isonicotinic acid hydrazide (1.46 mmol), 0.213 g of 3-hydroxybenzoic acid (1.54 mmol) and 0.175 g of 4′-methylbenzaldehyde (1.46 mmol) were added into a sample vial. The solids were dissolved in AP-grade hot methanol (6 ml), refluxed for 6 hours in a closed vial, and left to stand at room temperature open to the atmosphere. Colourless plates were afforded after 6 days. Mp 169–170 °C.



Scheme 4 The two different homosynthons expected for modified isoniazid, as well as the two heterosynthons used to co-crystallize the modified isoniazid with carboxylic acids.

Single crystal X-ray diffraction

Single crystal diffraction data were collected in ω scan mode on an Oxford Diffraction Gemini R Ultra diffractometer equipped with a Ruby CCD-detector with Mo-K_α radiation (λ = 0.71073 Å, graphite monochromator, mono-capillary collimator) for compounds **4**, **8** and **9**, and with Cu-K_α (λ = 1.5418 Å, multi-layer optics) for compounds **5**, **6**, **7**, **10**, **11** and **12** at 100 or 173 K using an Oxford Cryostream 700 cooler. Data reduction and cell refinement were carried out using CrysAlisPro.[25] Space group assignments were made using *XPREP2*[26] and empirical absorption corrections[25] on all compounds. In all cases, the structures were solved in the *WinGX*[27] suite of programs by direct methods using *SHELXS-97*[28] and refined using full-matrix least-squares/difference Fourier techniques on F^2 using *SHELXL-97*.[28] All non-hydrogen atoms were refined anisotropically. Thereafter, all hydrogen atoms attached to N and O atoms were located in the difference Fourier map and their coordinates refined freely with isotropic parameters 1.5 times (O) or 1.2 times (N) those of the heavy atoms to which they are attached. All C–H hydrogen atoms were placed at idealized positions and refined as riding atoms with isotropic parameters 1.2 times those of the heavy atoms to which they are attached.

The positional disorder around the carbon atom C(17) in **4** was resolved by finding alternate positions from the difference Fourier map for the atom. These atoms were then refined anisotropically together with their site occupancy such that the sum of the occupancies for the two alternate atom positions equalled one. The ratio of major to minor component is 81(1) to 19(1)%. The bond lengths and bond angles were restrained using the SADI instruction in *SHELX* to be within 0.01 Å of each other for the two parts. Hydrogen atom positions were then calculated for the respective atoms using a riding model.

The positional disorder around the four carbon atoms, C(9), C(10), C(11) and C(12), in **7** was resolved by finding alternate positions from the difference Fourier map for the respective atoms. These atoms were then refined anisotropically with site occupancies of 50% such that the sum of the occupancies for the two alternate atom positions equalled one. The bond lengths were restrained using the DFIX instruction in *SHELX* to be 1.39 Å. Hydrogen atom positions were then calculated for the respective atoms using a riding model.

The methyl group in **12** is disordered and the disorder modelled using the AFIX 123 instruction in *SHELX*.

ORTEP-style diagrams of the thermal displacement ellipsoids at the 50% probability level and molecular numbering scheme are given in Fig. 1 and 2. Diagrams and publication material were generated using *ORTEP-3*,[29] *PLATON*[30] and *DIAMOND*.[31] Experimental details of the X-ray analyses are provided in Tables 1 and 2. Crystallographic data for the co-crystals **2** and **3** were reported previously.[23]

Powder X-ray diffraction

Powder X-ray diffraction data for compounds **1**, **2**, **4–8** were collected on a Philips powder diffractometer using Cu$K_{\alpha 1}$ radiation, graphite monochromator on the diffracted beam and operating at 40 kV, 30 mA at 293 K. Powder X-ray diffraction data for compounds **3** and **9** were collected on a Stoe STADI MP

Table 3 Geometrical parameters for hydrogen bonds in unhydrated co-crystals **2–7**

Compound	*d*(D–H)/Å	*d*(H···A)/Å	*d*(D···A)/Å	∠(D–H···A)/°	Symmetry transformations
2					
O(1)–H(1)···N(1) (**a**)	0.98(2)	1.73(2)	2.711(2)	178(2)	—
C(11)–H(11)···O(2)	0.95	2.42	3.123(2)	131	—
O(3)–H(3)···N(3) (**b**)	0.86(2)	2.07(2)	2.881(2)	158(2)	$-x, -y + 1, -z + 1$
N(2)–H(2)···O(4) (**c**)	0.89(2)	1.99(2)	2.879(2)	174(2)	$x, -y + 1/2, z - 1/2$
3					
O(1)–H(1)···N(1) (**a**)	1.03(3)	1.62(3)	2.636(2)	172(3)	—
C(10)–H(10)···O(2)	0.95	2.67	3.317(2)	126	—
O(3)–H(3)···N(3) (**b**)	0.91(3)	1.97(3)	2.836(2)	159(2)	$-x + 1, y - 1/2, -z + 3/2$
N(2)–H(2)···O(4) (**c**)	0.85(3)	2.28(3)	3.103(2)	163(3)	$x, -y + 3/2, z - 1/2$
4					
O(1)–H(1)···N(1) (**a**)	1.00(2)	1.63(2)	2.630(1)	176(2)	—
C(10)–H(10)···O(2)	0.95	2.71	3.346(2)	125	—
O(3)–H(3)···N(3) (**b**)	0.87(2)	1.94(2)	2.785(2)	162(2)	$-x + 1, y - 1/2, -z + 3/2$
N(2)–H(2)···O(4) (**c**)	0.85(2)	2.357(2)	3.192(2)	169(1)	$x, -y + 3/2, z - 1/2$
5					
O(1)–H(1)···N(1) (**a**)	1.08(2)	1.55(2)	2.627(2)	177(2)	—
C(10)–H(10)···O(2)	0.95	2.63	3.288(2)	127	—
O(3)–H(3)···N(3) (**b**)	0.88(2)	2.02(2)	2.872(2)	161(2)	$-x + 1, y - 1/2, -z + 3/2$
N(2)–H(2)···O(4) (**c**)	0.83(2)	2.95(2)	3.740(2)	160(2)	$x, -y + 3/2, z - 1/2$
6					
O(1)–H(1)···N(1) (**a**)	1.08(2)	1.55(2)	2.622(2)	171(2)	—
O(3)–H(3)···O(4) (**b**)	0.87(2)	1.93(2)	2.782(2)	168(2)	$-x + 1, -y + 1, -z$
N(2)–H(2)···O(4) (**c**)	0.85(2)	3.08(2)	3.736(2)	135(2)	$x, -y + 3/2, z + 1/2$
7					
O(1)–H(1)···N(1) (**a**)	0.87(3)	1.87(3)	2.744(3)	177(4)	—
C(10A)–H(10A)···O(2)	0.95	2.84	3.498(11)	127	—
O(1)–H(1)···N(1) (**b**)	0.88(3)	1.88(3)	2.744(3)	177(4)	$-x + 3, -y + 1, -z + 1$
N(2)–H(2)···O(4) (**c**)	—	—	—	—	—

diffractometer using flat-plate bisecting transmission geometry and strictly monochromatic $CuK_{\alpha 1}$-radiation operating at 40 kV, 40 mA. Powder X-ray diffraction confirmed that the single crystal structures were representative of the bulk material (see ESI†).

