Supporting Information for

Characterization of Ephedrine HCl and Pseudoephedrine HCl Using Quadrupolar NMR Crystallography Guided Crystal Structure Prediction

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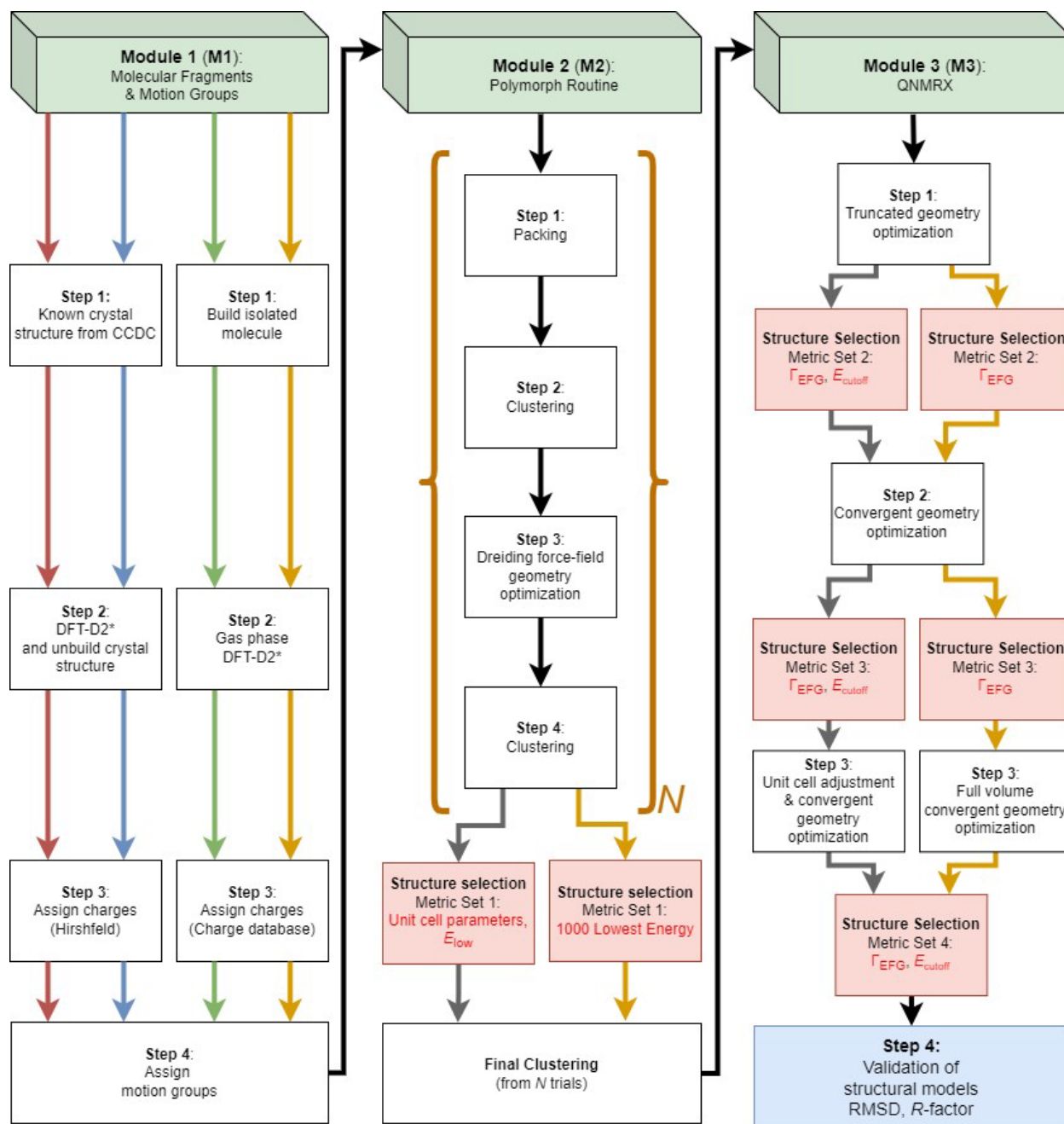[2] National High Magnetic Field Laboratory, Tallahassee, FL, 32310
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Scheme S1. QNMRX-CSP protocol flowchart. The red path indicates the benchmarking of the protocol starting from the known crystal