Molecular Recognition

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Dynamic Molecular Recognition in Solid State for Separating Mixtures of Isomeric Dicarboxylic Acids**

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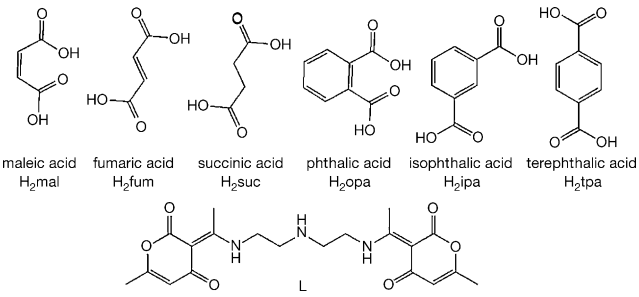
Dedicated to Martin Užarević

Molecular recognition[1] emerges from non-covalent interactions and is of paramount importance for understanding of biological processes, ranging from enzymatic activity to DNA base pairing,[2] as well as in the design of functional supramolecular systems,[3] for example, molecular motors,[4] sensors,[5] ion receptors,[6] or systems used in waste management.[7] In the specific area of selective anion binding, numerous anion receptors (hosts) and sensors have been developed.[8] The study of anion binding has traditionally been performed in solution[9] where the host often experiences conformational freedom to form complexes with a wide range of guests. However, selectivity in separation has usually been achieved only upon crystallization,[10–12] emphasizing the importance of intermolecular interactions in rigid crystal environment which lock the conformation of the host giving rise to its selectivity. In this context, recent advances in chemical reactivity achieved using mechanochemistry indicate that the concepts of supramolecular chemistry, such as templating,[13] may be applicable also to solvent-free reactions.[14] Mechanochemical reactivity can be highly dynamic[15] and has thus far been employed for solid-state differentiation between enantiomers,[16] supramolecular metathesis reactions,[17] and for thermodynamic product selection.[18] Although these reactions show specific interaction patterns between molecules comprising their respective solid phases, the possibility of selective binding and separation of target guest molecules from solid mixtures is, besides the pioneering studies by Etter[19] and Caira,[20] still an unexplored area.



Scheme 1. Dicarboxylic acids and the polyamine host L. The host binds anions as a cation (HL) resulting from protonation of the central amino group.

Here we focus on recognition and separation of isomeric or geometrically similar dicarboxylic acids (Scheme 1) from either their solid or solution mixtures using principles of supramolecular chemistry. The chosen acids belong to a class of guests of high biological[21] and industrial[22] relevance, and a considerable effort has been put into developing their sensors and receptors.[22] Typically, the receptor for each dicarboxylate had to be meticulously designed[23] because of the specific geometry of each acid molecule and their differing physicochemical properties. The importance of separation of the maleic/fumaric acid (H_2mal/H_2fum) stereoisomeric pair is not only related to the specific diastereomer recognition, but also arises from their conflicting biochemical behavior and abundant use of H_2fum in food and pharmaceutical industry.[21,24] We show here that the flexible polyamine receptor L[25,11] (Scheme 1) discriminates among H_2mal/H_2fum diastereomers, succinic acid (H_2suc), and three isomers of benzenedicarboxylic acid, by adapting its conformation and finally forming different solid hydrogen-bonded (HB) frameworks. Regardless of whether the recognition takes place in the solid state by milling or by crystallization from solution, the resulting supramolecular complexes are the same and the selectivity bias of L towards the guest acids is fully retained. Milling improved yields to quantitative and almost eliminated the use of solvent. L proved to be an exceptional receptor for H_2mal, also on the gram scale, excluding it from solid mixtures with even five other acids or from mixtures where there is a large surplus of a competing acid.

Reacting L and H_2mal in methanol (MeOH) or ethanol (EtOH) solutions yielded isoskeletal solvated solids, **1a** (Table 1 and Section S.2 in the Supporting Information),[26]

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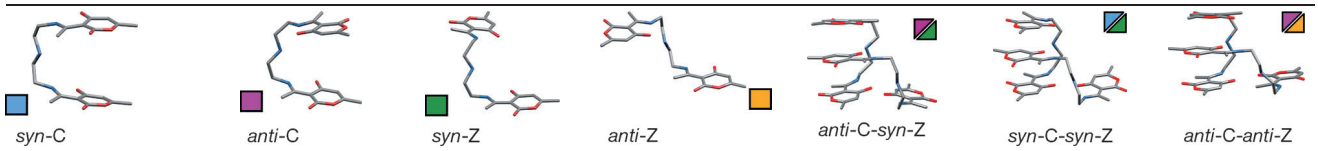
Table 1: Solid products obtained from solution and mechanochemical syntheses. The first row shows various conformations of HL found in the frameworks listed below; each conformation is coded by a colored square (for detailed information please check Section S.5.3 in Supporting Information).



