

Supporting Information

Nortriptyline hydrochloride solubility-pH profiles in saline phosphate buffer: drug-phosphate complexes and multiple pH_{max} domains with Gibbs phase rule ‘soft’ constraints

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Table S1. Low-to-high pH titrations: Preparation of stock suspensions

Set	$m_{\text{NorHCl}}(\text{g})$	$V_{\text{NaH}_2\text{PO}_4}(\text{mL})^{\text{a}}$	$V_{\text{HCl}}(\text{mL})^{\text{b}}$	pH
1	0.18045	2.700	0.300	1.66
2	0.59770	9.40	0.600	2.03
3	0.60050	9.40	0.600	2.10
4	0.30040	4.70	0.300	2.17

^a0.15 M NaH₂PO₄ (pH 4.32-4.34)^b $c_{\text{HCl}}=0.9397$ M**Table S2.** High-to-low pH titrations: Preparation of stock suspensions

Set	$m_{\text{NorHCl}}(\text{g})$	$V_{\text{NaH}_2\text{PO}_4}(\text{mL})^{\text{a}}$	$V_{\text{Na}_2\text{HPO}_4}(\text{mL})^{\text{b}}$	$V_{\text{NaOH}}(\text{mL})^{\text{c}}$	pH
5	0.60085	4.00	–	6.00	12.57
6	0.60080	7.00	–	3.00	11.24
7	0.60020	–	8.00	2.05	11.12

^a0.15 M NaH₂PO₄ (pH 4.32-4.34)^b0.15 M Na₂HPO₄ (pH 8.97)^c $c_{\text{NaOH}}=0.9065$ M**Table S3.** Phosphate-free titrations: Preparation of stock suspensions

Set	$m_{\text{NorHCl}}(\text{g})$	$V_{\text{NaCl}}(\text{mL})^{\text{a}}$	pH
8	0.59980	10.00	5.62
9	0.60030	10.00	5.90

^a0.15 M NaCl**Table S4. Titration Set 1** – nortriptyline hydrochloride low-to-high pH titration and solubility data^a

Vial	pH _{initial}	$V_{\text{NaOH}}(\mu\text{L})$	pH _{final}	$S(\text{M})$	log S
1	1.66	–	1.76	2.13×10^{-2}	-1.67
2	1.66	150.0	5.36	1.35×10^{-2}	-1.87
3	1.66	320.0	8.78	3.43×10^{-3}	-2.47

^aInitial suspension volume 1 ml. Phases separated by centrifugation.Titrant added in increments during mixing as pH was changing: $c_{\text{NaOH}}=0.9065$ M**Table S5. Titration Set 2** – nortriptyline hydrochloride low-to-high pH titration and solubility data^a

vial	pH _{initial}	$V_{\text{HCl}}(\mu\text{L})$	$V_{\text{NaOH}}(\mu\text{L})$	pH _{final}	$S(\text{M})$	log S
1	1.99	–	0	2.12	4.26×10^{-2}	-1.37
2	2.08	–	50.0	3.00	5.84×10^{-2}	-1.23
3	2.03	10.0	70.0	3.94	5.21×10^{-2}	-1.28
4	2.06	–	110.0	5.17	1.49×10^{-2}	-1.83
5	2.03	–	150.0	5.69	1.31×10^{-2}	-1.88
6	2.04	–	200.0	7.61	5.15×10^{-3}	-2.29
7	2.04	–	300.0	8.82	2.58×10^{-3}	-2.59
8	2.02	–	415.0	9.30	8.99×10^{-4}	-3.05

^a $c_{\text{HCl}}=0.9397$ M. Otherwise, see footnote in Table S4.

