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Supporting information

Phospholipophilicity of $C_xH_yN^+$ amines: Chromatographic descriptors and molecular simulations for understanding partitioning into membranes

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Table S1. Molecular properties of tested organic cations

#	Chemical name	pKa [a]	Smiles (cation)	Formula(N)	Vx(N)	C/H(N)	ring	log P [c]	log $D_{5.5}$
1	Benzylamine	9.3	c(ccc1C[NH3+])cc1	C7H9N	0.957	0.778	1	1.1	-1.9
2	4-Methylbenzylamine	9.4	c(cc(c1)C[NH3+])c(c1)C	C8H11N	1.098	0.727	1	1.6	-1.6
3	4-Butylbenzylamine	9.5	c(cc(c1)C[NH3+])c(c1)CCCC	C11H17N	1.521	0.647	1	3.1	-0.3
4	4-Octylbenzylamine	9.5	c(cc(c1)C[NH3+])c(c1)CCCCCCCC	C15H25N	2.084	0.600	1	5.3	1.9
5	2-Phenylethylamine	9.8	c(ccc1CC[NH3+])cc1	C8H11N	1.098	0.727	1	1.5	-1.5
6	Amphetamine	10.1	[NH3+]C(C)Cc(cccc1)c1	C9H13N	1.239	0.692	1	1.8	-1.3
7	3-Phenylpropylamine	10.2	c(ccc1CCC[NH3+])cc1	C9H13N	1.239	0.692	1	1.8	-1.4
8	4-Phenylbutylamine	10.4	c(ccc1CCCC[NH3+])cc1	C10H15N	1.380	0.667	1	2.4	-0.9
9	4-t-Butylcyclohexylamine [d,e]	10.5	CC(C)(C)C1CCC([NH3+])CC1	C10H21N	1.509	0.476	1	3.1	0.1
10	1-Hexylamine	10.6	CCCCCC[NH3+]	C6H15N	1.054	0.400	0	2.0	-1.2
11	1-Heptylamine	10.7	CCCCCCC[NH3+]	C7H17N	1.195	0.412	0	2.5	-0.6
12	1-Octylamine	10.7	CCCCCCCC[NH3+]	C8H19N	1.336	0.421	0	3.1	-0.3
13	1-Decylamine	10.6	CCCCCCCCCC[NH3+]	C10H23N	1.617	0.435	0	4.1	0.9
14	Tert-octylamine [d,f]	10.7	CC(C)(C)CC(C)(C)[NH3+]	C8H19N	1.336	0.421	0	2.3	-1.2
15	(±)-1-Aminoindane	9.2	c(ccc1C2[NH3+])cc1CC2	C9H11N	1.130	0.818	2	1.6	-1.4
16	Amantadine [d,f]	10.7	[NH3+]C12CC3CC(CC(C3)C1)C2	C10H17N	1.357	0.588	3	2.2	-0.6
17	1-Naphthylmethylamine	9.7	c1ccc2c(c1)cccc2C[NH3+]	C11H11N	1.326	1.000	2	2.3	-0.8
18	1-Naphthylamine [d,f]	3.9	c1cccc2cccc([NH3+])c12	C10H9N	1.185	1.111	2	2.2	
19	3,4-Dimethylaniline [d,f]	5.2	c1cc(C)c(C)cc1[NH3+]	C8H11N	1.098	0.727	1	1.9	
20	2,4,6-Trimethylaniline [d,f]	4.4	Cc1cc(C)c([NH3+])c(C)c1	C9H13N	1.239	0.692	1	2.3	
21	4-Octylaniline [d,f]	4.8	CCCCCCCCc1ccc([NH3+])cc1	C14H23N	1.943	0.609	1	5.1	
22	4-Decylaniline [d,f]	4.8	CCCCCCCCCCc1ccc([NH3+])cc1	C16H27N	2.225	0.593	1	6.2	
23	*N*-Methylbenzylamine	9.5	c(ccc1C[NH2+]C)cc1	C8H12N	1.120	0.667	1	1.5	-1.6
24	*N*-Ethylbenzylamine	9.6	c(ccc1C[NH2+]CC)cc1	C9H14N	1.260	0.643	1	2.1	-1.3
25	*N*-Butylbenzylamine	9.9	c(ccc1C[NH2+]CCCC)cc1	C11H18N	1.542	0.611	1	3.1	-0.4
26	*N*-Hexylbenzylamine	9.9	CCCCCC[NH2+]Cc1ccccc1	C13H22N	1.824	0.591	1	4.2	1.2
27	*N*-Octylbenzylamine	9.9	CCCCCCCC[NH2+]Cc1ccccc1	C15H26N	2.020	0.682	1	5.2	2.0
28	3-Methyl-N-Methylbenzylam.	9.7	Cc(cc(c1)C[NH2+](C))c(c1)	C9H14N	1.260	0.643	1	2.0	-1.0
29	Methamphetamine	9.9	c(ccc1CC([NH2+]C)C)cc1	C10H15N	1.380	0.667	1	1.9	-0.9
30	*N*-methylphenethylamine	10.1	c(ccc1CC[NH2+]C)cc1	C9H14N	1.260	0.643	1	1.6	-1.2
31	Dibenzylamine	9.1	c(ccc1C[NH2+]C-c(ccc2)cc2)cc1	C14H17N	1.749	0.824	2	3.4	0.2
32	Dicyclohexylamine [d,e]	11.1	C1CCC(CC1)[NH2+]C1CCCCC1	C12H23N	1.682	0.522	2	3.7	0.6
33	Dihexylamine [d,f]	10.8	CCCCCC[NH2+]CCCCCC	C12H27N	1.899	0.444	0	4.9	1.3