		H_2mal		H_2fum		H_2suc		H_2opa		H_2ipa		H_2tpa	
pK_{a1}, pK_{a2}[a]		5.61(5), 12.24(6)		7.76(3), 9.54(3)		8.83(2), 10.74(3)		7.10(2), 11.27(2)		8.31(1), 9.78(1)		_[b], _[b]	
	liquid	solv[c]	mech[c]	solv	mech	solv	mech	solv	mech	solv	mech	solv	mech
conformation													
structure	MeOH	**1a**	**1c**	**2a**	**2a**	**3a**[d]	**3**[f]	**4a**	**4a**	**5a**	**5a**	**6a**	**6a**
	EtOH	**1a**	**1c**	**2b**[e]	**2**[e]	**3b**[d]	**3**[f]	**4a**	**4a**	**5a**	**5a**	_[b]	**6**[d]
	MeCN	**1b**	**1c**	**2c**	**2c**	**3c**	**3c**	**4a**	**4a**	**5a**	**5a**	_[b]	**6**[d]
	$CHCl_3$	_[b]	**1b**	_[b]	**2d**[d]	_[b]	**3**[f]	_[b]	**4a**	_[b]	**5a**	_[b]	**6**[d]
	NG		**1b**		**2d**[d]		**3**[f]		**4a**		**5a**		**6**[d]

[a] pK_a values in methanol at (25.0±0.1) °C and I_c = 0.01 mol dm^{-3} (Et_4NCl). [b] Reactants not soluble. [c] solv: solution synthesis, mech: milling. [d] Crystal structure not determined. [e] Conformer type is *syn*-C-*syn*-Z. [f] PXRD patterns for milling products were of poor quality and complexation was confirmed by FTIR spectroscopy.

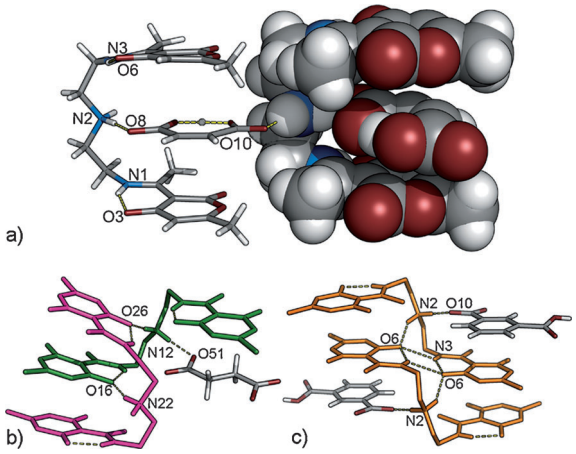


Figure 1. a) HL·Hmal complex (**1**). Hmal is anchored to HL by a strong HB between the two pyrone rings [*d*(pyrones Cg···Cg) = 6.6 Å]. b) CZ dimer in the **3c** framework. HL molecules in the dimer are associated by HBs; two dimers encapsulate the suc dianion; C conformer (green); Z conformer (purple). c) ZZ dimer of two HL cations (orange) in the framework **5a**. HL cations use the remaining N–H donors to bind the Hipa.

which are built from HL·Hmal supramolecular complexes (**1**, Figure 1a). Complexation in acetonitrile (MeCN) resulted in a nonsolvated HB framework **1b**. Neat grinding (NG) of reactants as well as liquid-assisted grinding (LAG) demonstrated that this multi-step process, which involves proton transfer and complexation, also takes place in solid state (Section S.2.3).

Mechanosynthesis resulted in quantitative yields of **1** in two solvent-free HB networks, the tetragonal **1b** (NG or LAG with $CHCl_3$) and the monoclinic **1c** (LAG with MeCN, MeOH, and EtOH). Further, NG of **1a** yielded an amorphous phase **1d** while LAG (MeCN or MeOH) transformed **1a** to **1c** (Figure S8).