structure (**§3.2.1**), the green path indicates the benchmarking of the protocol starting from a refined isolated molecule (**§3.2.2**), the blue path indicates the application **§3.2.3**, the yellow path indicates the application of **§3.2.4**. The grey path indicates the benchmarking and application of **§3.2.1**, **§3.2.2**, and **§3.2.3** and the black path indicates the parts of the protocol that all sections were applied to. Each module is highlighted in a green box, each of the applied metrics are in a red box, and the structural validation is highlighted in a blue box.
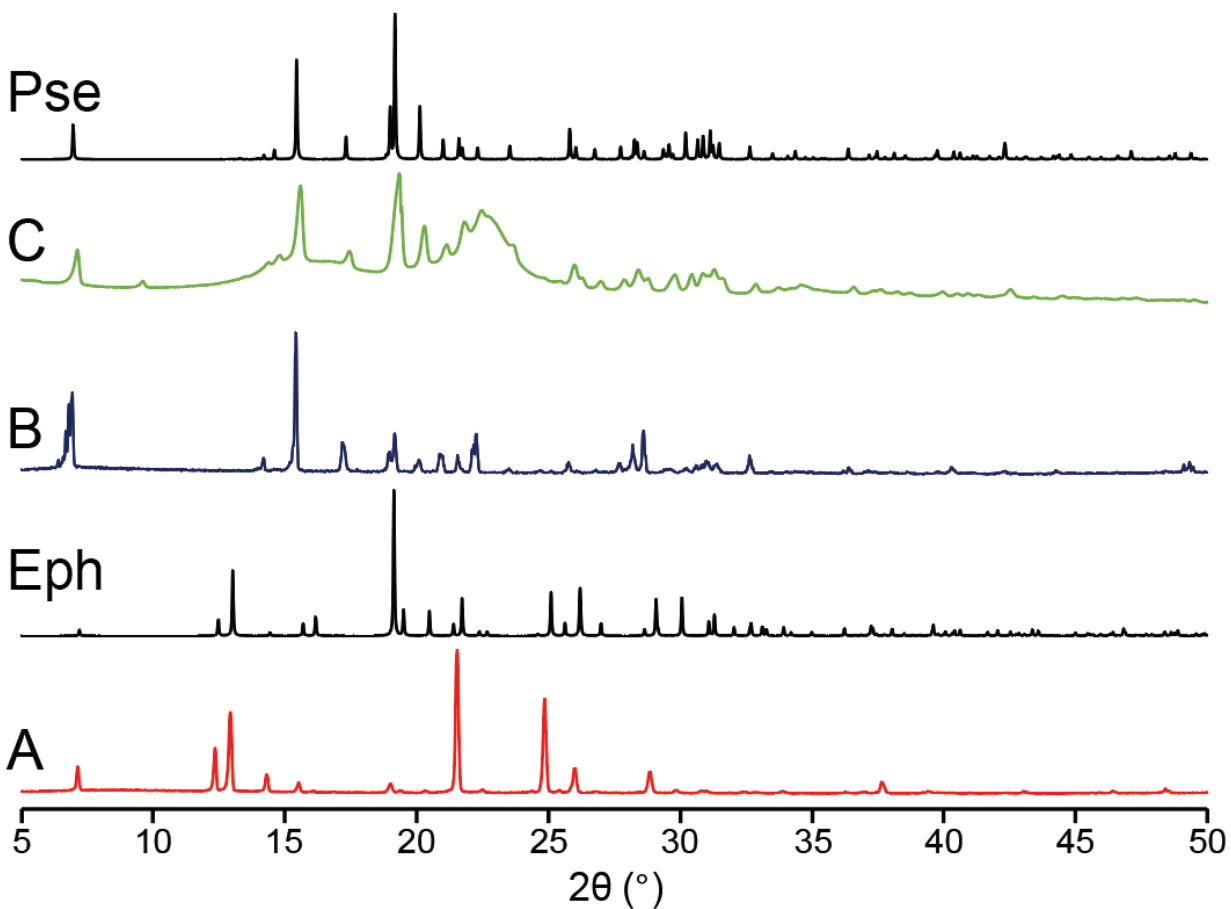
Figure S1. Simulated PXRD of the convergent geometry optimized crystal structures of Eph (Eph; black) and Pse (Pse; black) and the experimental PXRD patterns of (A; red) Eph, (B; blue) Pse, and (C; green) Sudafed. The experimental PXRD pattern of Pse features rough and spiky peaks *ca*. 7°. This roughness can be attributed to the sample not being fully grinded with a pestle prior to acquisition.