34	*N*-Ethylcyclohexylamine [d,e]	10.8	CC[NH2+]C1CCCCC1	C8H17N	1.227	0.471	1	2.2	-1.0
35	*N*-Methyloctylamine [d,e]	10.5	CCCCCCCC[NH2+]C	C9H21N	1.477	0.429	0	3.3	0.2
36	*N*-Methyldodecylamine [d,f]	10.5	CCCCCCCCCCCC[NH2+]C	C13H29N	2.040	0.448	0	5.4	2.1
37	Maprotiline [d,e]	10.2[b]	C12(c3c(C(c4c1cccc4)CC2)cccc3)CCC[NH2+]C	C20H23N	2.334	0.870	4	4.5	1.9
38	*N*-methylaniline [d,f]	4.9	C[NH2+]c1ccccc1	C7H9N	0.957	0.778	1	1.6	
39	*N*-ethyl-*M*-toluidine	5.3	c(cc(c1)C)cc1[NH2+]CC	C8H11N	1.098	0.727	1	2.6	
40	Pyridine	5.2	[nH+](ccc1)cc1	C5H5N	0.675	1.000	1	0.7	
41	Quinoline	4.9	[nH+](ccc1)c(ccc2)c1c2	C9H7N	1.044	1.286	2	2.1	
42	Acridine [d,g]	6.2	C1=CC2=CC3=CC=CC=C3[NH+]=C2C=C1	C13H9N	1.413	1.444	3	3.4	
43	2-Methylpyridine	6.0	[nH+](ccc1)c(c1)C	C6H7N	0.816	0.857	1	1.2	
44	2-Ethylpyridine	5.9	[nH+](ccc1)c(c1)CC	C7H9N	0.957	0.778	1	1.7	
45	3,4-Lutidine	6.5	[nH+](ccc1C)cc1C	C7H9N	0.957	0.778	1	1.7	
46	2,6-Dimethylpyridine	6.6	[nH+](c(cc1)C)c(c1)C	C7H9N	0.957	0.778	1	1.7	
47	2,4,6-Collidine	7.4	[nH+](c(cc1C)C)c(c1)C	C8H11N	1.098	0.727	1	2.1	
48	*N,N*-Dimethylbenzylamine	8.9	c(ccc1C[NH+](C)C)cc1	C9H13N	1.239	0.692	1	2.0	-1.1
49	*N,N*-Diethylbenzylamine [d,f]	9.5	c(ccc1C[NH+](CC)CC)cc1	C11H17N	1.521	0.647	1	3.0	0.4
50	*N,N*-Dimethyloctylamine [d,f]	9.8	CCCCCCCC[NH+](C)C	C10H23N	1.617	0.435	0	3.8	0.7
51	*N,N,N*-Tributylamine [d,f]	10.9	CCCC[NH+](CCCC)CCCC	C12H27N	1.899	0.444	0	4.8	1.1
52	*N,N,N*-Trihexylamine [d,f]	10.8	CCCCCC[NH+](CCCCCC)CCCCCC	C18H39N	2.745	0.462	0	8.0	4.5
53	*N,N*-Dimethylcyclohexylam.[de]	10.2	C[NH+](C)C1CCCCC1	C8H17N	1.227	0.471	1	2.1	-0.8
54	*N,N*-Diethylaniline	6.6	c(ccc1[NH+](CC)CC)cc1	C10H15N	1.380	0.667	1	3.4	
55	Imipramine	9.4	N1(-c3ccccc3CC-c2ccccc12)CCC[NH+](C)C	C19H24N2	2.402	0.792	3	4.8	1.6
56	Amitriptyline (HCl) [d,f]	9.4	C1(\c2c(CCc3c1cccc3)cccc2)=C\CC[NH+](C)C	C20H23N	2.400	0.870	3	4.9	1.7
57	Fenpropidin [d,f]	10.1	c1cc(C(C)(C)C)ccc1CC(C)C[NH+]2CCCCC2	C19H31N	2.539	0.613	2	5.9	2.7
58	Octyltrimethyl-amm.	NA	CCCCCCCC[N+](C)(C)C	C11H28N	1.823	0.393	0		
59	Decyltrimethyl-amm. [d,f]	NA	CCCCCCCCCC[N+](C)(C)C	C13H30N	2.062	0.433	0		
60	1-Butylpyridinium [d,f]	NA	c1cccc[n+]1CCCC	C9H14N	1.260	0.643	1		
61	MPP+ (I) [d,f]	NA	c1(c2ccccc2)cc[n+](C)cc1	C12H12N	1.446	1.000	2		
62	Phenyltrimethyl-amm .	NA	c(ccc1[N+](C)(C)C)cc1	C9H14N	1.690	0.265	1		
63	Benzyltrimethyl-amm.	NA	C[N+](C)(C)(Cc1ccccc1)	C10H16N	1.401	0.625	1		
64	Benzyltriethyl-amm.	NA	CC[N+](CC)(CC)(Cc1ccccc1)	C13H22N	1.824	0.591	1		
65	Benzyltripropyl-amm.	NA	CCC[N+](CCC)(CCC)(Cc1ccccc1)	C16H28N	2.247	0.571	1		
66	Benzyltributyl-amm.	NA	CCCC[N+](CCCC)(CCCC)(Cc1ccccc1)	C19H34N	2.669	0.559	1		
67	Benzydimethylhexyl-amm.	NA	CCCCCC[N+](C)(C)(Cc1ccccc1)	C15H26N	2.106	0.577	1		
68	Benzydimethyloctyl-amm.	NA	CCCCCCCC[N+](C)(C)(Cc1ccccc1)	C17H30N	2.388	0.567	1		
69	Benzydimethyldecyl-amm.	NA	CCCCCCCCCC[N+](C)(C)(Cc1ccccc1)	C19H34N	2.669	0.559	1		
70	Benzydimethdodecyl-amm[d,f]	NA	CCCCCCCCCCCC[N+](C)(C)(Cc1ccccc1)	C21H38N	2.951	0.553	1		