Self-assembly of L with H_2fum resulted in two HB networks: **2a** from MeOH and **2b** from EtOH, where HL binds different anions (Hfum and fum in **2a** and Hfum in **2b**). Reaction of L with H_2fum or with H_2suc in MeCN yielded isostructural HB solids **2c** and **3c,** respectively, where the acid molecules are found in all three protonation states. The same complexes were obtained using LAG (MeCN), as confirmed by FTIR spectroscopy; the PXRD data were ambiguous because of poorly diffracting products (Sections S.2 and S.4).

Among the three benzenedicarboxylic acids, the *ortho* isomer, phthalic acid (H_2opa), readily gave the complex HL·Hopa (**4**) in a tetragonal HB framework (**4a**), from MeOH solution and by grinding. Recognition of isophthalic acid (H_2ipa) and terephthalic acid (H_2tpa) resulted in new types of supramolecular complexes, HL·Hipa (**5**) and $(HL)_2$·(Htpa)·1/2(tpa) (**6**), and the corresponding HB solids, **5a** and **6a**. The solubility of H_2tpa was too low for solution experiments, but complexation with HL was achieved quantitatively by LAG using MeOH, yielding **6a**.

Crystal structures of the complexes revealed conformational adaptability of HL towards specific geometries of each acid (Section S.5). In ten crystal structures we found altogether 18 conformers of HL. Based on the relative positions and orientations of the pyrone fragments, these can be grouped in four main conformer types (Table 1 and Section S.5.3). With Hmal and Hopa, molecular tweezers (*syn*-C conformer) anchors the anion by an N–H···O hydrogen bond (Figure 1a and Sections S.5.4 and S.5.8). Neighboring complexes are linked over Hmal by N2–H···O10 hydrogen bonds, forming chains, which assemble into layers leaving pockets which in **1a** accommodate solvent molecules (Figure 2a). In **1c** these voids remain empty and shrink (Figure 2b). **1a** and **1b** differ in stacking of HB layers in the final 3D framework (Section S.5.4).

In **2a–c**, **3c**, and **6a** two HL cations form dimers (CZ dimers), where instead of an anion, one HL (C conformer) anchors by an N–H···O hydrogen bond the pyrone moiety of

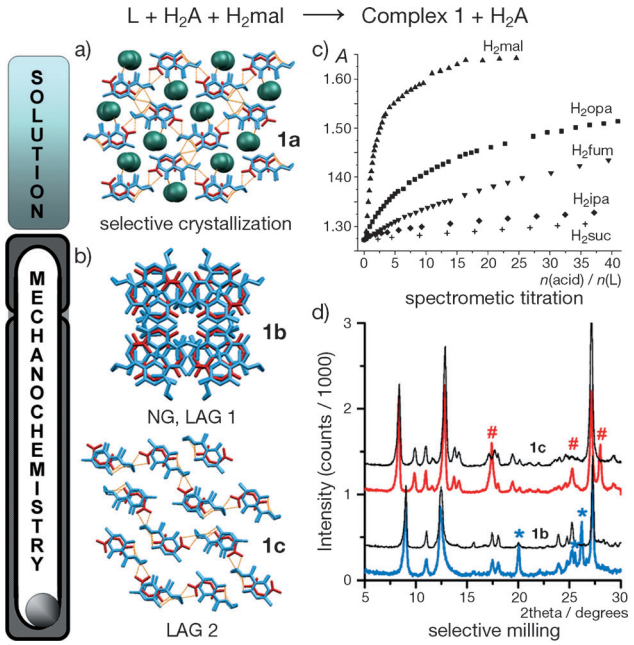


Figure 2. a) HL binds Hmal from binary mixtures with other acids to form a) **1a** from solution and b) **1b** or **1c** using mechanochemistry; LAG 1 used $CHCl_3$ whereas LAG 2 used MeOH or MeCN. c) Spectral changes at 312 nm arising from complex formation upon addition of dicarboxylic acid solutions to the solution of L ($c = 5 \times 10^{-5}$ mol dm^{-3}); solvent: MeOH and *A*: absorbance. d) Powder XRD patterns during selective milling. Blue: mixture after grinding of L with H_2mal/H_2suc where the peaks belonging to H_2suc are marked with (⁎). Red: mixture after grinding of L with H_2mal/H_2tpa where the peaks belonging to H_2tpa are marked with (#).