Results

The results are divided into two sets of compounds, those co-crystals that are non-hydrates (Fig. 1) and those that are hydrates (Fig. 2). The source of the water is the condensation reaction, which means that there will always be a stoichiometric amount of water present in the crystallization solution, apart from any moisture that enters from the atmosphere or is present in the solvent.

Expected synthons

In our previous work, by looking at only the carbohydrazide functional group on the unaltered isoniazid, we searched the CSD[32] for the most common homosynthons exhibited by this functional group in the absence of any other molecules or functional groups in 47 structures. There, we found two chain synthons, *C*(3) and *C*(4), and four ring synthons, $R_2^2(6)$, $R_2^2(10)$, $R_3^3(10)$ and $R_4^2(10)$.[23] These synthons are in agreement with a more detailed study of hydrogen bonding synthons in organic hydrazides.[33] Upon conversion of the NH_2 group to a N=C group, to create a *N*-acylhydrazone functional group, the number of hydrogen bond donors is reduced from three to one. In a process akin to the one used for the carbohydrazide functional group, we searched the CSD for homosynthons of the *N*-acylhydrazone, however this time by including the pyridine functional group.[34] Of the 55 well determined structures found, the *C*(7) (Scheme 4a) heterosynthon is observed 28 times, while the homosynthon *C*(4) is observed 23 times (Scheme 4b). The difference between the two synthons lies in the identity of the acceptor site atom, being the single lone pair of the pyridine N atom in *C*(7) and one of the two lone pairs on the O atom in *C*(4). The *C*(4) homosynthon is not unexpected as it is one of the most commonly observed hydrogen bonding patterns for amides.[35] The expected heterosynthon is unchanged, the hydrogen bond from the carboxylic acid to the pyridine nitrogen. This heterosynthon exists in two geometric variants. The carboxylic acid group and the pyridine ring can be co-planar, to form a $R_2^2(7)$ hydrogen bonded ring with a supporting weak C–H···O hydrogen bond (Scheme 4c). If the two groups are not co-planar, the heterosynthon forms a discrete *D* hydrogen bond (Scheme 4d). The predictability of the carboxylic acid···pyridine heterosynthon is supported by evidence in the literature. In the previous work with isoniazid co-crystals, all 9 of the co-crystals feature this heterosynthon.[23] In the related co-crystal systems involving isonicotinamide (39/40)[36] and nicotinamide (20/22)[37] together with carboxylic acids, either of the two heterosynthons, *D* or $R_2^2(7)$, repeatedly appears, with relative frequency shown in brackets.

By combining the modified isoniazid with the acid mHBA, the total number of hydrogen bond donors is three if the co-crystal does not contain water (**2–7**, Table 3). For clarity, the hydrogen

Table 4 Geometrical parameters for hydrogen bonds in hydrated co-crystals **8–12**

Compound	d(D–H)/Å	d(H···A)/Å	d(D···A)/Å	∠(D–H···A)/°	Symmetry transformations
8					
O(1)–H(1)···N(1) (**a**)	1.01(2)	1.62(2)	2.619(2)	169(2)	—
C(10)–H(10)···O(2)	0.95	3.48	3.929(2)	112	—
O(3)–H(3)···O(4) (**b**)	0.88(2)	1.85(2)	2.718(2)	171(2)	$-x+1, -y, -z+1$
N(2)–H(2)···O(1W) (**c**)	0.87(1)	2.12(2)	2.978(2)	172(2)	—
O(1W)–H(1W)···N(3) (**d**)	0.87(2)	2.15(2)	2.999(2)	163(1)	$x+1, y, z$
O(1W)–H(2W)···O(2) (**e**)	0.86(2)	1.90(2)	2.767(2)	178(2)	$-x+2, -y+1, -z+1$
9					
O(1)–H(1)···N(1) (**a**)	0.91(3)	1.73(3)	2.621(2)	165(2)	—
C(10)–H(10)···O(2)	0.95	3.34	3.808(2)	113	—
O(3)–H(3)···O(4) (**b**)	0.85(2)	1.88(2)	2.721(2)	170(2)	$-x+1, -y, -z+1$
N(2)–H(2)···O(1W) (**c**)	0.85(2)	2.15(2)	2.985(2)	170(2)	—
O(1W)–H(1W)···N(3) (**d**)	0.87(2)	2.18(2)	3.020(2)	163(2)	$x+1, y, z$
O(1W)–H(2W)···O(2) (**e**)	0.85(2)	1.93(2)	2.778(2)	177(2)	$-x+2, -y+1, -z+1$
10					
O(1)–H(1)···N(1) (**a**)	1.04(3)	1.57(3)	2.605(2)	172(2)	—
C(10)–H(10)···O(2)	0.95	3.49	3.919(2)	110	—
O(3)–H(3)···O(4) (**b**)	0.92(3)	1.81(3)	2.717(2)	169(2)	$-x+1, -y, -z+1$
N(2)–H(2)···O(1W) (**c**)	0.89(2)	2.06(2)	2.936(2)	168(2)	—
O(1W)–H(1W)···N(3) (**d**)	0.86(3)	2.16(3)	3.017(2)	173(2)	$x+1, y, z$
O(1W)–H(2W)···O(2) (**e**)	0.89(2)	1.93(3)	2.809(2)	173(2)	$-x+2, -y+1, -z+1$
11					
O(1)–H(1)···N(1) (**a**)	1.11(2)	1.50(2)	2.602(2)	168(2)	—
C(10)–H(10)···O(2)	0.95	3.14	3.663(2)	116	—
O(3)–H(3)···O(4) (**b**)	0.88(2)	1.80(2)	2.679(2)	172(2)	$-x+1, -y, -z+1$
N(2)–H(2)···O(1W) (**c**)	0.95(2)	2.62(2)	3.179(2)	118	—
O(1W)–H(1W)···N(3) (**d**)	0.87(2)	2.14(2)	2.991(2)	166(2)	$x+1, y, z$
O(1W)–H(2W)···O(2) (**e**)	0.88(2)	1.92(2)	2.786(2)	170(2)	$-x+2, -y+1, -z+1$
12					
O(1)–H(1)···N(1) (**a**)	0.88(3)	1.77(3)	2.632(2)	167(2)	—
C(10)–H(10)···O(2)	0.95	3.61	4.025(2)	110	—
O(3)–H(3)···O(4) (**b**)	0.95(3)	1.80(3)	2.726(2)	165(2)	$-x+1, -y, -z+1$
N(2)–H(2)···O(1W) (**c**)	0.89(2)	1.96(2)	2.840(2)	172(2)	—
O(1W)–H(1W)···N(3) (**d**)	0.85(2)	2.21(2)	3.027(2)	161(2)	$x+1, y, z$
O(1W)–H(2W)···O(2) (**e**)	0.87(2)	1.88(2)	2.741(2)	171(2)	$-x+2, -y+1, -z+1$

bond formed by the carboxylic acid H(1) is marked with a bold **a**, the phenol H(3) marked with a bold **b**, and the amide H(2) by a bold **c**. For the hydrated co-crystals **8–12** (Table 4), the letters **d** (H(1W)) and **e** (H(2W)) are used in addition for the two H's on the water molecule. When assigning the graph set notations, we will only use the **a**, **b**, **c**, **d** and **e** hydrogen bonds. Any C–H···O hydrogen bonds are shown but are not included in the designation.