[a] experimental pKa (SRC/EPISuite), grey values www.chemicalize.org (July 2015). [b] ref (1). [c] logP/log$D_{5.5}$ (log$D_{5.5}$ only for bases with pK_a>7.4) from ACD/Labs (www.chemspider.com). [d] not in Droge & Goss (2). [e] Alfa-Aesar, Ward Hill, MA, USA. [f] Sigma-Aldrich(-Fluka), Zwijndrecht, NL. [g] Acros, Geel, BEL.

Table S2. COSMOmic predictions (COSMOthermX V. C30_1501, 17/12/2014), with membrane potential settings as in Bittermann *et al.* (3)

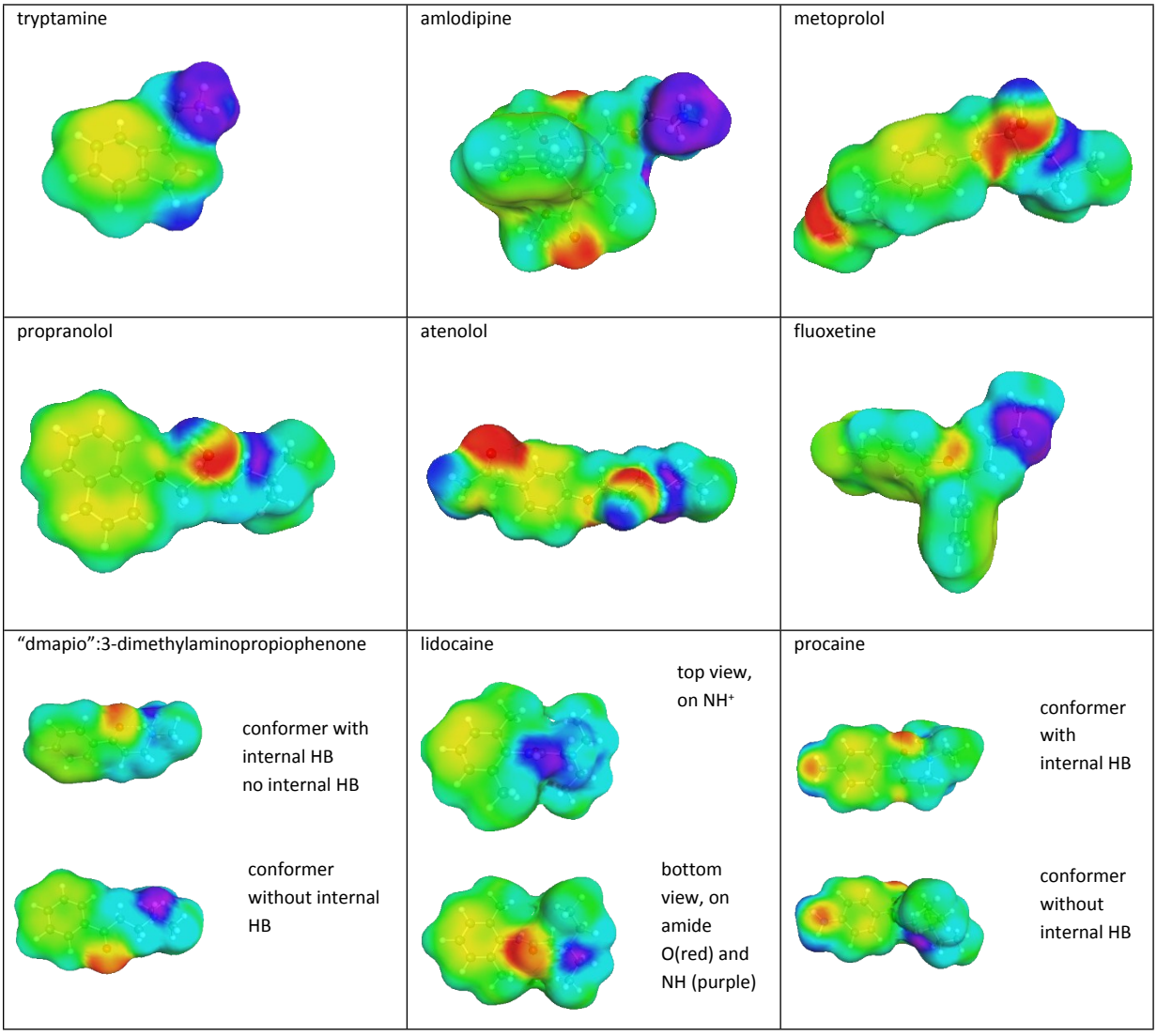
#	Chemical name	logK_{DMPC}	energy minimum depth (A)	logK_{POPC}	ΔPOPC-DMPC	# conform.	Max ΔlogK conform
1	Benzylamine	1.49	12.5	2.65	1.2	2	0.2
2	4-Methylbenzylamine	1.96	12.5	3.09	1.1	1	
3	4-Butylbenzylamine	3.49	10.5	4.62	1.1	3	0.2
4	4-Octylbenzylamine	5.89	8.5	7.03	1.1	1	
5	2-Phenylethylamine	1.89	12.5	3.13	1.2	2	0.5
6	Amphetamine	1.84	12.5	3.01	1.2	3	0.7
7	3-Phenylpropylamine	2.20	11.5	3.45	1.2	6	1.2
8	4-Phenylbutylamine	2.65	10.5	3.92	1.3	6	0.5
9	4-*tert*-Butylcyclohexylamine	2.73	11.5	3.82	1.1	2	0.4
10	1-Hexylamine	2.26	11.5	3.44	1.2	6	0.7
11	1-Heptylamine	2.80	11.5	3.99	1.2	5	0.9
12	1-Octylamine	3.36	10.5	4.55	1.2	5	0.8
13	1-Decylamine	4.48	9.5	5.67	1.2	5	0.8
14	*tert*-Octylamine	1.64	12.5	2.61	1.0	2	0.4
15	(±)-1-Aminoindane	1.59	12.5	2.67	1.1	2	0.1
16	Adamantamine	1.61	12.5	2.57	1.0	1	
17	1-Naphthylmethylamine	2.27	12.5	3.37	1.1	1	
18	1-Naphthylamine	1.94	12.5	2.90	1.0	2	0.3
19	3,4-Dimethylaniline	2.07	12.5	3.03	1.0	1	
20	2,4,6-Trimethylaniline	1.76	12.5	2.72	1.0	1	
21	4-Octylaniline	5.59	8.5	6.62	1.0	2	0.6
22	4-Decylaniline	6.75	7.5	7.80	1.0	1	
23	*N*-Methylbenzylamine	0.80	12.5	1.97	1.2	2	0.3
24	*N*-Ethylbenzylamine	0.72	12.5	1.80	1.1	4	0.5
25	*N*-Butylbenzylamine	1.43	12.5	2.32	0.9	6	0.7
26	*N*-Hexylbenzylamine	2.30	11.5	3.13	0.8	6	0.9
27	*N*-Octylbenzylamine	3.05	11.5	3.99	0.9	4	0.3
28	3-Methyl-*N*-Methylbenzylamine	1.23	12.5	2.34	1.1	2	0.3
29	Methamphetamine	1.16	12.5	2.31	1.1	8	0.8
30	*N*-methylphenethylamine	1.17	12.5	2.40	1.2	4	0.6
31	Dibenzylamine	1.57	12.5	2.47	0.9	4	0.4
32	Dicyclohexylamine	1.11	10.5	1.65	0.5	7	0.9
33	Dihexylamine	2.44	10.5	3.22	0.8	6	0.4
34	*N*-Ethylcyclohexylamine	0.47	12.5	1.41	0.9	6	0.6
35	*N*-Methyloctylamine	2.62	10.5	3.76	1.1	7	0.5
36	*N*-Methyldodecylamine	4.87	8.5	6.01	1.1	3	0.4
37	Maprotiline	3.36	10.5	4.60	1.2	6	0.5
38	*N*-methylaniline	0.61	12.5	1.74	1.1	2	0.0
39	*N*-ethyl-*M*-toluidine	1.03	12.5	1.96	0.9	2	0.2
40	Pyridine	-0.66	13.5	0.77	1.4	1	
41	Quinoline	-0.10	12.5	1.00	1.1	1	
42	Acridine	0.33	11.5	1.07	0.7	1	
43	2-Methylpyridine	-0.74	13.5	0.56	1.3	1	
44	2-Ethylpyridine	-0.43	13.5	0.71	1.1	2	0.4
45	3,4-Lutidine	-0.12	12.5	0.95	1.1	1	
46	2,6-Dimethylpyridine	-0.80	13.5	0.36	1.2	1	
47	2,4,6-Collidine	-0.34	11.5	0.57	0.9	1	
48	*N,N*-Dimethylbenzylamine	0.38	12.5	1.58	1.2	2	0.3
49	*N,N*-Diethylbenzylamine	0.35	10.5	1.23	0.9	6	0.4
50	*N,N*-Dimethyloctylamine	2.21	10.5	3.35	1.1	5	0.8
51	*N,N,N*-Tributylamine	1.89	10.5	2.22	0.3	6	0.3
52	*N,N,N*-Trihexylamine	4.64	9.5	4.68	0.0	6	0.5
53	*N,N*-Dimethylcyclohexylamine	0.14	10.5	1.17	1.0	3	0.5
54	*N,N*-Diethylaniline	0.24	11.5	1.13	0.9	3	0.2
55	Imipramine	2.60	10.5	3.86	1.3	6	0.4
56	Amitriptyline	3.34	9.5	3.74	0.4	4	0.4
57	Fenpropidin	2.93	9.5	3.67	0.7	6	0.5
58	Octyltrimethylammonium	1.92	10.5	3.03	1.1	2	0.4
59	Decyltrimethylammonium	3.04	8.5	4.16	1.1	2	0.4
60	1Butylpyridinium	0.05	11.5	1.10	1.1	2	0.3
61	MPP+	0.37	11.5	1.45	1.1	1	
62	Phenyltrimethylammonium	-0.31	12.5	0.90	1.2	1	
63	Benzyltrimethylammonium	-0.06	12.5	1.12	1.2	1	
64	Benzyltriethylammonium	0.37	10.5	0.99	0.6	2	0.1
65	Benzyltripropylammonium	1.75	9.5	1.91	0.2	3	0.2
66	Benzyltributylammonium	3.33	9.5	3.33	0.0	1	
67	Benzydimethylhexylammonium	1.69	10.5	2.37	0.7	4	0.3
68	Benzydimethyloctylammonium	2.81	10.5	3.45	0.6	3	0.4
69	Benzydimethyldecylammonium	3.89	9.5	4.56	0.7	2	0.4
70	Benzydimethyldodecylammonium	4.98	9.5	5.65	0.7	2	0.4

Table S3. Experimental membrane sorption affinities for polar amines with IAM-HPLC, and predicted membrane affinities using multiparameter models (including amine type corrective increments): Eq.3 for COSMOmic DMPC and Eq.5 for logP.