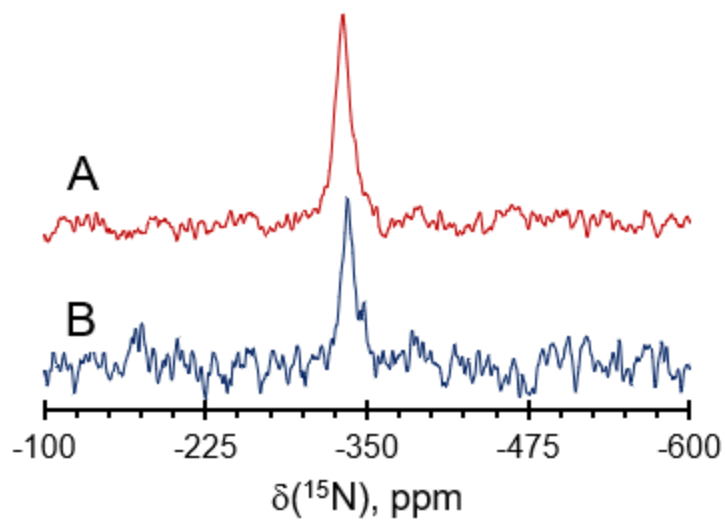
Figure S2. $^1H \rightarrow {}^{15}N$ CP/MAS NMR spectra of (A; red) Eph and (B; blue) Pse acquired at 9.4 T and $\nu_{rot} = 5$ kHz. The spectra feature single peaks corresponding to the nitrogen atoms in the charged secondary amine groups with $\delta_{iso}(^{15}N) = -331(10)$ ppm (Eph) and $-335(10)$ ppm (Pse).
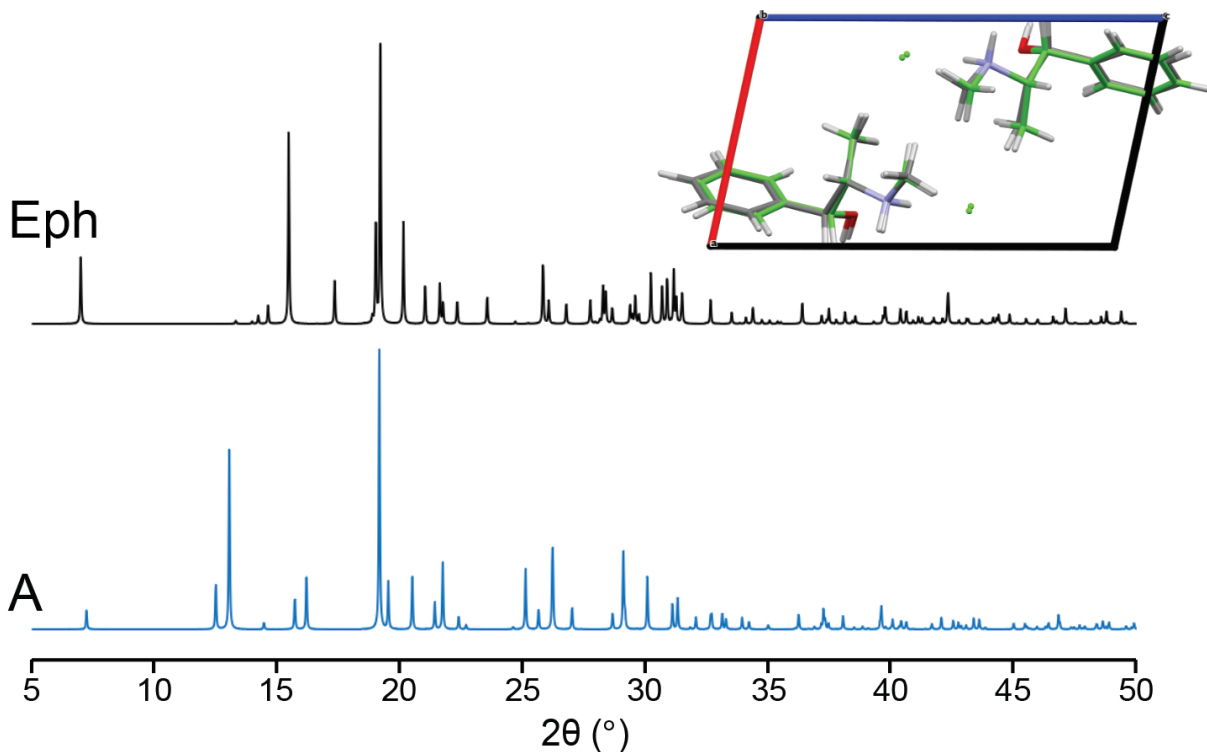
Figure S3. Simulated PXRD of the DFT-D2* geometry optimized known crystal structure of Eph (Eph; black) and structure 3-12 (A; blue), which failed structural validation based on poor agreement with simulated PXRD and CCDC thresholds.
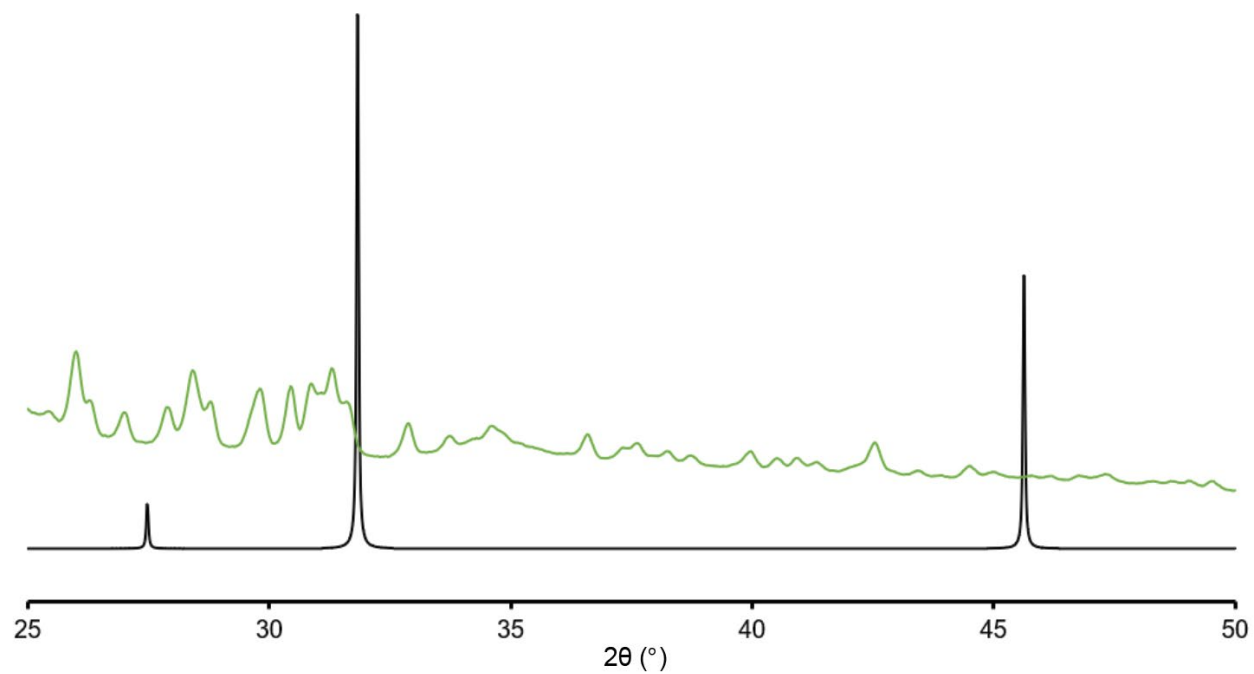
Figure S4. Simulated PXRD of NaCl (black) and experimental (green) PXRD pattern of Sudafed.
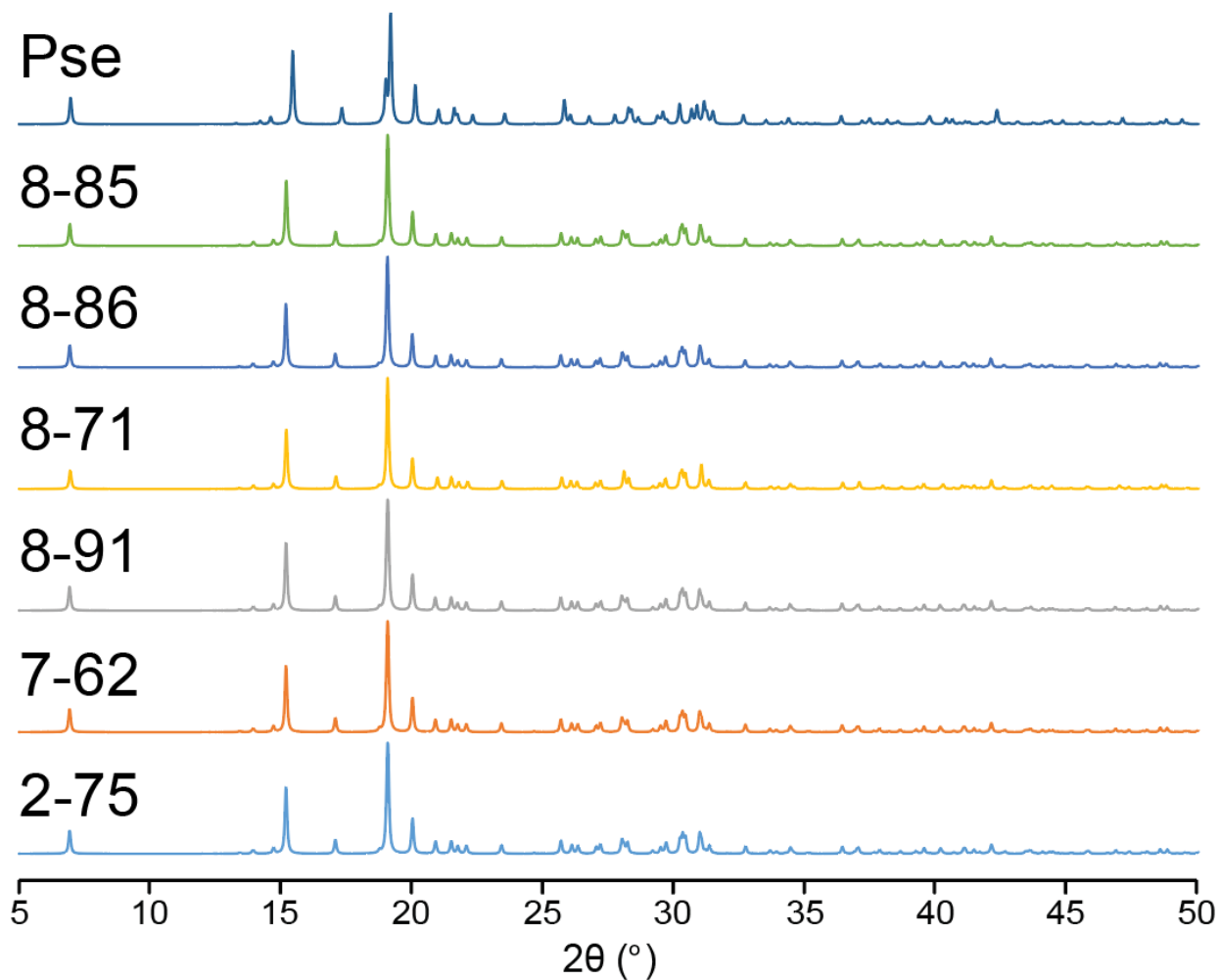
Figure S5. Simulated PXRD patterns of the six candidate structures from $P2_12_12_1$ for Sudafed (**Table 8**), and of the convergent geometry optimized known crystal structure of Pse (Pse).