Attempted co-crystallization of unmodified isoniazid with mHBA

The preparation of the co-crystal between isoniazid and mHBA (**1**) was attempted from a large number of solvents, yet only the individual components ever crystallized out. Attempts employing liquid-assisted grinding were also unsuccessful (see ESI†).

The unhydrates 2–7 using modified isoniazid

Co-crystals **2** and **3** were reported previsously,[23] but are here included together with relabelled Ortep style diagrams to aid in comparison with the related co-crystals reported in this work. The unhydrated co-crystals **2–6** also share common structural features (co-crystal **7** will be described separately). The 5 co-crystals **2–6** can be subdivided into two structural groupings. Group 1 consists of co-crystals **3**, **4** and **5**, and group 2 of co-crystals **2** and **6**. Group 1's all have the same hydrogen bonding patterns as well as similar unit cell parameters. The structural description for this group will be based on co-crystal **3**. Co-crystal **3**, which was described briefly before,[23] consists of two hydrogen bond patterns: it has a $C_2^2(15)$ and a $C(4)$ chain (Fig. 3). The larger chain is made up of the COOH···N_{pyr} (**a**) and the OH···N=C (**b**) hydrogen bond in between, and extends along the b-axis (molecules are related by a two-fold screw axis). This chain, using the two heterosynthons, forms the intermolecular attraction between the two different molecules being co-crystallized. The third hydrogen bonded interaction is the $C(4)$ N(2)–H(2)···O(4) (**c**) homosynthon between the modified isoniazid (N'-(butan-2-ylidene)isonicotinohydrazide), forming a chain along the c-axis (molecules are related by a c-glide) (Fig. 4).

Co-crystal **4** has the same hydrogen bonded interactions (see Table 3 for comparison). However, in co-crystal **5** with the same $C_2^2(15)$ pattern, one can see the steric influence of the chosen modifier (cyclooctane) as it sterically hinders the amide proton H(2) from approaching the carbonyl O(4). The donor–acceptor distance for this $C(4)$ chain is 3.740(2) Å but one can still clearly see the amide groups pointing at each other to form a $C(4)$ chain with an angle of 160(2)° (Fig. 5). One might describe this situation as the modifying group "masking" the other hydrogen bonding functionality of the modified isoniazid molecules. Note

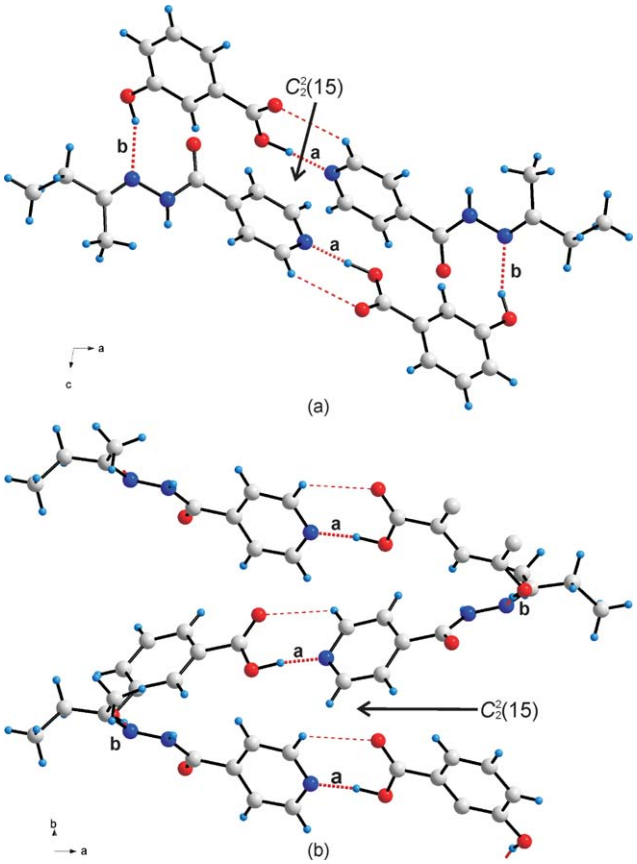


Fig. 3 Two views of the $C_2^2(15)$ chains formed by the COOH···N_{pyr} (**a**) and the OH···N=C (**b**) hydrogen bonds in co-crystal **3** that has butan-2-ylidene as the modifier group. Note that the butan-2-ylidene modifier has no influence on the :N(3) lone pair.

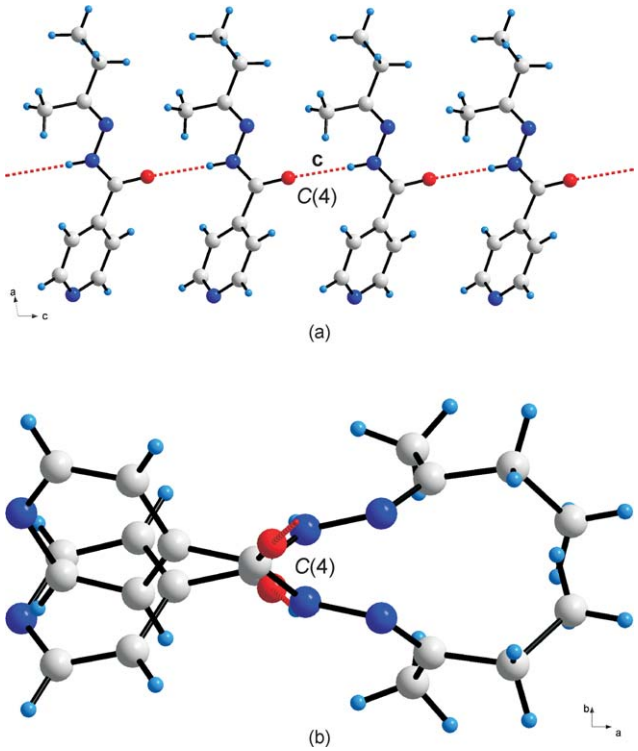


Fig. 4 Two views of the *C*(4) homosynthon formed by the N(2)–H(2)···O(4) (**c**) hydrogen bond in co-crystal **3**. Note that the butan-2-ylidene modifier has no influence on the *C*(4) homosynthon. All it has done is remove the two amine H atoms found on the original isoniazid molecule.

the relative arrangement of the modified isoniazid molecules (*N*′-(cyclooctylidene)iso-nicotinohydrazide), which have overlapping pyridine rings but with the modifiers apart (Fig. 6). This arrangement is also seen in **4** and **5**.

Group 2 contains co-crystals **2** and **6**. The former has an isolated $R_4^4(30)$ ring formed by the COOH···N_{pyr} (**a**) and the OH···N=C (**b**) hydrogen bonds, instead of a $C_2^2(15)$ chain (Fig. 7). Nonetheless, it still features the *C*(4) chain as it has the smallest modifying group (acetone). Co-crystal **6** is similar. The ring is $R_4^4(28)$ instead as the phenol hydrogen bonds to the amide oxygen atom O(4) instead of the hydrazone N(3) (Fig. 8). In this case, the bulky modifying group, 4′-methylacetophenone, exerts a steric influence, which prevents the phenol group from hydrogen bonding with N(3) (Fig. 8). Co-crystal **6** also has a *C*(4) homosynthon, but as in the case of co-crystal **5**, the steric bulk of the modifying group hinders the approach of the amide H(2) to the carbonyl O(4), resulting in a non-linear close contact of 135 (2)°. The modified isoniazid molecules in the chain have a parallel orientation to each other, different to the overlapping orientation as seen in **4** and **5** (Fig. 9).