the other HL (*syn*- or *anti*-Z conformers; Figure 1b, Sections S.5.5 to S.5.7, and S.5.10). The anions are bound by N–H···O hydrogen bonds involving the protonated N–H of both conformers. HL in the C conformation was not observed in the previously described supramolecular complexes[11,12] so it seems that the formation of tweezers is particularly beneficial for planar HB acceptors. Nearly identical supramolecular architectures in **4a**/**1b** and **2c**/**3c** pairs suggest also a templating role of the acid, since the carboxylic groups in Hmal/Hopa and Hfum/Hsuc pairs are in similar relative arrangements (Scheme 1). The only crystal structure where HL does not assume the C conformation is **5a** where two HL cations assume the *anti*-Z conformation and form a ZZ dimer (Figure 1c). Hipa anions form HB chains surrounded by ZZ dimers (Section S.5.9). The structure of **6a** reveals an identical HB pattern between the HL and anions as in other CZ dimers (Section S.5.10) while the anions assemble as in **2a**.

Competitive crystallization experiments from MeOH containing pairs of dicarboxylic acids (each in 1:1 molar ratio to L) revealed the highest affinity of L for H_2mal, yielding **1a** exclusively (Table S12). H_2tpa was not included in solution-affinity studies because of its poor solubility in methanol. Altogether, the established selectivity follows the series [Eq. (1)]:

$$H_2mal > H_2opa > H_2ipa > H_2fum \approx H_2suc \quad (1)$$

Among several equilibria in methanol solution (including deprotonation of the acid, protonation of L and binding of the anion), changes in the UV/Vis spectra observed upon addition of acid solutions into the solution of L were mainly caused by complexation.[12] Spectrophotometric titrations revealed that binding affinities in solution matched those observed by crystallization, with the steepest titration curve obtained for complexation of Hmal (Figure 2c). The absence of spectral changes during titrations where the acid solution was replaced by a hydrogencarboxylate salt solution indicated that the protonation of L was the key step for complexation (Sections S.6.4 and S.6.5). Thus, the selectivity of HL for Hmal in MeOH could have been determined by the lowest pK_{a1} value of H_2mal (Table 1). By deprotonation, H_2mal would ensure formation of HL, leaving at the same time the competing acids fully protonated and inactive for binding with HL (Section S.6.3). Thus, in another series of competitive crystallizations, we have replaced H_2mal by NaHmal whereas the competitors were introduced as acids. The observed selectivity trend was identical to the one established previously, with **1a** being the exclusive product of crystallization, albeit in lower yields (Section S.7). This suggested that the selectivity of HL towards Hmal is not solely the result of highest acidity of H_2mal, but also of specific interactions within the HL·Hmal complex, with yields dependent on the protonation extent.

The affinity of L towards the solid acids was tested by selective milling experiments where the L was ground with solid mixtures of dicarboxylic acids (Section S.8). NG or LAG ($CHCl_3$) of L, H_2mal, and equimolar amount of other inspected acids yielded the **1b** framework quantitatively. LAG using MeOH or MeCN yielded **1c** in all cases except for the H_2mal/H_2opa mixture where **1b** was harvested. Whereas L and H_2mal were always fully consumed, each competing acid remained as a distinct solid (Figure 2d and S95–S99).

The ultimate test for selectivity of HL towards Hmal was a milling experiment where L was ground with a mixture of all six acids. Complex **1** was invariably formed: LAG with MeOH or MeCN yielded **1c** whereas **1d** was obtained in NG and LAG using $CHCl_3$. When L was milled with H_2mal and H_2fum or H_2opa in 1:1:10 ratio, **1** was again obtained, with no traces of H_2mal or complexes **2** or **4** (Section S.8.4). The relative selectivity of L for the other acids was established analogously (Figures S100–S109). In selective milling experiments, molecular recognition and binding were not hindered by solvent properties and by poor solubility of the reactants as was the case for H_2tpa in solution experiments. The selectivity bias in mechanochemical reactions thus extended the one determined in competitive crystallizations, leading to the following sequence (Eq. (2); Table S13 and Section S.8.1):

$$H_2mal > H_2opa > H_2ipa > H_2fum \approx H_2suc > H_2tpa \quad (2)$$

To better understand the dynamics of the solid state recognition and binding processes we investigated NG and LAG (using MeCN or $CHCl_3$) of L with mixtures of H_2mal/H_2fum and H_2mal/H_2opa in a time-resolved manner (Section S.8.2). Time-resolved NG resulted in product amorphization after 20 minutes of milling. However, LAG using