Table S6. Titration Set 3 – nortriptyline hydrochloride low-to-high pH titration and solubility data^a

vial	pH	V_{NaOH} (μL)	pH_{final}	S (M)	$\log S$
1	2.10	–	2.14	3.01×10^{-2}	-1.522
2	2.09	50.0	3.11	3.97×10^{-2}	-1.401
3	2.09	60.0	4.16	4.35×10^{-2}	-1.362
4	2.08	110.0	5.19	1.11×10^{-2}	-1.955
5	2.05	160.0	5.94	8.21×10^{-3}	-2.086
6	2.07	200.0	7.41	3.91×10^{-3}	-2.408
7	2.08	300.0	8.92	2.28×10^{-3}	-2.642
8	2.03	420.0	9.77	2.41×10^{-4}	-3.618
9	2.03	440.0	10.34	9.19×10^{-5}	-4.036
10	2.01	500.0	11.35	6.59×10^{-5}	-4.181

^aSee footnote in Table S4.**Table S7. Titration Set 4** – nortriptyline hydrochloride low-to-high pH titration and solubility data^a

vial	$\text{pH}_{\text{initial}}$	V_{NaOH} (μL)	pH_{final}	S (M)	$\log S$
1	2.11	50	2.99	5.77×10^{-2}	-1.24
2	2.15	190	6.81	5.07×10^{-3}	-2.30
3	2.15	520	11.33	6.12×10^{-5}	-4.21
4	2.16	580	12.04	6.93×10^{-5}	-4.16
5	2.22	685	12.41	7.76×10^{-5}	-4.11

^aSee footnote in Table S4.**Table S8. Titration Set 5** – nortriptyline hydrochloride high-to-low pH titration and solubility data^a

vial	$\text{pH}_{\text{initial}}$	V_{NaOH} (μL)	V_{HCl} (μL)	pH_{final}	S (M)	$\log S$
1	12.39	–	600.0	1.47	5.73×10^{-3}	-2.242
2	12.42	16.0	450.0	2.39	5.54×10^{-3}	-2.257
3	12.54	–	400.0	4.92	5.69×10^{-3}	-2.245
4	12.47	–	400.0	5.94	5.58×10^{-3}	-2.253
5	12.24	–	325.0	7.04	5.66×10^{-3}	-2.247
6	11.94	–	300.0	8.12	6.20×10^{-3}	-2.208
7	12.11	–	300.0	8.79	2.28×10^{-3}	-2.643
8	11.97	–	260.0	10.11	1.04×10^{-4}	-3.981
9	12.43	–	185.0	11.86	3.81×10^{-5}	-4.419
10	12.26	–	–	12.49	3.52×10^{-5}	-4.454

^a $c_{\text{HCl}}=0.9397$ M. Otherwise, see footnote in Table S4.

Table S9. Titration Set 6 – nortriptyline hydrochloride high-to-low pH titration and solubility data^a

vial	pH _{initial}	V _{HCl} (μL)	V _{NaOH} (μL)	pH _{final}	S (M)	logS
1	11.26	500.0	205.0	1.48	6.08×10 ⁻³	-2.216
2	11.30	240.0	–	2.40	7.37×10 ⁻³	-2.132
3	11.21	300.0	–	3.23	8.21×10 ⁻³	-2.085
4	11.16	225.0	–	4.49	7.33×10 ⁻³	-2.135
5	11.34	150.0	–	6.26	6.93×10 ⁻³	-2.160
6	11.30	135.0	–	7.83	4.77×10 ⁻³	-2.322
7	11.49	50.0	–	8.93	2.33×10 ⁻³	-2.634
8	11.39	35.0	50.0	9.45	5.46×10 ⁻⁴	-3.263
9	11.10	–	–	10.10	1.42×10 ⁻⁴	-3.848
10	11.35	–	20.0	10.75	7.59×10 ⁻⁵	-4.120

^ac_{HCl}=0.9397 M. Otherwise, see footnote in Table S4.**Table S10. Titration Set 7** – nortriptyline hydrochloride high-to-low pH titration and solubility data^a

vial	pH	V _{NaOH} (μL)	V _{HCl} (μL)	pH _{final}	S (M)	logS
1	11.12	–	300.0	2.25	7.30×10 ⁻³	-2.137
2	11.24	15.0	230.0	3.21	6.87×10 ⁻³	-2.163
3	11.00	20.0	240.0	5.19	6.38×10 ⁻³	-2.195
4	10.86	–	200.0	6.32	6.24×10 ⁻³	-2.205
5	11.10	–	120.0	8.77	2.84×10 ⁻³	-2.546
6	10.88	–	10.0	9.44	6.11×10 ⁻⁴	-3.214
7	11.04	10.0	–	10.03	1.52×10 ⁻⁴	-3.819
8	10.59	100.0	–	11.48	6.26×10 ⁻⁵	-4.204