Isoniazid modified with benzophenone (7)

Co-crystal **7** has the bulkiest modifying group, benzophenone, and this has a significant effect on the hydrogen bonding and the crystal packing. The asymmetric unit of this co-crystal contains one modified isoniazid molecule (*N*′-(diphenylmethylene) iso-nicotinohydrazide) and one half a mHBA acid molecule. This is unusual, as the mHBA acid does not have a molecular centre of inversion. However, in this case, the mHBA acid molecule crystallizes with static disorder around a centre of inversion. The mHBA molecule has the carboxylic acid group and four C atoms of the aromatic ring in the asymmetric unit. The carboxylic acid functions as both the carboxylic acid group as well as the phenol group. The two missing C atoms of the aromatic ring are generated by the O(2) atom and the C(7) atom of the carboxylic acid functional group. In other words, the mHBA molecule exists in two different orientations in between the modified isoniazid, shown clearly in Fig. 10a and b. The cause of this unusual arrangement is the modifying group. The benzophenone has made the N(3) atom completely inaccessible for the phenol as an acceptor group. Now, the carbonyl O(4) of the amide is still accessible, but instead the phenol H(3) hydrogen bonds to the pyridine ring, *in an identical fashion to the carboxylic acid*. This requires the H atom of the phenol to point away from the carboxylic acid ring, thus creating an eight-membered chain H(1)–O(1)–C(7)–C(1)–C(1)^{i}–C(7)^{i}–O(1)^{i}–H(1)^{i} with inversion symmetry [(i): $-x+3$, $-y+1$, $-z+1$]. In addition, the amide H(2) has now been completely masked and hence no *C*(4) homosynthon is formed. Hence, we now have a zero-dimensional crystal packing due to the steric bulk of the modifying group masking the H(2) donor and the lone pair of :N(3) of the amide group. The carbonyl O(4) has two lone pairs, which are accessible but due to packing effects, they are not used.

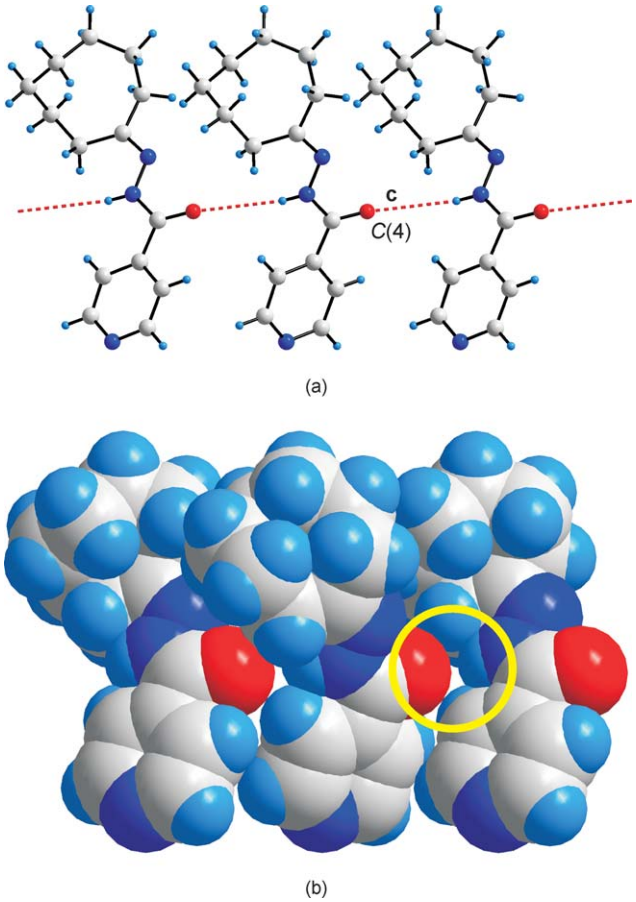


Fig. 5 View of the *C*(4) homosynthon in ball and stick (a) and space filling (b) representations of co-crystal **5**. The yellow circle shows the increased separation between the O(4) acceptor and the H(2) donor due to the modifier group cyclooctylidene. The DHA acceptor angle is 160(2)° and the D···A distance 3.740(2) Å.

The conformation of the pyridine ring is also affected by the new hydrogen bonding. The ring exists in two different conformations relative to the rest of the modified isoniazid molecule, and in addition, to the acid molecule. In one conformation (**A**), the pyridine ring is essentially co-planar with the *N*-acylhydrazone group (N(2)–C(13)–C(8)–C(9A): 2.6°) and the mHBA molecule to form the $R_2^2(7)$ heterosynthon; this is the scenario when the carboxylic acid hydrogen bonds to the pyridine. When the phenol instead hydrogen bonds to the pyridine, the alternative conformation (**B**) of the pyridine ring is adopted, where the torsion angle is 30.9° (N(2)–C(13)–C(8)–C(9B)), and the pyridine ring is not co-planar with either the *N*-acylhydrazone group or the mHBA molecule.

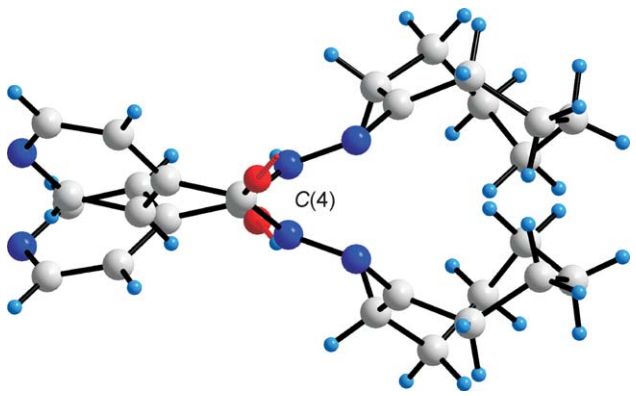


Fig. 6 The relative arrangement of two modified isoniazids in co-crystal **5**, where the steric bulk of the cyclooctylidene modifiers has the pyridine rings overlapping, similarly to the modified isoniazid shown in Fig. 4.

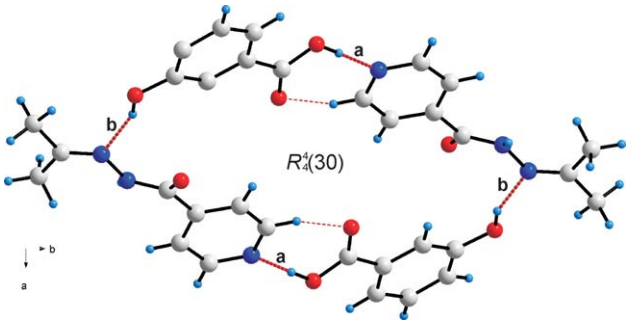


Fig. 7 View of the $R_4^4(30)$ ring formed by the COOH···N_{pyr} (**a**) and the OH···N=C (**b**) hydrogen bonds in co-crystal **2** that has propan-2-ylidene as the modifier group. Note that the propan-2-ylidene modifier has no influence on the :N(3) lone pair.

