Supplementary Information

Design and Synthesis of Solid State Structures with Conjugate Acid-Base Pair Interactions

Sathyanarayana Reddy Perumalla and Changquan Calvin Sun*

Department of Pharmaceutics, College of Pharmacy, University of Minnesota,
9-127B Weaver-Densford Hall, 308 Harvard Street S.E., Minneapolis, MN 55455.
Fax: 612-626-2125; Tel: 612-624-3722; Email: sunx0053@umn.edu

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S1. Experimental section

S-naproxen and S-naproxen sodium were purchased from Aldrich and Spectrum Chemicals respectively. Nicotinamide was purchased from Fluka. All these materials were used as received without further purification. Nicotinamide hydrochloride was prepared by adding an excess amount of concentrated hydrochloric acid to an ethanol solution of nicotinamide followed by slow evaporation at room temperature. The resultant phase was confirmed to be the same as the reported structure [1] by powder X-ray diffraction (Figure S1). Nicotinamide hydrochloride thus obtained was used to prepare Nicotinamide hemi hydrochloride hydrate, **2**.

[1] A. I. Gubin, N. N. Nurakhmetov, M. Z. Buranbaev, R. I. Mul'kina, R. S. Erkasov, *Kristallografiya* **1989**, *34*, 238-239.

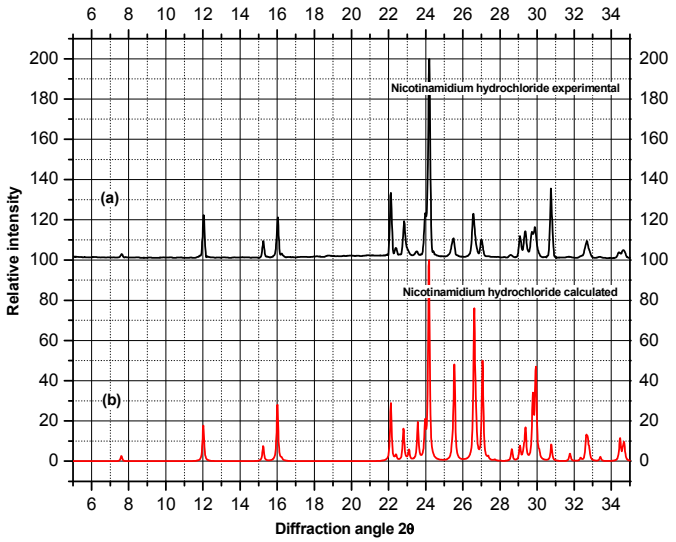

Figure S1. Comparison of experimental and calculated powder patterns of nicotinamidium hydrochloride.

Syntheses of sodium hydrogen bis(naproxate) methanol solvate, 1, single crystals:

Method 1: 115 mg of Naproxen (**NAP**) (0.5 mmol) and 126 mg Naproxen sodium (**NapNa**) (0.5 mmol) were dissolved in 1.4 ml of hot methanol. The resultant solution was filtered and the vial was kept at room temperature. Good quality single crystals were obtained in about one week.

Method 2: 230 mg of Naproxen (NAP) (1 mmol) and 41 mg sodium acetate (0.5 mmol), 2:1 equivalent, were dissolved in 2.6 ml of hot methanol and the resulting solution was kept at room temperature. Good quality single crystals were obtained in about one week.

Synthesis of nicotinamide hemi hydrochloride hydrate, 2, single crystals: 244 mg of nicotinimide and 318 mg nicotinimide hydrochloride, 1:1 equivalent, were dissolved in 5 ml ethanol-water (1:1 v/v) mixture and the resulting solution was kept at room temperature for slow evaporation. Good quality crystals were grown in two weeks.

Slurry experiments: Slurry was made by suspending 1:1 equivalents of conjugate acid base pairs (i.e., NAP:NAPNa and NICA:NICAHCl) in a solvent. The resultant mixture was stirred for three days followed by evaporating the solvent at room temperature. The resultant crystalline materials were analyzed by X-ray diffraction methods.