^ac_{HCl}=0.9397 M. Otherwise, see footnote in Table S4.**Table S11. Titration Set 8** – phosphate-free nortriptyline hydrochloride titration and solubility data^a

vial	pH _{initial}	V _{NaOH} (μL)	V _{HCl} (μL)	pH _{final}	S (M)	logS
1	5.73	35.0	50.0	1.80	1.14×10 ⁻²	-1.944
2	5.67	–	3.0	2.45	1.35×10 ⁻²	-1.870
3	6.37	5.0	5.0	6.68	1.29×10 ⁻²	-1.891
4	6.13	–	–	7.12	1.30×10 ⁻²	-1.886
5	5.56	5.0	–	7.77	1.33×10 ⁻²	-1.875
6	5.72	24.0	18.0	7.80	1.22×10 ⁻²	-1.914
7	7.52	273.0	160.0	7.93	8.74×10 ⁻³	-2.059
8	6.91	174.0	–	8.49	3.25×10 ⁻³	-2.489
9	6.48	205.0	–	10.64	7.61×10 ⁻⁵	-4.119
10	5.82	140.0	100.0	12.05	6.14×10 ⁻⁵	-4.212

^ac_{HCl}=0.9397 M. Otherwise, see footnote in Table S4.

Table S12. Titration Set 9 – phosphate-free nortriptyline hydrochloride titration and solubility data^a

vial	pH _{initial}	V _{NaOH} (μL)	V _{HCl} (μL)	pH _{final} *	S (M)	logS
1	5.87	–	10.0	2.00	1.18×10 ⁻²	-1.928
2	5.92	4.0	5.0	3.05	1.22×10 ⁻²	-1.912
3	6.11	9.3	9.7	3.56	1.18×10 ⁻²	-1.926
4	5.74	0.7	0.7	4.19	1.26×10 ⁻²	-1.901
5	6.13	–	–	5.81	1.20×10 ⁻²	-1.920
6	6.03	3.0	1.7	7.58	1.21×10 ⁻²	-1.918
7	6.32	101.0	–	7.73	9.05×10 ⁻³	-2.043
8	5.94	187.0	3.0	9.06	1.86×10 ⁻³	-2.731
9	6.01	250.0	2.7	11.13	6.81×10 ⁻⁵	-4.167
10	6.07	300.0	–	12.37	7.45×10 ⁻⁵	-4.128

^ac_{HCl}=0.9397 M. Otherwise, see footnote in Table S4.**Table S13. Titration Set 10** – chloride-free nortriptyline hydrochloride titration and solubility data^a

vial	pH _{initial}	V _{H₃PO₄} (μl)	V _{NaOH} (μL)	pH _{final}	S (M)	logS
1	4.98	185.0	–	1.82	1.14×10 ⁻²	-1.942
2	4.98	113.0	–	2.11	1.03×10 ⁻²	-1.986
3	4.92	64.0	–	2.54	9.02×10 ⁻³	-2.045
4	4.97	37.0	–	3.12	8.48×10 ⁻³	-2.072
5	4.96	29.0	–	3.65	8.80×10 ⁻³	-2.055
6	4.96	26.0	1.0	4.02	8.64×10 ⁻³	-2.064
7	4.88	6.0	–	4.92	9.94×10 ⁻³	-2.003
8	5.00	–	–	4.98	9.21×10 ⁻³	-2.036
9	4.90	–	45.0	5.74	4.19×10 ⁻³	-2.378
10	4.98	–	75.0	6.07	3.30×10 ⁻³	-2.482

^asee footnote in Table S4.**Table S14. Titration Set 11** – chloride-free nortriptyline hydrochloride titration and solubility data^a

vial	m _{oil} (g)	m _{NaH₂PO₄·2H₂O} (g)	V _{water} (ml)	pH _{initial}	V _{H₃PO₄} (μL)	pH _{final}	S (M)	logS
1	0.05120	0.06595	1.000	6.02	680.0	1.82	1.50×10 ⁻²	-1.823
2	0.05135	0.06515	1.000	5.99	501.0	1.99	1.27×10 ⁻²	-1.898
3	0.05250	0.06525	1.000	5.98	305.0	2.40	1.03×10 ⁻²	-1.989
4	0.05020	0.06550	1.000	5.99	200.0	2.87	9.72×10 ⁻³	-2.012
5	0.05130	0.06685	1.000	5.98	155.0	3.60	9.22×10 ⁻³	-2.035
6	0.05185	0.06555	1.000	6.11	45.0	5.36	6.18×10 ⁻³	-2.209
7	0.05155	0.06435	1.000	6.04	–	5.93	3.73×10 ⁻³	-2.428

^asee footnote in Table S4.