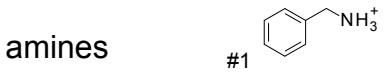
Chemical name	$\log K_{plipw}$ (IAM-HPLC) [a]	Vx	# COSMOmic conformers	$\log K_{DMPC}$ (calc.)	δ_{dmpc} Eq.3	Eq.3 fitted $\log K_{plipw}$	$\log P$ (calc.)	δ_{logP} Eq.5	Eq.5 fitted $\log K_{plipw}$
tryptamine	1.91	1.328	5	1.958	-0.51	1.45	2.65	-0.35	1.03
amlodipine	4.15	3.024	6	3.926	-0.51	3.42	3.09	-0.35	3.81
metoprolol	2.06	2.260	5	2.129	+0.34	2.46	4.62	-1.03	0.76
propranolol	3.12	2.148	6	2.662	+0.34	3.00	7.03	-1.03	2.07
atenolol	1.26	2.176	5	0.265	+0.34	0.60	3.13	-1.03	-0.93
fluoxetine	4.28	2.300	6	3.67	+0.34	4.01	3.01	-1.03	3.06
"dmapio"	1.33	1.536	5	0.45	+0.76	1.21	3.45	-1.50	0.24
lidocaine	1.66	1.977	5	1.133	+0.76	1.89	3.92	-1.50	2.13
procaine	1.57	2.059	6	0.666	+0.76	1.43	3.82	-1.50	0.86

[a] from ref (4).

visualization of representative conformers for these 9 polar amines (purple = high positive surface charge, green=neutral surface, red = negative surface charge):

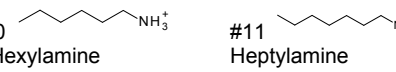


1° amines



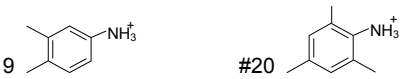
#1 Benzylamine | #2 4-Methylbenzylamine | #3 4-Butylbenzylamine | #4 4-Octylbenzylamine

#5 2-Phenylethylamine | #6 Amphetamine | #7 3-Phenylpropylamine | #8 4-Phenylbutylamine | #9 4-Tert-butyl-cyclohexylamine



#10 1-Hexylamine | #11 1-Heptylamine | #12 1-Octylamine | #13 1-Decylamine | #14 Tert-octylamine

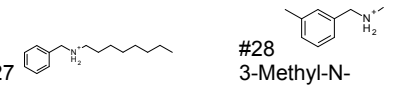
#15 (±)-1-Aminoindane | #16 Amantadine | #17 1-Naphthylmethylamine | #18 1-Naphthylamine



#19 3,4-Dimethylaniline | #20 2,4,6-Trimethylaniline | #21 4-Octylaniline | #22 4-Decylaniline

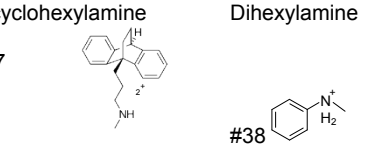
2° amines

#23 *N*-Methylbenzylamine | #24 *N*-Ethylbenzylamine | #25 *N*-Butylbenzylamine | #26 *N*-Hexylbenzylamine



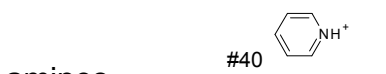
#27 *N*-Octylbenzylamine | #28 3-Methyl-N-Methylbenzylamine | #29 Methamphetamine | #30 *N*-Methylphenethylamine | #31 Dibenzylamine

#32 Dicyclohexylamine | #33 Dihexylamine | #34 *N*-Ethyl cyclohexylamine | #35 *N*-Methyloctylamine | #36 *N*-methyldodecylamine



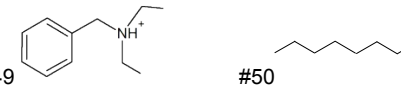
#37 Maprotiline | #38 *N*-Methylaniline | #39 *N*-Ethyl-M-toluidine

3° amines

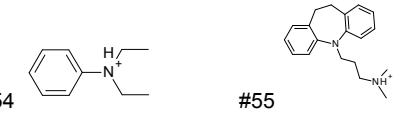


#40 Pyridine | #41 Quinoline | #42 Acridine | #43 2-Methylpyridine

#44 2-Ethylpyridine | #45 3,4-Lutidine | #46 2,6-Dimethylpyridine | #47 2,4,6-Collidine | #48 *N,N*-Dimethylbenzylamine

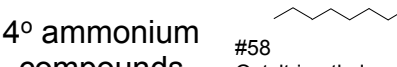


#49 *N,N*-Diethylbenzylamine | #50 *N,N*-Dimethyloctylamine | #51 *N,N,N*-Tributylamine | #52 *N,N,N*-Trihexylamine | #53 *N,N*-Dimethyl-cyclohexylamine

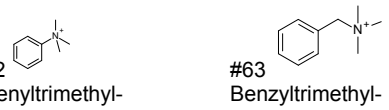


#54 *N,N*-Diethylaniline | #55 Imipramine | #56 Amitriptyline | #57 Fenpropidin

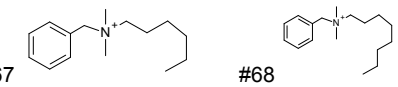
4° ammonium compounds



#58 Octyltrimethyl-ammonium | #59 Decyltrimethyl-ammonium | #60 1-Butylpyridinium | #61 MPP+



#62 Phenyltrimethyl-ammonium | #63 Benzyltrimethyl-ammonium | #64 Benzyltriethyl-ammonium | #65 Benzyltripropylammonium | #66 Benzyltributylammonium



#67 Benzyldimethylhexyl-ammonium | #68 Benzyldimethyloctyl-ammonium | #69 Benzyldimethyldecyl-ammonium | #70 Benzyldimethyldodecyl-ammonium

Figure S1. Test compound structures (cationic species)

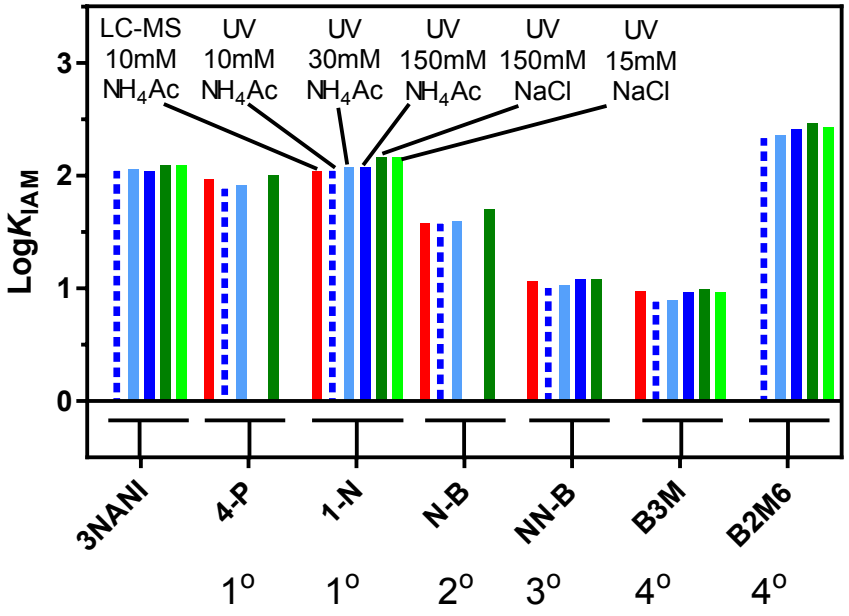


Figure S2. Negligible influence of different aqueous eluent compositions, all buffered at pH 5.0, on the apparent sorption affinity to the IAM material, for the neutral reference compound 3-nitroaniline, and six organic cations: 4-phenylbutylamine ("4-P", #8), 1-naphthylmethylamine ("1-N", #17), *N*-benzylbutylamine ("N-B", #26), *N,N*-dimethylbenzylamine ("NN-B", #48), Benzyltrimethylammonium ("B3M", #63) and Benzyldimethylhexylammonium ("B2M6", #67). 4-P and 1-N are primary amines (1°), N-B a 2° amine, NN-B a 3° amine, and B3M and B2M6 quaternary ammonium compounds (4°).