In case of NAP, all the resultant crystalline materials were mixture of initial components except from DMF, where large crystals were grown in the slurry. Subsequently single crystal X-ray analysis confirmed it as a naproxen sodium dimethyl formamide solvate, **3** (See Figure S2 and Table S4 for details). The dried solid was a mixture of **3** and NAP based

on powder X-ray data. CCDC 856966 contains the supplementary crystallographic data for this Structure.

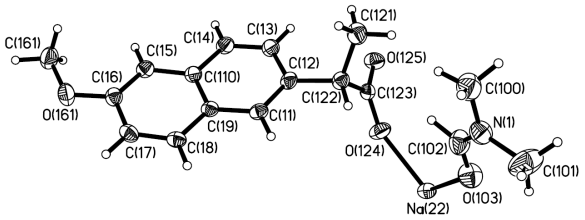

Figure S2. ORTEP (50% probability level) diagram of Naproxen sodium dimethyl formamide solvate, **3**, isolated while screening for a new solid form with conjugate acid-base interactions.

In case of NICA from ten different solvents the resultant crystalline materials were mixtures of starting materials and **2** (Figures S3 and S4).

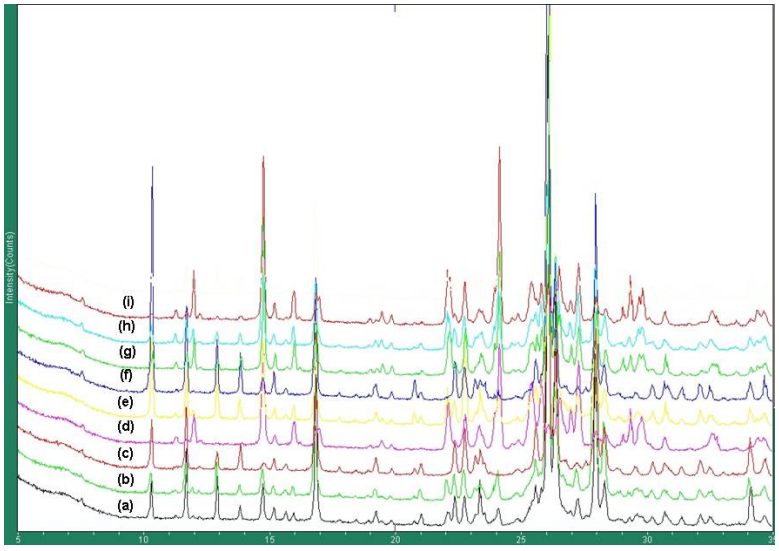

Figure S3. PXRD patterns of the crystalline materials obtained form (a) Methanol (b) Ethanol (c) water (d) Chloroform (e) Isopropyl alcohol (f) N,N-dimethyl formamide (g) Acetone (h) Ethyl acetate, and (i) Acetonitrile.