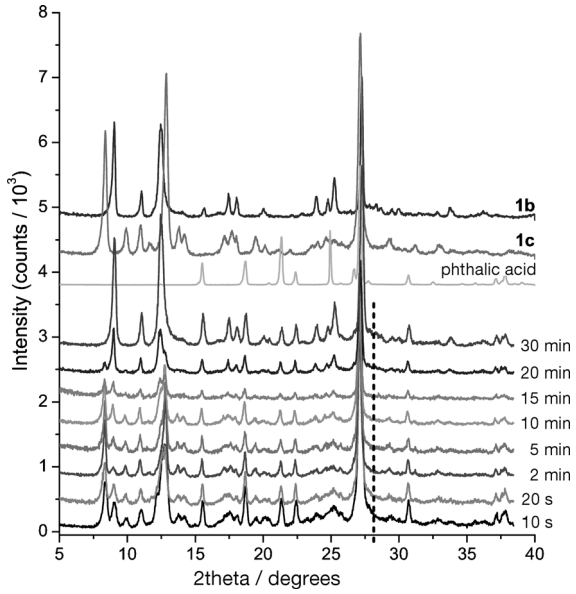


Figure 3. Time-resolved diffractograms of L/H_2mal/H_2opa mixture during the LAG (MeCN). No traces of free L or H_2mal could be observed after 20 s of milling. The dashed black line at $2\theta \approx 28°$ marks the position of the strongest reflection of H_2mal.

MeCN accelerated the formation of **1** and the complexation was finished after only 20 s (in NG after 120 s; in LAG using $CHCl_3$ after 60 s). In the H_2mal/H_2opa competing system, the initially formed **1c** was transformed to **1b** after 30 minutes of LAG using MeCN (Figure 3). In the LAG using $CHCl_3$, exclusively **1b** was observed, resulting in a **1b**/H_2opa mixture. Since each acid readily reacted with L, it seemed surprising that only complexes with Hmal were detected, even at the very early stages of grinding.

Another set of milling experiments revealed that H_2mal readily displaced other acids from their already formed solid complexes. Solids **2a** and **4a** were subjected to LAG ($CHCl_3$) with H_2mal in 1:1 molar ratio. Pure **1b** was obtained in both cases, whereas Hfum and Hopa were displaced from their complexes as solid acids (Section S.8.3).

The detection of complexes with other acids during milling could thus have been hindered by fast exchange reactions in the ball mill. Indeed, manual neat grinding of a mixture of L/H_2mal/H_2opa in an agate mortar first showed traces of transient **4a**; Hopa was later replaced by Hmal finally yielding **1b**. In addition, when the MeCN slurry of solid H_2mal and complexes **2**–**6** was stirred for 5 h, Hmal replaced the anions from their complexes yielding **1b**. Thus, selectivity in separation of Hmal seems to be based on thermodynamic stability of solids comprised of **1**.

Finally, we have tested the practical applicability of selective binding in a gram-scale (Section S.8.5). We based separation on the difference in solubilities of solids comprising **1** and pure acids. Thus, grinding the mixture of acids with L yielded solid mixture of **1a** and the competing acid. The latter was separated by immersing in the minimal amount of an appropriate solvent (e.g. MeCN or EtOH) in which the acids dissolved while **1a** remained as a solid (Figure S120 and S121, Section S.8.6). H_2mal and L were recovered from **1** by addition of a suitable base, and separated by extracting L with CH_2Cl_2.

To summarize, we have shown that the anion recognition and separation can be performed effectively in the solid state by mechanochemistry with the same selectivity bias as obtained by solution crystallization. The host L readily formed supramolecular complexes with six investigated dicarboxylic acids regardless of whether the reaction was conducted in solution or in solid state. However, L proved to be an exceptional receptor for maleic acid, binding it from both solution and solid mixtures even with large excess of competitors. Notably, mechanochemical routes circumvent limitations of solution-based separation, as evidenced by facile binding of poorly soluble terephthalic acid, while at the same time providing enough energy and mobility to the host and guest molecules required for selective recognition. Taken together, these results indicate a vast potential of molecular recognition in the solid state for separation purposes.

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[26] All Figures and Sections denoted with "S" are part of the Supporting Information.