Table S1. Experimental details for the acquisition of $^1H\rightarrow{^{13}C}$ and $^1H\rightarrow{^{15}N}$ CP/MAS spectra.

	^{13}C CP/MAS			^{15}N CP/MAS	
	Eph	Pse	Sudafed	Eph	Pse
B_0 (T)	9.4		14.1	9.4	
Time domain size	2048		4096	8144	
Dwell time (µs)	6.133		3.589	6.133	
Acquisition time (ms)	12.5		14.7	5.0	
Spectral width (kHz)	81.522		138.889	81.522	
Number of scans	288	256	256	109861	85646
Recycle delay (s)	10.0	12.5	18	2.0	
Spinning rate (kHz)	12.5		12	5.0	
^1H Hartmann-Hahn matching field (kHz)	50		50	80	
Contact time (ms)	1.5		1	2.0	
^1H π/2 pulse width (µs)	5.0		2.5	5.0	
^1H SPINAL-64 decoupling field (kHz)	50		100	30	
Total experiment time (min)	48	53	77	3662	2855

Table S2. Experimental details for the acquisition of $^{35}Cl\{^{1}H\}$ spectra.

	9.4, Static		21.1 T, Static		21.1 T, MAS		18.8 T	
	Eph	Pse	Eph	Pse	Eph	Pse	Sudafed	
Experiment	Hahn echo		Quad. echo		Bloch decay		Hahn echo	Bloch decay
Time domain size	1024		2048		4096		2048	1024
Dwell time (μs)	10	3.33	5.0		10		5.0	11
Acquisition time (ms)	1.02	3.41	10.24		4.10		10.24	11.26
Spectral width (kHz)	50	150	100		50		100	45.454
Number of scans	8192	19580	6144	14336	4096		32768	
Recycle delay (s)	0.5	0.75	5.0		2.0		0.75	
Spinning rate (kHz)	n/a		n/a		5.0	10.0	n/a	6
π/2 CT selective pulse width (μs)	14.3	4.8	2.0		2.0		2.5	
^{1}H decoupling field (kHz)	30		60		60		50	
Total experiment time (min)	68	245	512	1195	136		421	

Table S3. Crystallographic information for Eph and Pse.

	Space Group	a (Å)	b (Å)	c (Å)	α (º)	β (º)	γ (º)	Volume(Å^3)	Z	Z'
Eph[a]	$P2_1$	7.2557	6.1228	12.5486	90.00	102.223	90.00	544.837	2	1
Pse[a]	$P2_12_12_1$	25.358	6.428	6.901	90.00	90.00	90.00	1124.871	4	1

[a] CSD reference codes for crystal structures Eph (EPHECL02), and Pse (PEPHCL).

Table S4. Experimental ^{13}C isotropic chemical shifts.

		C_1 (ppm)	C_2 (ppm)	C_3 (ppm)	C_4 (ppm)	C_5 (ppm)
Eph	Exp.	7.2(5)	34.2(6)	63.7(9)	73.0(8)	140.2(4)
Pse	Exp.	13.1(5)	34.1(6)	63.0(9)	77.0(6)	140.4(5)

Table S5. Hirshfeld charges from the QNMRX-CSP charge database.