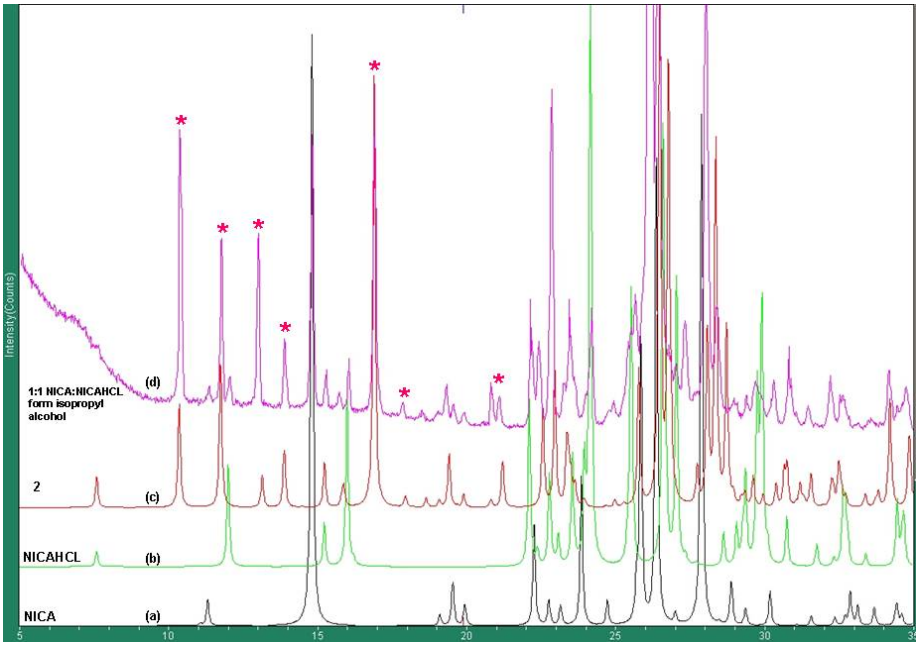

Figure S4. PXRD patterns of (a) NICA (calculated) (b) NICAHCl (calculated) (c) **2** (calculated)**,** and (d) powder obtained from Isopropyl alcohol. The presence of diffraction peaks (highlighted by stars), matching those of 2, indicates partial conversion of starting powders to **2**.

S2. X-Ray difference Fourier maps used to locate the positions of hydrogen involved in conjugate acid-base pair interactions in crystal 1 and 2.

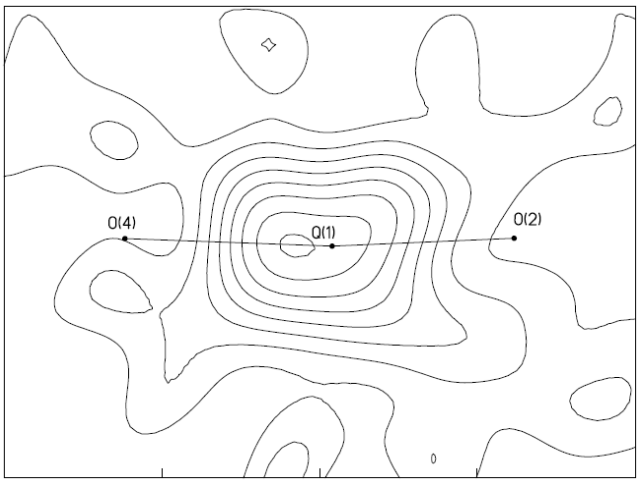

Figure S5. X-Ray difference Fourier map in the region surrounding O4 and O2 in the crystal structure of **1** indicates that the hydrogen is diffused between them.

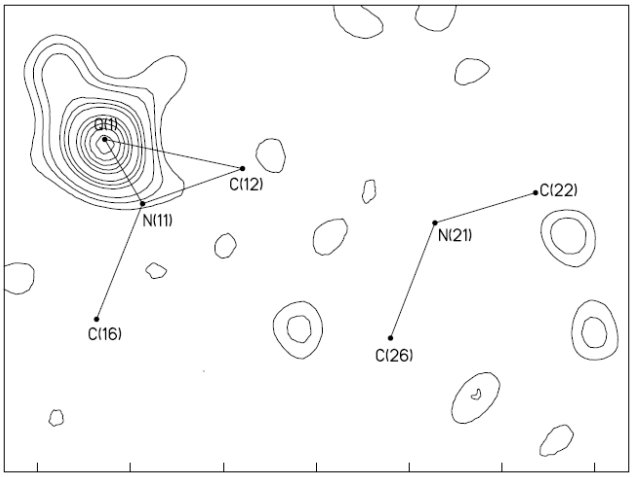

Figure S6. X-Ray difference Fourier map of **2** shows the single maximum of 0.69 e $Å^{-3}$, corresponding to the hydrogen, near N11**.** The asymmetric nature of the hydrogen position reflects the different chemical environments surrounding the two nicotinamide molecules.