The hydrates 8–12 using modified isoniazid

The remaining five co-crystals fall into the hydrated co-crystal category. In these structures the reaction side product of the modifying group reaction was incorporated into the co-crystallization reaction and the crystal lattice. Co-crystals **8–12** can all be grouped together. They all show the same hydrogen bonding

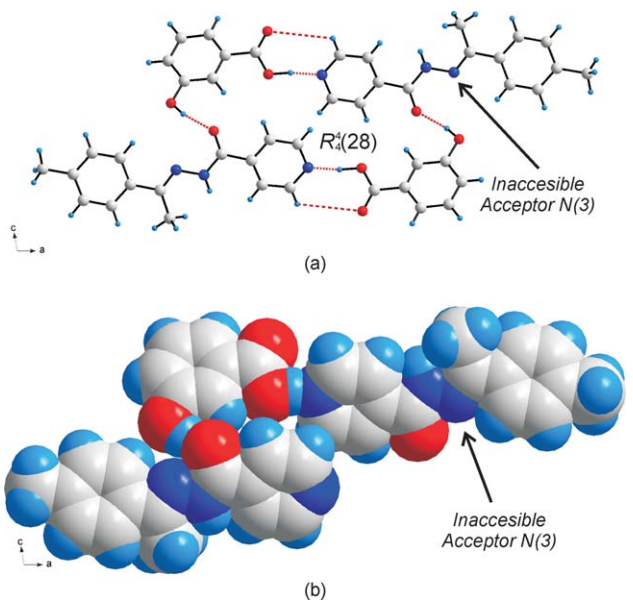


Fig. 8 Ball and stick (a) and space filling (b) views of the $R_4^4(28)$ ring formed by the COOH···N_{pyr} (**a**) and the OH···N=C (**b**) hydrogen bonds in co-crystal **6** that has 1-*p*-tolylethylidene as the modifier group. Note that 1-*p*-tolylethylidene modifier now has a steric or masking influence on the :N(3) lone pair, such that the H(3) hydrogen atom from mHBA now hydrogen bonds to O(4).

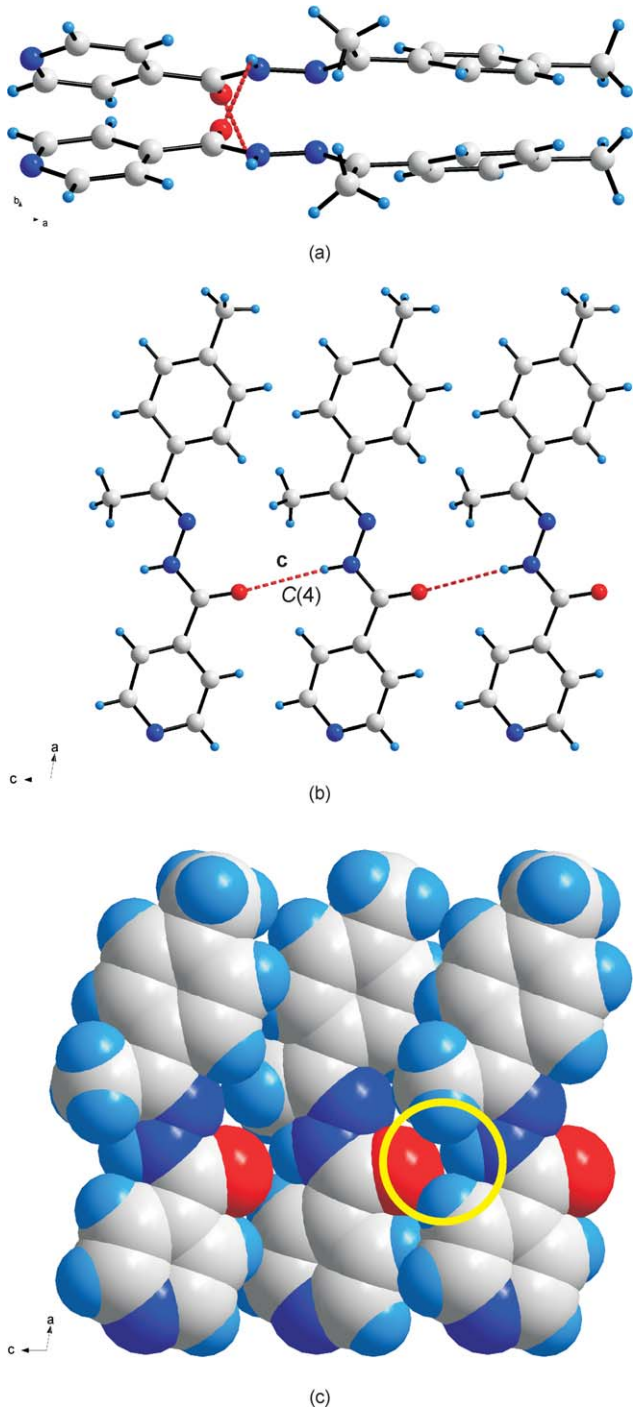


Fig. 9 Two views (a) and (b) of the *C*(4) homosynthon in ball and stick, and space filling (c) representations of co-crystal **6**. The yellow circle shows the increased separation between the O(4) acceptor and the H(2) donor due to the modifier group 1-*p*-tolylethylidene. The DHA acceptor angle is now 135(2)° and the D···A is 3.736(2) Å.

features and crystal packing. Except for **11**, all crystallize in the triclinic space group $P\bar{1}$ and have similar unit cell parameters. Co-crystal **11** has similar *a* and *b* cell axes, but with a doubling of *c* in the monoclinic space group $P2_1/n$ (see Table 2). The hydrogen bonded interactions consist of two rings. The larger ring is identical to the $R_4^4(28)$ ring seen in **6** and uses the **a** and

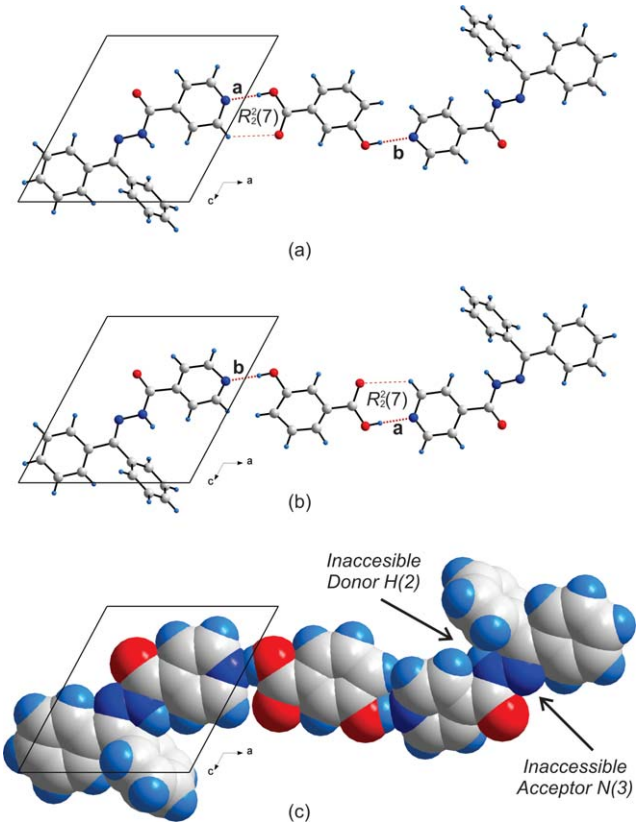


Fig. 10 Two equivalent representations (a and b) of the hydrogen bonding interactions of the modified isoniazid with mHBA. (a) shows conformation **A** and **B**, where the heterosynthon COOH···N_{pyr} (**a**) is part of the asymmetric unit and hydrogen bonds to the modified isoniazid. The heterosynthon OH···N_{pyr} (**b**) hydrogen bonds to the symmetry equivalent modified isoniazid [symmetry operator: $-x+3$, $-y+1$, $-z+1$]. (b) shows the reverse scenario, where the OH···N_{pyr} (**b**) heterosynthon is part of the asymmetric unit. (c) The *C*(4) homosynthon is not observed, as the modifier diphenylmethylene masks both the :N(3) lone pair and the H(2) donor.