The red bar on the left represents logK_{IAM} obtained with LC-MS in 10 mM NH_4Ac (not for 3NANI and B2M6), the broken blue line next to it is the UV derived logK_{IAM} in 10 mM NH_4Ac, followed by logK_{IAM} obtained in other eluent compositions.

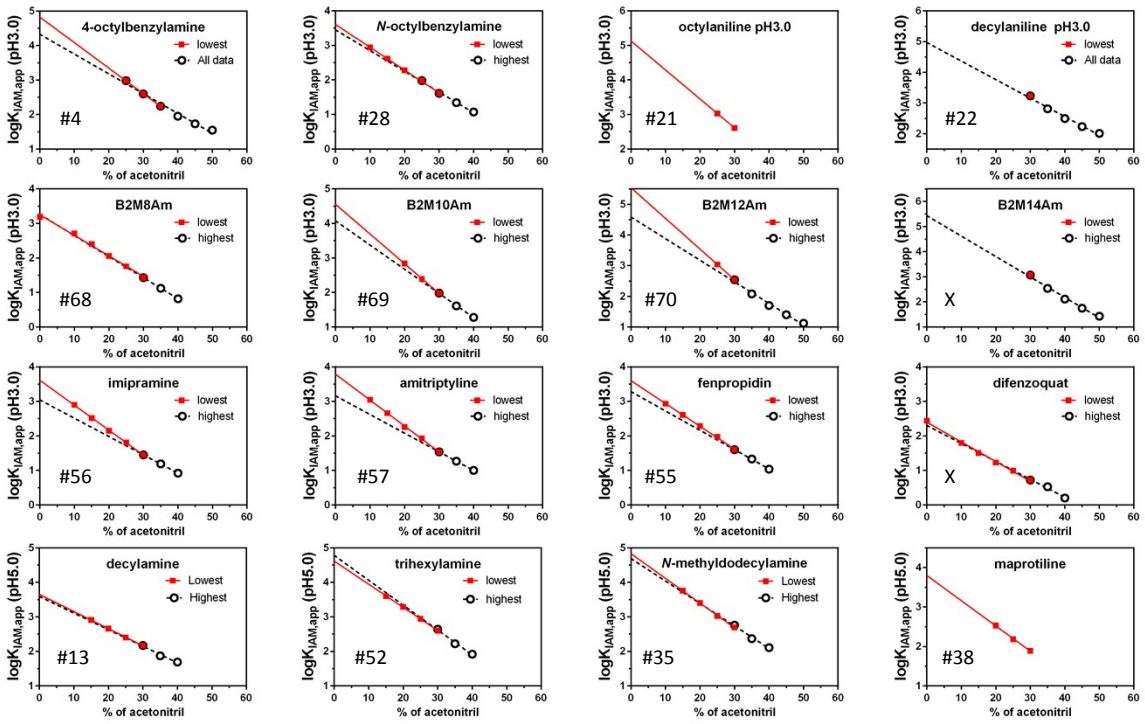


Figure S3. Apparent sorption coefficients to IAM column material at various acetonitrile mixtures with pH3.0 (UV-HPLC data) or pH5.0 (LC-MS data) buffer. The black circles represent measurements in eluents with ≥30% acetonitrile, the trends of which generally lead to an underestimation of the extrapolated sorption coefficients in fully aqueous buffer, as indicated by broken lines. Red square data points and fitted solid (red) linear line were used to obtain sorption coefficients in fully aqueous buffer.

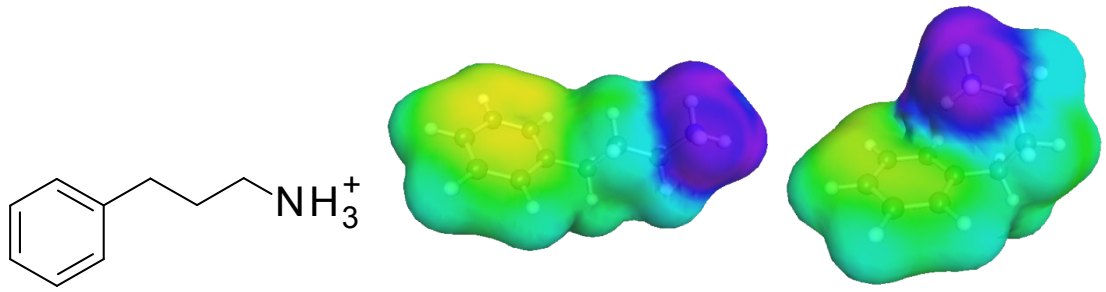


Figure S4. Different conformer input structures for 3-phenylpropylamine (#7), for which COSMOmic predicts logK_{DMPC} values of 2.27 (left structure) or 1.12 (right structure).

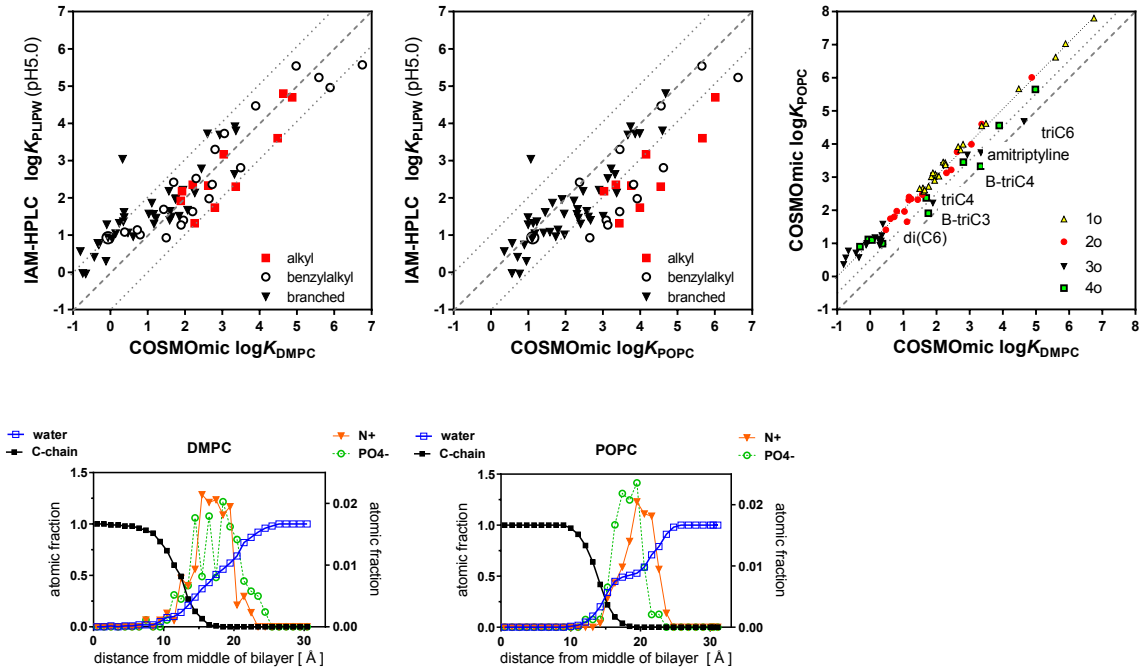


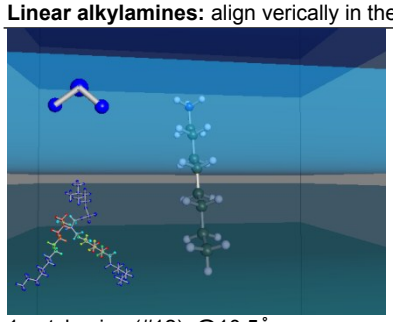
Figure S5.