It is usually difficult to locate the exact position of hydrogen by X-ray diffraction. However, regardless the exact position of hydrogen, it is clear that the hydrogen bond interaction between acid-base conjugated pair is present in both crystals.

S3. X-Ray crystallographic data collection strategy and refinement

All crystals were placed onto the tip of a 0.1 mm diameter glass fiber and mounted on a Siemens CCD area detector diffractometer for a data collection at 173(2) K using MoK_α radiation (graphite monochromator).[1] The intensity data were corrected for absorption and decay (SADABS).[2] The structure was solved using Bruker SHELXTL and refined using Bruker SHELXTL.[3,4] A direct-methods solution was calculated, which provided most non-hydrogen atoms from the E-map. Full-matrix least squares/difference Fourier cycles were performed, which located the remaining non-hydrogen atoms. All non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms for structures **1** and **2** were located from the difference Fourier map except for -CH3

hydrogen atoms on the methanol molecules in **1,** which were placed in idealized positions and allowed to ride on their parent atoms in the refinement cycles. All hydrogen atoms for structure **3** were placed in idealized positions and allowed to ride on their parent atoms in the refinement cycles. Details of hydrogen bond distances[5] in the crystal structures of **1** and **2** are given in Table S1.

Data collection and structure solution were conducted at the X-Ray Crystallographic Laboratory, S146 Kolthoff Hall, Department of Chemistry, University of Minnesota.

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1 SMART V5.054, Bruker Analytical X-ray Systems, Madison, WI (2001).

2 An empirical correction for absorption anisotropy,R. Blessing, *Acta Cryst.* **A51**, 33-38(1995).

3 SAINT+ V6.45, Bruker Analytical X-Ray Systems,Madison, WI (2003).

4 SHELXTL V6.14, Bruker Analytical X-Ray Systems,Madison, WI (2000).

5 A. L. Spek, *Acta. Cryst.***A46**, C34 (1990). PLATON, A Multipurpose Crystallographic Tool, Utrecht University, Utrecht, The Netherlands, A. L.Spek (2000).

Table S1. Hydrogen bond distances (Å) and angles (°) in the crystal structures of **1** and **2**.

D-H···A[a]	D-H(Å)	H···A(Å)	D···A(Å)	D-H···A(deg)
Sodium hydrogen bis(naproxate) methanol solvate, **1**				
O(5)-H(5A)···O(261)	0.99(4)	1.84(4)	2.825(2)	170(3)
O(6)-H(6)···O(161)	0.87(3)	2.06(3)	2.883(2)	157(3)
O(2)-H(2)···O(4)	1.18(3)	1.30(3)	2.4781(19)	177(3)
C(13)-H(13)···O(1)	0.99(2)	2.33(2)	3.270(2)	159.4(18)
C(23)-H(23)···O(3)	0.98(2)	2.44(2)	3.392(2)	167.2(17)
Nicotinamide hemihydrochloride hydrate, **2**				
O(100)-H(101)···Cl(1)	0.84(3)	2.36(3)	3.207(2)	178(2)
O(100)-H(102)···Cl(1)	0.79(2)	2.37(2)	3.1517(16)	170(2)
N(11)-H(11)···N(21)	0.92(2)	1.85(2)	2.7694(19)	175.9(18)
N(17)-H(17A)···Cl(1)	0.90(2)	2.38(2)	3.2749(15)	174.1(17)
N(17)-H(17B)···O(27)	0.882(18)	2.031(19)	2.9120(18)	179(3)
N(27)-H(27A)···O(100)	0.88(2)	2.02(2)	2.894(2)	173.4(17)
N(27)-H(27B)···O(17)	0.880(18)	2.078(19)	2.9536(18)	172.6(19)
C(12)-H(12)···Cl(1)	0.975(16)	2.490(16)	3.4019(16)	155.7(12)
C(16)-H(16)···Cl(1)	0.955(18)	2.676(18)	3.4193(17)	135.1(14)

[a] D= Donar, A= Acceptor

Table S2. Crystal data and structure refinement for **1**.