Table S15. Elemental analysis of solids isolated from **Titration Set 9** (phosphate-free).

Sample	pH	% C	%H	%N	Proposed Compound Composition ^a
1	2.00	74.32	6.95	4.64	NorH.Cl
2	3.05	74.54	7.09	4.74	NorH.Cl
3	3.56	74.40	7.00	4.63	NorH.Cl
4	4.19	72.27	6.85	4.70	NorH.Cl
5	5.81	74.86	6.86	4.64	NorH.Cl
6	7.58	73.92	6.91	4.58	NorH.Cl

^a Possibly hydrated**Table S16.** Elemental analysis of solids isolated from **Titration Set 3**.

Sample	pH	% C	%H	%N	Proposed Compound Composition ^a
1	2.14	73.55	6.69	4.53	NorH.Cl
2	3.11	73.75	6.70	4.55	NorH.Cl
4	5.19	69.11	6.90	4.29	(NorH) ₂ .HPO ₄
5	5.94	65.26	6.93	4.04	(NorH) ₂ .HPO ₄
6	7.41	65.45	6.92	4.05	(NorH) ₂ .HPO ₄

^a Possibly hydrated**Table S17.** Elemental analysis of solids isolated from **Titration Set 6**.

Sample	pH	% C	%H	%N	Proposed Compound Composition ^a
1	1.48	69.87	6.57	4.34	NorH.Cl
2	2.40	69.09	6.46	4.28	NorH.Cl
3	3.23	72.40	6.65	4.49	NorH.Cl
4	4.49	69.69	6.54	4.32	NorH.Cl
5	6.26	66.05	6.74	4.08	(NorH) ₂ .HPO ₄
6	7.83	65.53	7.00	4.04	(NorH) ₂ .HPO ₄

^a Possibly hydrated**Table S18.** Elemental analysis of solids isolated from **Titration Set 7**.

Sample	pH	% C	%H	%N	Proposed Compound Composition ^a
1	2.25	70.55	6.65	4.38	NorH.Cl
2	3.21	69.44	6.56	4.31	NorH.Cl
3	5.19	68.16	6.45	4.22	NorH.Cl
4	6.32	65.43	6.88	4.05	(NorH) ₂ .HPO ₄