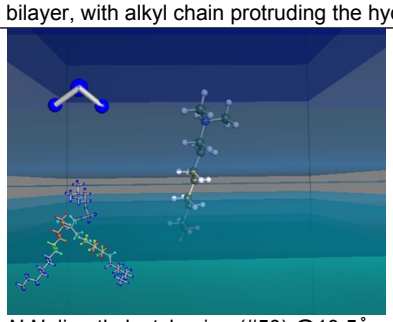
(Top row) IAM-HPLC based logK_{PLIPW} values plotted against COSMOmic predictions for $C_xH_yN^+$ amines in DMPC **(left)** and POPC **(middle)** systems, and logK_{DMPC} plotted against logK_{POPC} **(right)** separated out for different amine types and outliers. Broken lines indicate 1:1 relation, dotted lines a 1:10 relation.

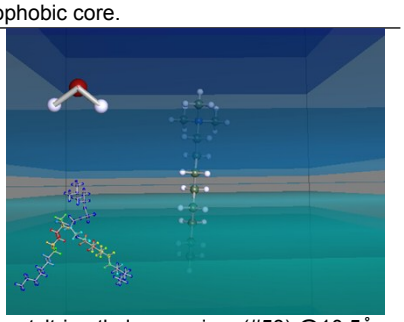
(Bottom row) Atomic distribution of water, alkyl chains, cationic ammonium groups and anionic phosphate groups in the DMPC **(left)** and POPC **(right)** bilayer system used by COSMOmic. The depth range in which N^+ and PO_4^- groups occur seem to fully overlap in the DMPC system, while on average PO_4^- groups are located deeper in the membrane than N^+ groups in the POPC system. Water molecules fully penetrate the depth range of the headgroups of both systems, while being absent in the hydrophobic cores.

On average, the POPC predicted sorption coefficients are 0.97 log units higher than the DMPC predictions (range 0.0 – 1.4 log units). The compounds that are predicted to have a relatively lower affinity to DMPC than to POPC compared to other amines (difference <0.5 log units), are indicated:
di(C6) = dicyclohexylamine (#37),
triC4 = tributylamine (#51),
triC6 = trihexylamine (#52),
B-triC3 = benzyltripropylammonium (#65)
B-triC4 = benzyltributylammonium (#66)
amitriptyline = tricyclic antidepressant (0.4 log units difference), while the closely related tricyclic antidepressant imipramine shows 1.3 log units difference.

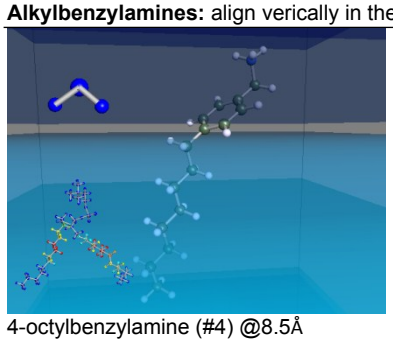
Linear alkylamines: align verically in the bilayer, with alkyl chain protruding the hydrophobic core.

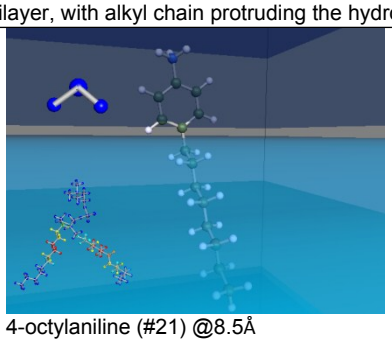

1-octylamine (#12). @10.5Å

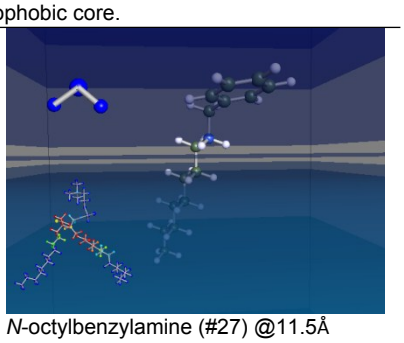

N,N-dimethyloctylamine (#50) @10.5Å


octyltrimethylammonium (#58) @10.5Å

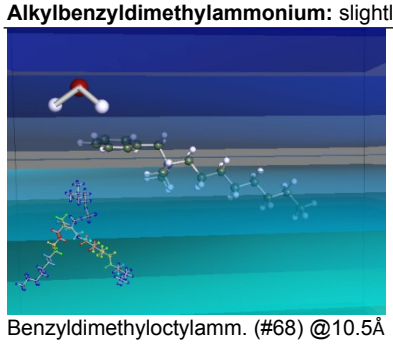
Alkylbenzylamines: align verically in the bilayer, with alkyl chain protruding the hydrophobic core.

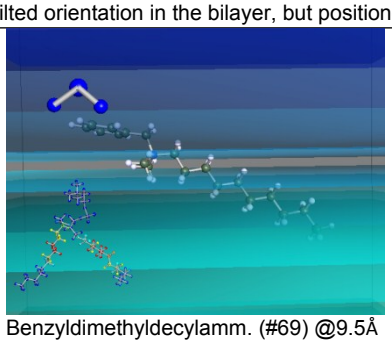

4-octylbenzylamine (#4) @8.5Å

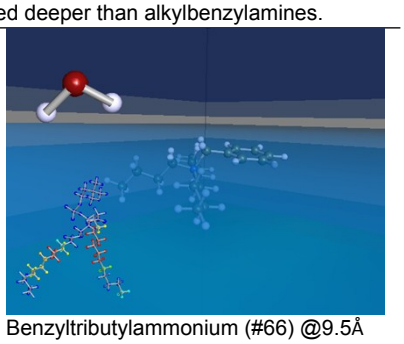

4-octylaniline (#21) @8.5Å


N-octylbenzylamine (#27) @11.5Å

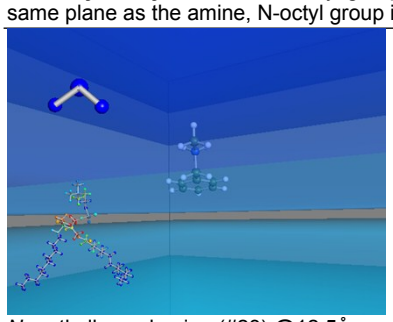
Alkylbenzyldimethylammonium: slightly tilted orientation in the bilayer, but positioned deeper than alkylbenzylamines.

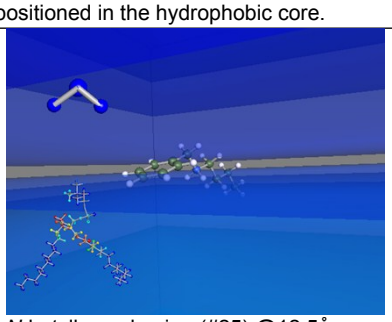

Benzyldimethyloctylamm. (#68) @10.5Å

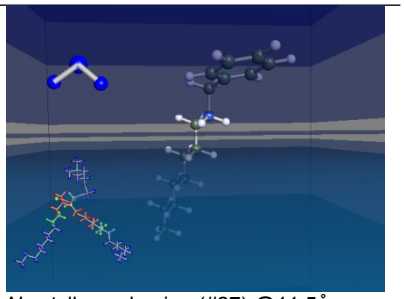

Benzyldimethyldecylamm. (#69) @9.5Å


Benzyltributylammonium (#66) @9.5Å

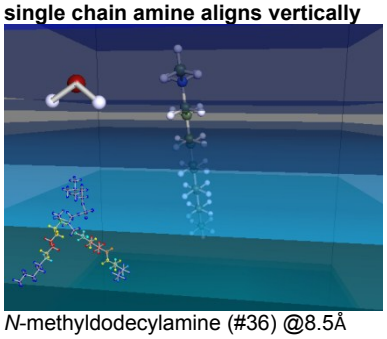
2° N-alkylbenzylamines: N-methyl group positioned above the amine in the membrane's headgroup, N-butyl group in the same plane as the amine, N-octyl group is positioned in the hydrophobic core.