Empirical formula	C30 H35 Na O8	
Formula weight	546.57	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 8.8921(12) Å	α = 90°.
	b = 5.7750(8) Å	β = 95.899(3)°.
	c = 26.920(4) Å	γ = 90°.
Volume	1375.1(3) Å^3	
Z	2	
Density (calculated)	1.320 Mg/m^3	
Absorption coefficient	0.108 mm^{-1}	
F(000)	580	
Crystal size	0.45 x 0.36 x 0.33 mm^3	
Theta range for data collection	0.76 to 27.52°.	
Index ranges	-11<=h<=11, -7<=k<=7, -34<=l<=35	
Reflections collected	16083	
Independent reflections	6255 [R(int) = 0.0249]	
Completeness to theta = 27.52°	99.4 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9652 and 0.9530	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6255 / 1 / 468	
Goodness-of-fit on F^2	1.037	
Final R indices [I>2sigma(I)]	R1 = 0.0374, wR2 = 0.0903	
R indices (all data)	R1 = 0.0497, wR2 = 0.0957	
Absolute structure parameter	0.0(4)	
Largest diff. peak and hole	0.204 and -0.261 e.Å^{-3}	

Table S3. Crystal data and structure refinement for **2**.

Empirical formula	C12 H15 Cl N4 O3	
Formula weight	298.73	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 6.8600(10) Å	α = 78.960(2)°.
	b = 8.7768(12) Å	β = 82.287(2)°.
	c = 11.8950(16) Å	γ = 80.200(2)°.
Volume	688.84(17) Å^3	
Z	2	
Density (calculated)	1.440 Mg/m^3	
Absorption coefficient	0.291 mm^{-1}	
F(000)	312	
Crystal size	0.36 x 0.28 x 0.20 mm^3	
Theta range for data collection	1.75 to 26.42°.	
Index ranges	-8<=h<=8, -10<=k<=10, -14<=l<=14	
Reflections collected	7622	
Independent reflections	2813 [R(int) = 0.0240]	
Completeness to theta = 26.42°	99.4 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9441 and 0.9026	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2813 / 0 / 241	
Goodness-of-fit on F^2	1.018	
Final R indices [I>2sigma(I)]	R1 = 0.0313, wR2 = 0.0809	
R indices (all data)	R1 = 0.0428, wR2 = 0.0861	
Largest diff. peak and hole	0.210 and -0.268 e.Å^{-3}	

Table S4. Crystal data and structure refinement for **3**.

Empirical formula	C17 H20 N Na O4	
Formula weight	325.33	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 8.5777(12) Å	α = 90°.
	b = 5.8968(8) Å	β = 92.350(2)°.
	c = 16.506(2) Å	γ = 90°.
Volume	834.2(2) Å^3	
Z	2	
Density (calculated)	1.295 Mg/m^3	
Absorption coefficient	0.114 mm^{-1}	
F(000)	344	
Crystal size	0.38 x 0.32 x 0.19 mm^3	
Theta range for data collection	2.38 to 26.39°.	
Index ranges	-10<=h<=10, -7<=k<=7, -20<=l<=20	
Reflections collected	9218	
Independent reflections	3395 [R(int) = 0.0191]	
Completeness to theta = 26.39°	99.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9787 and 0.9581	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3395 / 1 / 216	
Goodness-of-fit on F^2	1.050	
Final R indices [I>2sigma(I)]	R1 = 0.0315, wR2 = 0.0813	
R indices (all data)	R1 = 0.0354, wR2 = 0.0837	
Absolute structure parameter	0.2(3)	
Largest diff. peak and hole	0.328 and -0.241 e.Å^{-3}	