^a Possibly hydrated

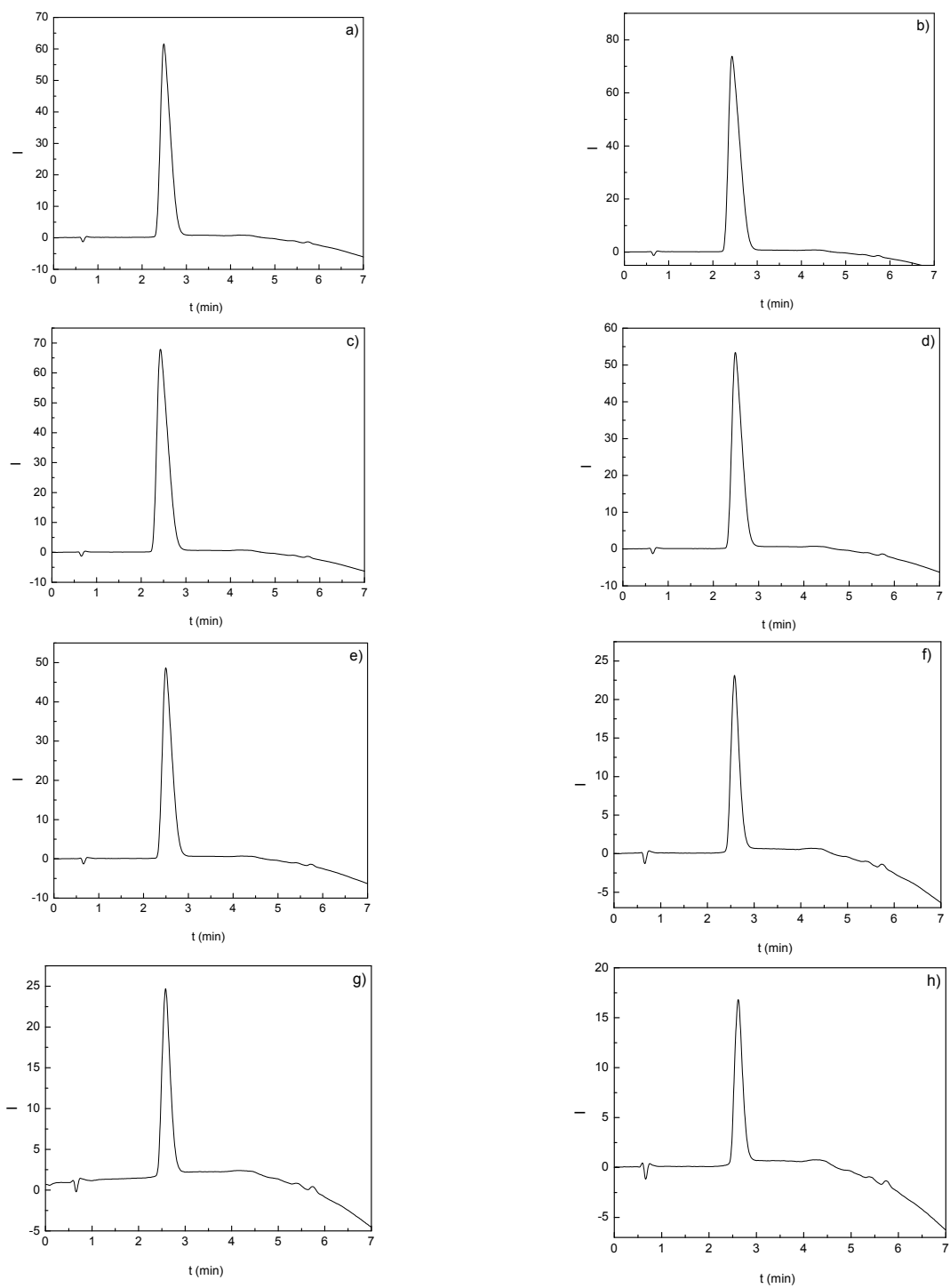


Figure S1. HPLC Chromatograms for Titration Set 2 samples at different pH values:
a) Sample 1 – pH 2.12, diluted 100×; b) Sample 2 – pH 3.00, diluted 100×; c) Sample 3 – pH 3.94, diluted 100×;
d) Sample 4 – pH 5.17, diluted 40×; e) Sample 5 – pH 5.69, diluted 40×; f) Sample 6 – pH 7.61, diluted 40×;
g) Sample 8 – pH 8.82, diluted 20×; h) Sample 9 – pH 9.30, diluted 10×.

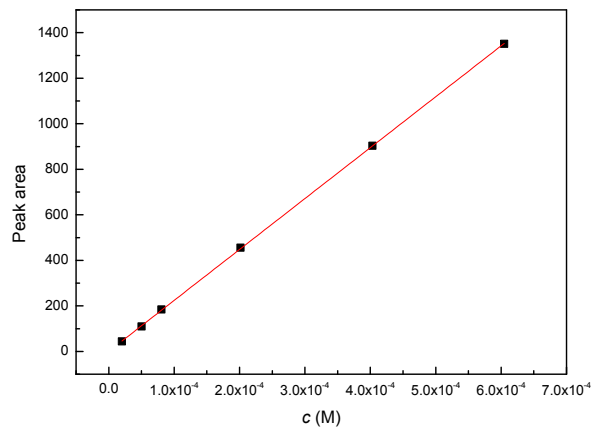


Figure S2. Calibration diagram for nortriptyline (concentration range 2.02×10^{-5} – 6.05×10^{-4} M)
Linear fit: Peak area = $2.2359 \times 10^6 c + 0.6408$