b hydrogen bonds. The second, smaller ring, $R_2^2(26)$, uses the O(1)–H(1)···N(1) (**a**), the N(2)–H(2)···O(1W) (**c**) and O(1W)–H(1W)···O(2) (**d**) hydrogen bonds. These two rings alternate to form a 1-D ribbon (Fig. 11a). Adjacent ribbons are connected by the O(1W)–H(2W)···O(2) (**e**) hydrogen bond (Fig. 11b). There are no *C*(4) homosynthons in the hydrated co-crystals, with the amide H(2) hydrogen bonding in each instance to the water molecule.

Discussion

The aim of this work was to prepare co-crystals with isoniazid and mHBA, while concurrently modifying the hydrogen bonding functionality of the isoniazid molecule by adding stoichiometric amounts of simple ketones to the co-crystallization solution. The amount of ketone added was not constant but at least a stoichiometric 1 : 1 ratio to the isoniazid was present each time. The ketones functioned as the co-crystallization solvent in the preparation of **2**, **3** and **4**, respectively acetone, 2-butanone and cyclopentanone, and were used in excess. These are examples in which the modifying group acts as a solvent and no other

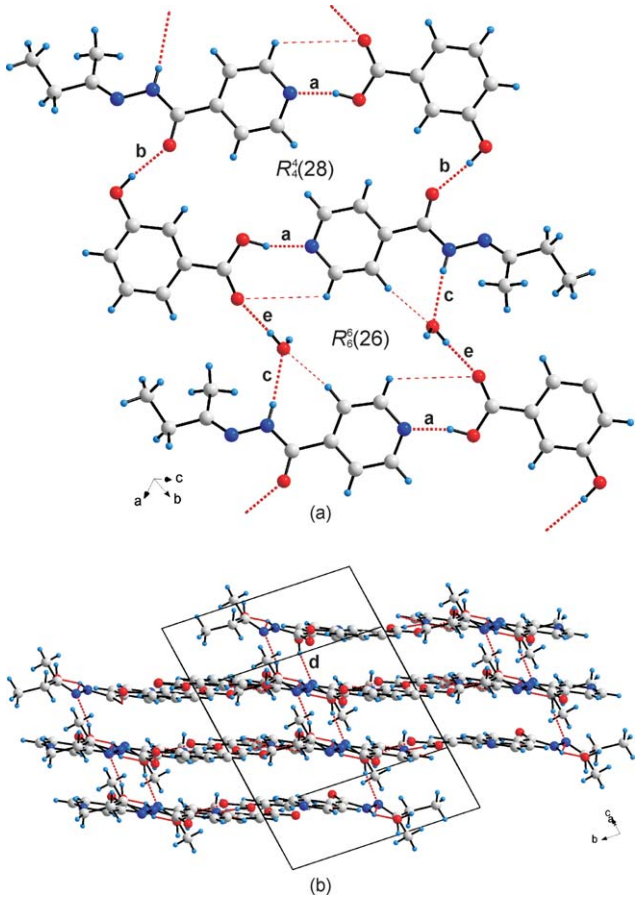
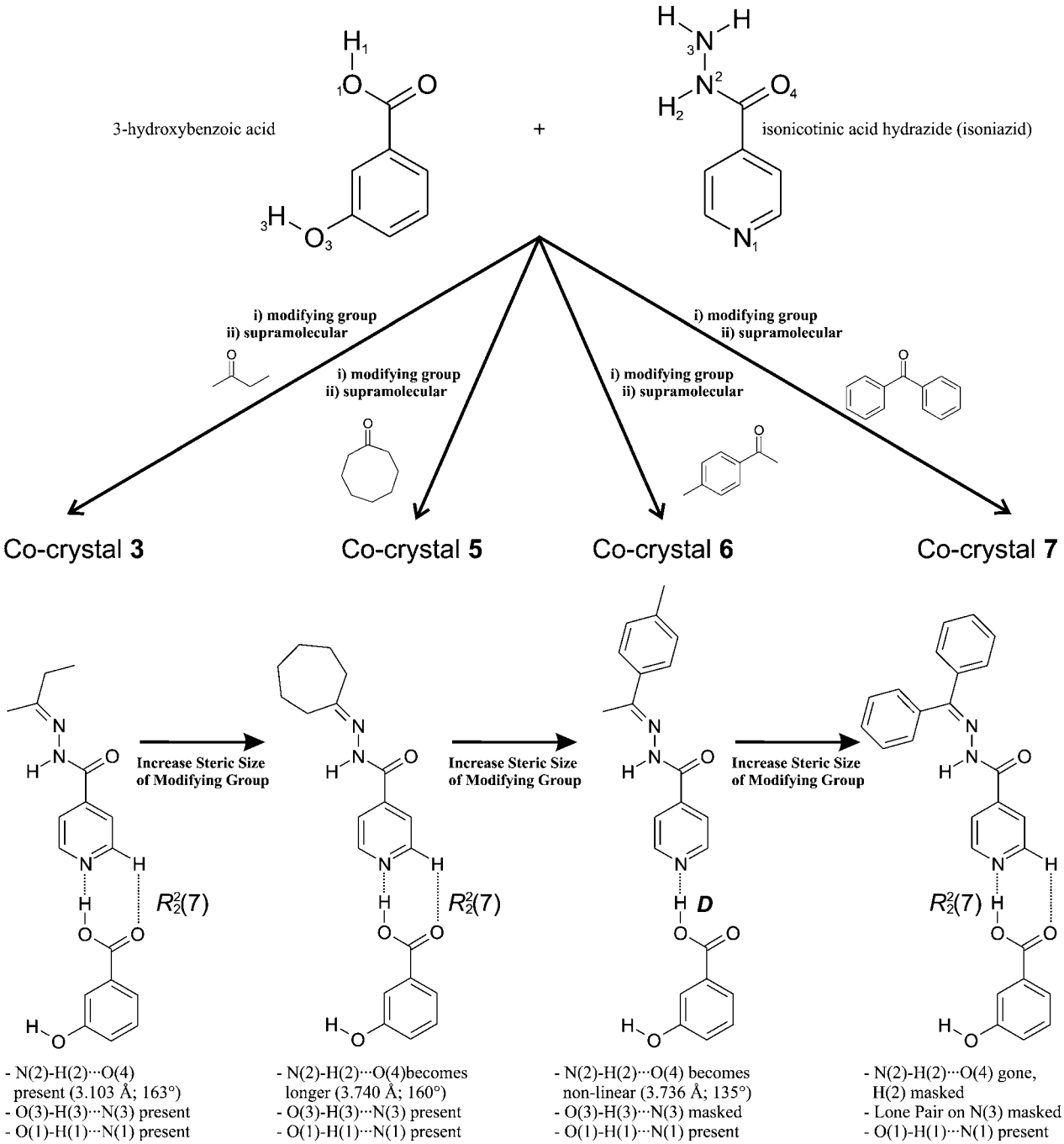