N-methylbenzylamine (#23) @12.5Å

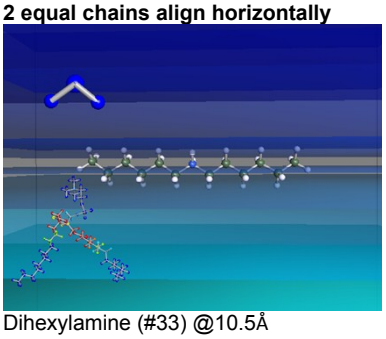

N-butylbenzylamine (#25) @12.5Å


N-octylbenzylamine (#27) @11.5Å

single chain amine aligns vertically


N-methyldodecylamine (#36) @8.5Å

2 equal chains align horizontally


Dihexylamine (#33) @10.5Å

only 1 of 3 equal chains towards core

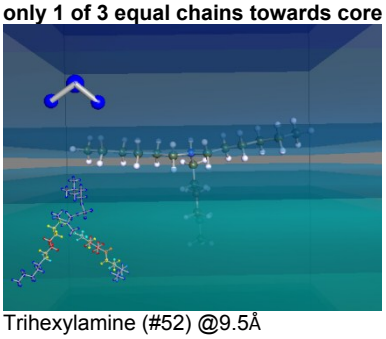

Trihexylamine (#52) @9.5Å

Figure S6. Ideal orientation of various amines according to COSMOmic simulation in DMPC system. Top of the graph is towards bulk water, bottom of the graph is towards membrane interior. Distance of the centre of the molecule at ideal orientation from the centre of the bilayer is given in Ångstrom.

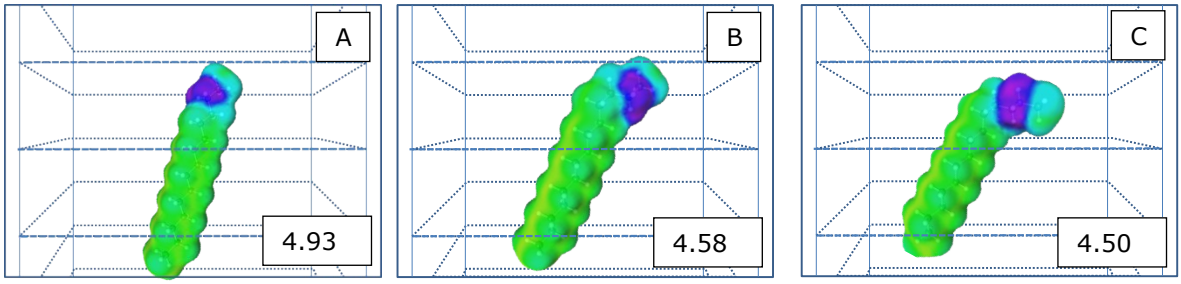


Figure S7. COSMOmic simulation on the ideal orientation of *N*-methyldodecylamine (#35), using the three most likely conformers (A-C), and the overall sorption affinity to DMPC (logK_{DMPC_cosmo} in L/kg lipid). The conformer weighted logK_{DMPC_cosmo} is 4.87, *indicating a dominant contribution of the fully stretched conformer*. Top of the graph is bulk water, bottom of the graph is membrane interior. The charged nitrogen is colored purple in the surface charge optimized conformer structures, indicating the different curvature of the alkyl chains in the conformer set and the resulting influence on the predicted logK_{DMPC_cosmo}.

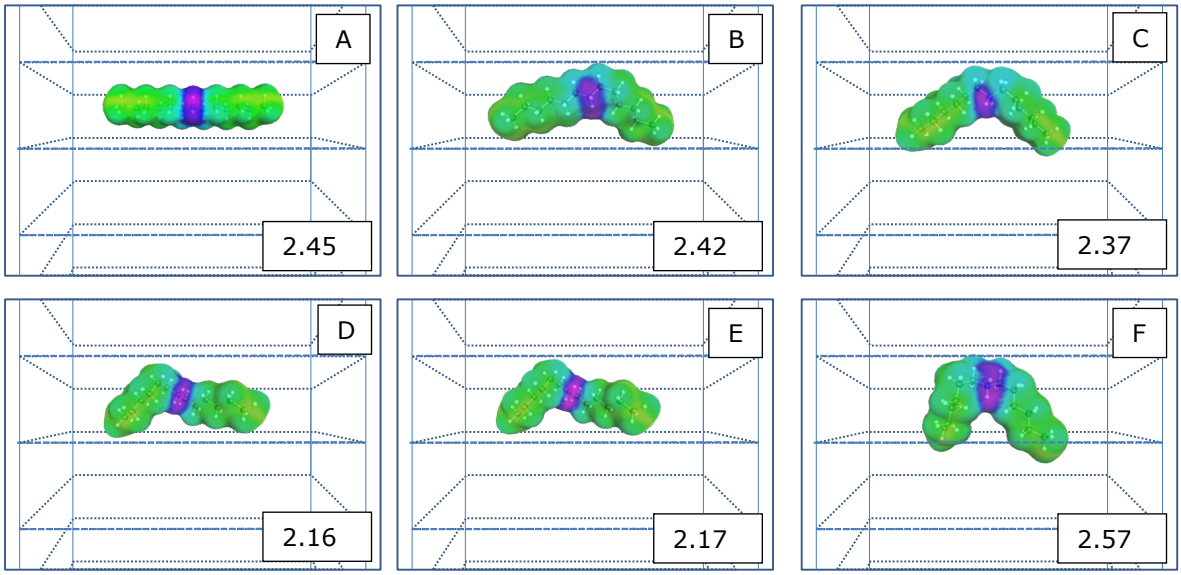


Figure S8. COSMOmic simulation on the ideal orientation of dihexylamine (#36), using six most likely conformers (A-F), and the overall sorption affinity to dmpc (logK_{DMPC} in L/kg lipid). The conformer weighted logK_{DMPC} is 2.44. Top of the graph is bulk water, bottom of the graph is membrane interior.

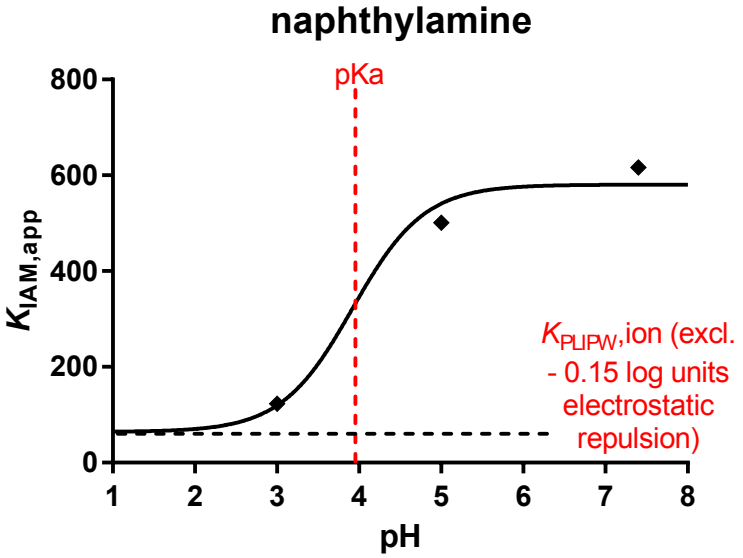


Figure S9. Optimized IAM-HPLC sorption coefficients (high salinity) at pH 3.0, 5.0 and 7.4 for the weak base naphthylamine (#18), fitted with a Henderson Hasselbalch curve (as in ref (5)) to determine the logK_{PLIPW} for both the cationic (1.80) and neutral base species (2.77).