Atomic Position [a]	Eph [b]	Pse [b]	Database [c]	Modified [d]
C1	-0.120	-0.120	-0.130	-0.130
C2	-0.050	-0.050	-0.130	-0.130
C3	0.040	0.040	-0.120	-0.120
C4	0.030	0.040	-0.120	-0.120
C5	0.000	0.000	0.027	**0.030**
C6	-0.04	-0.040	-0.048	**-0.040**
C7	-0.03	-0.040	-0.048	**-0.040**
C8	-0.04	-0.040	-0.048	**-0.040**
C9	-0.04	-0.040	-0.048	**-0.040**
C10	-0.05	-0.040	-0.048	**-0.040**
H1	0.030	0.030	0.036	**0.060**
H2	0.040	0.030	0.036	**0.060**
H3	0.040	0.040	0.036	**0.060**
H4	0.040	0.040	0.036	**0.060**
H5	0.040	0.050	0.036	**0.060**
H6	0.040	0.050	0.036	**0.060**
H7	0.090	0.090	0.100	0.100
H8	0.100	0.100	0.100	0.100
H9	0.050	0.04	0.036	**0.060**
H10	0.020	0.03	0.036	**0.060**
H11	0.090	0.09	0.100	0.100
H12	0.04	0.030	0.036	**0.060**
H13	0.04	0.040	0.036	**0.060**
H14	0.03	0.040	0.036	**0.060**
H15	0.04	0.040	0.036	**0.060**
H16	0.03	0.040	0.036	**0.060**
O	-0.180	-0.190	-0.157	**-0.150**
N	0.010	0.010	0.010	0.010
Cl	-0.300	-0.320	-0.300	**-0.270**

[a] For labeling of atomic position see **Scheme 1**.
[b] Hishfeld charges obtained from the convergent geometry optimized known crystal structure.
[c] Hirshfeld charges obtained from the charge database. For information on how the charge database was constructed see **Supplement 1**.
[d] Hirshfeld charges that were modified from the database to apply a net charge of zero. Bold terms under the modified section are provided to show which charges were modified.

Table S6. CSD datamine summary of the top seven space groups.

	$P2_1/c$	$P\bar{1}$	$P2_12_12_1$	$P2_1$	$C2/c$	$Pbca$	$Pna2_1$
Population	1552	856	801	543	251	184	83
Percentage	32.9	18.2	17	11.5	5.3	3.9	1.8
Z	4	2	4	2	8	8	4

Supplement 1: Charge Database. When QNMRX-CSP is started from a refined isolated molecule there is the need to provide a set of Hirshfeld charges, see **Scheme S1**, M1 Step 3. Therefore, in Peach *et al.* 2024,[1] a Charge Database was constructed by refining 43 organic HCl salts obtained from the CCDC and refining the structures using convergent geometry optimizations. The atoms of each organic HCL salt were groups based on their functional groups and the average Hirshfeld charge for each functional group was tabulated. For the structural models used herein, we have balanced the net charges applied to our isolated molecule to be equal to zero by modifying the charges with the highest standard deviation. For our results herein, see **Table S5**.

Supplement 2: Computational Workstations. All calculations were run on either of two workstations both operating with a Windows 10 Pro operating system: a) The first featuring two Intel® Xeon Silver 4110 processors with a base frequency of 2.10 GHz for 8 core/16 threads, two NVIDIA® Quadro P2000 graphics cards, 192 GB of 2400 MHz RAM, and two NVMe solid-state hard drives, one KIOXIA 512 GB (reserved for OS and programs) and a SAMSUNG® 1024 GB (reserved for data storage). b) The second workstation features two Intel® Silver 4214R processors with a base frequency of 3.50 GHz for 12 cores/24 threads, two NIVIDIA® T1000 graphics cards, 384 GB of 2933 MHz RAM, two NVMe solid-state hard drives, a M.2 512 GB PCle (reserved for OS and programs) and a M.2 1024 GB PCle (reserved for data storage).

References

(1) Peach, A. A.; Fleischer, C. H. I.; Levin, K.; Holmes, S. T.; Sanchez, J. E.; Schurko, R. W. Quadrupolar NMR Crystallography Guided Crystal Structure Prediction (QNMRX-CSP). *CrystEngComm* In review.