Fig. 11 (a) and (b) show the generic hydrogen bonding and packing architecture for the hydrated co-crystals **8–12**; shown here is co-crystal **8**.

reagents are added. This was possible as the ketones have a sufficiently low boiling point to act as crystallization solvents for slow evaporation, and the isoniazid and mHBA molecules are both soluble in them. For the co-crystals **5**, **6** and **7**, the ketones or aldehydes used were cyclooctanone, 4′-methylacetophenone and benzophenone respectively. In these three cases, the modifiers are not suitable as solvents due to the lack of solubility and high boiling points (benzophenone is a solid and hence completely unsuitable). Stoichiometric amounts of the modifiers were added and all the components dissolved in methanol. In all crystallizations, the condensation reaction was induced by keeping the solutions hot for a few hours. Fortunately, the modified isoniazids remain sufficiently soluble to co-crystallize out with the mHBA, even when large groups are added *e.g.*, benzophenone in **7**. Co-crystals **2–7** all have the two amine hydrogen bond donors of the carbohydrazide group removed from the isoniazid molecule. In this sense, the hydrogen bonding ability of the isoniazid is reduced, *i.e. modified*. This modification was already achieved by using acetone in **2**. The reason for using increasingly larger modifiers was to observe the influence of the chosen modifying groups on the third hydrogen bond donor, the amide H(2), as well as the lone pair of the :N(3) atom. The :N(3) lone pair is adjacent to the site where the modifiers are added, and hence can be easily masked by a suitably sized molecule. This occurs by using a bulky phenyl ring such as in 4′-methylacetophenone and benzophenone. In all the other modifiers employed, the :N(2) lone pair is unmasked and acts as an acceptor for the phenol of the mHBA. The N(2)–H(2) donor is further away from the ketones but is masked by the modifiers cyclooctylidene (**5**), 1-*p*-tolylethylidene (**6**) and diphenylmethylene (**7**). This observation is based on the increase in distance from the H(2) donor to the O(4) carbonyl acceptor of adjacent modified isoniazids, such that the *C*(4) homosynthon becomes a close contact in **5** and **6** and is completely absent in **7**. The *C*(4) homosynthon is still clearly observed in co-crystals with less bulky ketones, as in **2**, **3** and **4**. The *C*(7) homosynthon is never observed, possibly because of the greater acidity and donor ability of the carboxylic acid hydrogen of mHBA over the amide H. Our most successful attempt to modify all the donors of the isoniazid and the acceptor lone pair on :N(3) is co-crystal **7**. Fig. 10c clearly demonstrates how the positions of the two phenyl rings on the modifying diphenylmethylene group fill much of the space around the H(2) donor and the :N(3) lone pair, making them inaccessible and completely *masking* their potential hydrogen bonding interactions. A summary of the modifying and masking effect that best illustrates the concept of covalent assistance to supramolecular synthesis is presented in Scheme 5.

When making these observations on co-crystals **2–7**, where the position of the modifying group relative to the H(2) donor and the :N(3) acceptor has a masking influence, that influence is dependent on the conformation of the modifying group relative to the rest of the isoniazid molecule. There is free rotation around the N(2)–N(3) single bond. In the solid state, we find that the modifying group is rotated such that the N=C double bond is *syn* to the amide H(2) proton (see torsion angles H(2)–N(2)–N(3)–C(14) in Table 5). As a consequence, the torsion angle C(13)–N(2)–N(3)–C(14), listed in Table 5, has its modulus around 180°. This is in fact a very desirable scenario for modifying the hydrogen bonding, as it allows the steric influence to be maximised when attempting to mask the H(2) donor. The reason for this conformation, and the reason for not observing the *anti* case, is most likely the presence of the carbonyl O(4) group, which is bulkier than the H atom. Molecular modelling calculations done on the *N*′-(propan-2-ylidene)isonicotinohydrazide molecule as a model system show that the *anti* conformation is much more stable than the *syn* conformation.§ Nonetheless, there is no apparent reason to rule out other possible conformations, *i.e.* it is theoretically possible to obtain polymorphs of these co-crystals that could have other conformations due to packing effects. These polymorphs could conceivably show different hydrogen bonding patterns due to the different steric consequences.

§ Geometry optimizations were performed with Gaussian 03[38] using the B3LYP method,[39] a density functional theory (DFT) type of calculation with hybrid functionals, and the 6–31+g(d,p) basis set.[40] These show that the barrier to rotation around the N(2)–N(3) bond is 32.9 kJ mol^{-1}, with the *syn*-conformation (C(13)–N(2)–N(3)–C(14) = 0°) 25.0 kJ mol^{-1} higher in energy than the *anti* conformation (180°) found in the crystal structure. According to the Boltzmann equation this difference in energy would result in only 0.0040% of the *syn*-conformation being found in the gas phase. Interestingly the lowest energy conformations are staggered ones, with C(13)–N(2)–N(3)–C(14) torsion angles of ±70°, 7.8 kJ mol^{-1} lower in energy than the crystal structure conformation. However, this corresponds to a conformation around N(2) slightly distorted from planarity, which may lead to a reduction in the strength of the N–H···O hydrogen bond, and is thus not energetically favorable within the crystal structure.



Scheme 5 Summary of the modifying and masking effect of four chosen co-crystals that best illustrate the covalent assistance to supramolecular synthesis concept. The increasing steric size of the modifying group allows for the selective masking of the H(2) donor and N(3) acceptor in co-crystals **3**, **5**, **6** and **7**.

The masking of the lone pair on the :N(3) atom is less influenced by the conformation of the modifying group than by the actual condensation reaction when the modifying group is added. In this case, the unsymmetrical ketones always add such that the lone pair is *syn* to the bulkiest part of the modifying group, *i.e.* the ethyl part in 2-butanone, or the aromatic ring in 4′-methylacetophenone. Hence, the masking of the lone pair can be achieved immediately by adding bulky unsymmetrical ketones.

The hydrate co-crystals were not intended or desired results. The nine ketones were chosen such that the steric effects could be observed for all the different modifiers. The attempts with cyclohexanone, cycloheptanone and 4′-methylbenzaldehyde could therefore not be included in the series of unhydrated co-crystals. Nonetheless, all five hydrated co-crystals contribute to the *in situ* modification concept proposed here.