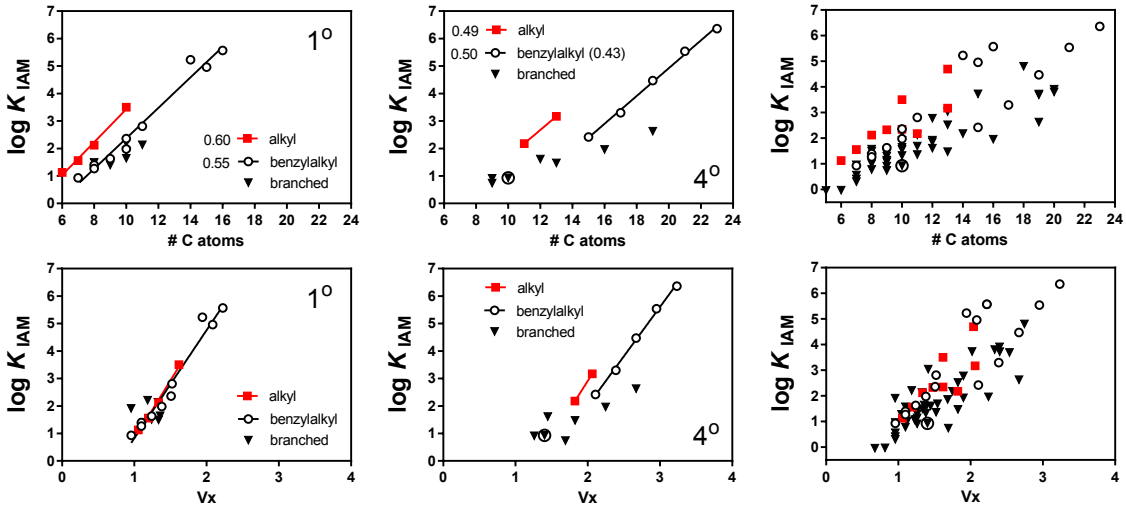


Figure S10. Optimized IAM-HPLC sorption coefficients (at high salinity pH5.0, so ~logK_{PLIPW}) in relation to the number of carbon atoms in each compound **(#C, upper row)** or McGowans volume **(Vx, lower row)**. For series of simple primary amines **(1°, left)**; simple quaternary ammonium compounds **(4°, middle)**; and all tested CxHyN+ compounds **(right)**. Benzylalkyl structures contain 1 aromatic ring and a single linear alkyl chain, which is positioned at the para-position of the ring relative to the charged nitrogen group, or between the charged nitrogen and the benzene ring (only for 1° amines). The slopes of the regression lines for the alkyl and benzylalkyl compounds are next to the legend in the top row plots, for 4° benzylalkyl the slope (0.43) includes the small B3MAm (#C=10), without B3Mam the slope is 0.50.

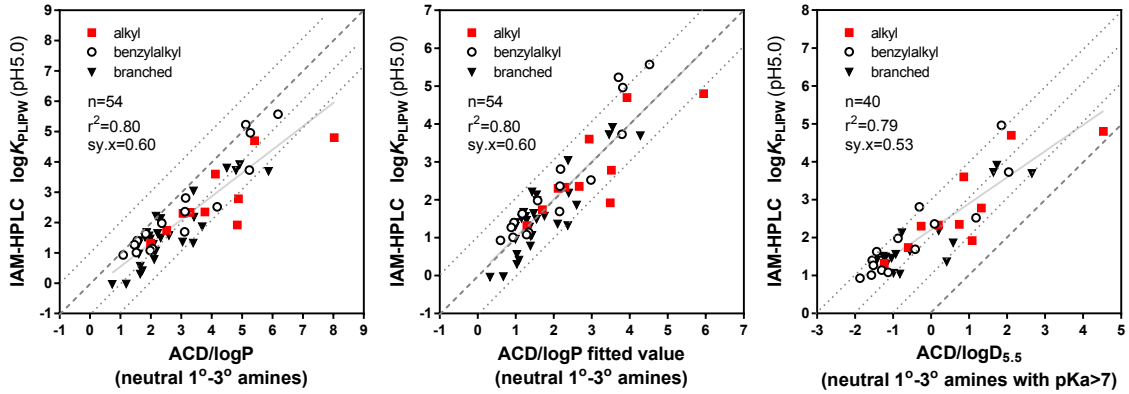


Figure S11. Comparison between IAM-HPLC phospholipid sorption coefficients and ACD/Labs predictions of octanol-water distribution: **(left)** logP values for neutral base species for all 1°, 2° and 3° amines; **(middle)** observed vs. fitted values using the logP regression; **(right)** log$D_{5.5}$ values for all 1°, 2° and 3° amines with pKa>7 (n=40), so that the log$D_{5.5}$ represents the octanol-water distribution coefficient of the organic cation (predicted to be on average 3.16 log units lower than logP). Broken lines indicate 1:1 relation, dotted lines tenfold deviations.
ACD-Labs predictions obtained via Chemspider.com July 2015.

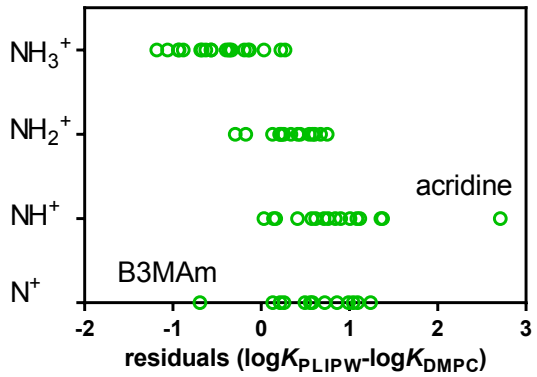


Figure S12. Residuals between observed phospholipid-water sorption coefficients vs. COSMOmic predicted values (logK_{DMPC}) for the different amine types.

CITATIONS

1. Cabot JM, Fuguet E & Rosés M (2014) Determination of acidity constants of sparingly soluble drugs in aqueous solution by the internal standard capillary electrophoresis method. *Electrophoresis* 35(24): 3564-3569.

2. Droge STJ & Goss KU (2013) Ion-exchange affinity of organic cations to natural organic matter: Influence of amine type and nonionic interactions at two different pHs. *Environ Sci Technol* 47: 798-806.

3. Bittermann K, *et al* (2014) Prediction of phospholipid-water partition coefficients of ionic organic chemicals using the mechanistic model COSMOmic. *J Phys Chem B* 118(51): 14833-14842.

4. Droge STJ (2016) Dealing with confounding pH-dependent surface charges in immobilized artificial membrane HPLC columns. *Anal Chem* 88(1): 960-967.

5. Austin RP, Davis AM & Manners CN (1995) Partitioning of ionizing molecules between aqueous buffers and phospholipid-vesicles. *J Pharm Sci* 84(10): 1180-1183.