Co-crystals **8** and **9**, which are the related hydrated versions of the unhydrated co-crystals **2** and **3**, were prepared by carrying

Table 5 Summary of modifications in unhydrated co-crystals **2–7**

	2	**3**	**4**	**5**	**6**	**7**
Modifying group	Propan-2-ylidene	Butan-2-ylidene	Cyclopentylidene	Cyclooctylidene	1-*p*-Tolylethylidene	Diphenylmethylene
Removal of NH_2 donor	Yes	Yes	Yes	Yes	Yes	Yes
Masking of N(2)–H(2) donor	No	No	No	A bit	A bit	Yes
Masking of :N(3) lone pair	No	No	No	No	Yes	Yes
C(4) homosynthon observed	Yes	Yes	Yes	Close contact	Close contact	No
O(1)–H(1)···N(1) heterosynthon	Yes, $R_2^2(7)$	Yes, $R_2^2(7)$	Yes, $R_2^2(7)$	Yes, $R_2^2(7)$	Yes, *D*	Yes, $R_2^2(7)$
O(3)–H(3)···X	N(3)	N(3)	N(3)	N(3)	O(4)	N(1)
Hydrogen bond patterns	$R_4^4(30)$	$C_2^2(15)$	$C_2^2(15)$	$C_2^2(15)$	$R_4^4(28)$	None
Mod. isoniazid: H(2)–N(2)–N(3)–C(14)/°	34.3(2)	8.9(2)	11.7(2)	1.1(2)	1.9(2)	−2.5(2)
Mod. isoniazid: C(13)–N(2)–N(3)–C(14)/°	−167.3(1)	177.7(2)	176.2(1)	−179.9(1)	−177.1(1)	179.5(2)
Mod. isoniazid: N(2)–C(13)–C(8)–C(9)/°	−33.0(2)	−29.4(3)	−26.0(2)	−10.4(2)	−6.3(2)	3.3(6) C(9A), 31.7(6) C(9B)
mHBA: O(1)–C(7)–C(1)–C(2)/°	−173.8(1)	12.2(3)	13.5(2)	16.2(2)	7.2(2)	175(1)[a]

[a] Estimated from O(1)–C(7)–C(1)–C(1)^{i} angle, where (i): $3 - x$, $1 - y$, $1 - z$.

out the crystallization without heating to test if it is possible to obtain co-crystals **2** and **3** (prepared originally by heating the vial). The condensation reaction did occur but led to hydrated co-crystals **8** and **9** of the modified isoniazid and mHBA. The hydrated co-crystals **10–12** were prepared similarly (by heating) in the same way as **2–7**, yet water co-crystallized with them. As mentioned above, water is a by-product of the aptly named "condensation" reaction and hence is unavoidably present when the co-crystallization process starts. One possible strategy for preventing the inclusion of water in the co-crystal structure is the addition of molecular sieves to the crystallization vial as was done previously when preparing both hydrated and unhydrated ammonium sulfonate salts.[41] The crystal packing when there is water present has so far led to isostructurality of the five hydrated co-crystals. Even in the presence of the water molecule, our primary heterosynthon, the O(1)–H(1)···N(1) hydrogen bond, is observed and connects the mHBA with the modified isoniazid. Additionally, the heterosynthon observed in **6**, O(3)–H(3)···O(4), is observed in all five hydrated co-crystals. Hence, all five hydrated co-crystals have the identical $R_4^4(28)$ ring. The similarity ends after that. The H(2) donor, which in the unhydrated co-crystals was used in the *C*(4) homosynthon, now hydrogen bonds to the water. In these hydrated co-crystals, the modifying group is not able to prevent (by masking) the hydrogen bond to the water molecule, mainly as the small size of the water molecule allows it to fit in. The water molecule plays the same hydrogen bonding role in all five structures regardless of the type of modifying group used (see Table 4). The two hydrogen atoms on the water hydrogen bond to N(3) and O(2). It is to be seen in future work if the same architecture is observed with a larger variety of modifying groups. Conformationally, the geometry of the modified isoniazids is identical to the unhydrated co-crystals, where the N=C is *syn* to the amide H(2) (see Table 6 for relevant torsion angles). Curiously, in all five hydrated co-crystals, the :N(3) lone pair is not used as an acceptor; instead the carbonyl O(4) acts as an acceptor to the phenol H(3). This non-use cannot be said to be due to the modifiers, as we have seen in **2** and **3** that it is possible for N(3) to act as an acceptor for the H(3) hydrogen bond donor.

The conformation of the mHBA acid molecule in the co-crystals is consistently planar in terms of the rotation around the C(1)–C(7) bond. The modulus of the torsion angle O(1)–C(7)–C(1)–C(2) is *syn*-periplanar in all co-crystals except for **2** and **7**. This means that the acid H(1) is on the same side as the phenol H(3). In **7**, the two H's are related by a centre of inversion and are necessarily *anti* to each other.

Table 6 Summary of modifications in hydrated co-crystals **8–12**

	8	**9**	**10**	**11**	**12**
Modifying group	Propan-2-ylidene	Butan-2-ylidene	Cyclohexylidene	Cycloheptylidene	4-Methylbenzylidene
Removal of NH_2 donor	Yes	Yes	Yes	Yes	Yes
Masking of :N(3) lone pair[a]	Yes	Yes	Yes	Yes	Yes
C(4) homosynthon	No	No	No	No	No
O(1)–H(1)···N(1) heterosynthon	Yes, $R_2^2(7)$	Yes, $R_2^2(7)$	Yes, $R_2^2(7)$	Yes, $R_2^2(7)$	Yes, $R_2^2(7)$
O(3)–H(3)···O(4)	Yes	Yes	Yes	Yes	Yes
Hydrogen bond patterns	$R_4^4(28)$, $R_6^6(26)$	$R_4^4(28)$, $R_6^6(26)$	$R_4^4(28)$, $R_6^6(26)$	$R_4^4(28)$, $R_6^6(26)$	$R_4^4(28)$, $R_6^6(26)$
Mod. isoniazid: H(2)–N(2)–N(3)–C(14)/°	−24.9(2)	−27.3(2)	−32.7(2)	−37.7(7)	−3.7(2)
Mod. isoniazid: C(13)–N(2)–N(3)–C(14)/°	161.3(2)	157.8(2)	150.9(2)	150.3(1)	176.1(1)
Mod. isoniazid: N(2)–C(13)–C(8)–C(9)/°	−4.9(2)	−9.6(2)	−10.3(2)	−22.1(2)	−4.9(2)
mHBA: O(1)–C(7)–C(1)–C(2)/°	−7.4(2)	1.2(2)	0.6(2)	7.8(2)	−4.5(2)

[a] Not clear if this is due to packing effects or due to the water molecule preferentially hydrogen bonding to the carbonyl O atom.

Conclusion

An additional concept and tool in supramolecular synthesis has been introduced with which to engineer (modify) the assembly of multi-component molecular complexes. By making use of modifying groups, we have exerted some measure of control on how two molecules co-crystallize, by substantially reducing the number of hydrogen bonding interactions, primarily by a covalent reaction and secondarily by the steric influence, masking the remainder of the hydrogen bonding donors and acceptors on the supramolecular reagent isoniazid. What makes this modifying process distinct from previous ones is that it is an *in situ* process, where the modifying process takes place in the same vessel as the co-crystallizing process, and finally, where even the solvent molecules are used as modifying groups.

Acknowledgements

This work was supported in part by Grant No. 2004118 from the United States—Israel Binational Science Foundation (Jerusalem). A.L. thanks the South African National Research Foundation for a postdoctoral scholarship (SFP2007070400002) and the Oppenheimer Memorial Trust for financial support. The authors thank Dr Dmitry Mogilyanski (Ben-Gurion University) and Dr Daniel Többens (University of Innsbruck) for powder diffraction work, Dr Vincent Smith (University of Stellenbosch) for help with refining co-crystal **7**, Dr Catharine Esterhuysen (University of Stellenbosch) for modelling assistance, and Prof. Gautam Desiraju for insightful comments at a poster presentation of some of this work.

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