Supporting Information: On the structure of prilocaine in aqueous and amphiphilic solutions

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NMR

The ^{1}H NMR spectra for prilocaine·HCl (HPLC) and prilocaine freebase (PLC) in $CDCl_3$ are shown in Fig. 1. The successful conversion of HPLC to PLC is clear from the significant upfield shift of H_{N2} from $\sim$10.5 ppm for HPLC to $\sim$2.6 in PLC. The ^{1}H spectra for HPLC in D_2O is also shown.

Seed potentials

Tables 1 & 2 show the seed potentials used for the EPSR simulation for HPLC in water and PLC in water/methanol solutions as described in the main text.

Methyl-N1 interactions

Figure 2 shows the -CH_3-N1 interactions between PLC and methanol in the methanol/water solutions as mentioned in the main text.

Methyl orientation below the methylphenyl ring

Figure 4 shows the Euler angle probability density maps used to generate the most likely orientation of methanol below the methylphenyl ring as depicted in Fig. 11 of the main text and and Figure 3 shows the definitions for the angles used in the analysis

Orientation of bridging water around N2

Figure 5 shows the Euler angle orientational probability maps for water around N2 on PLC used to generate Figure 13 in the main text. There is an expected symmetry in shifting ψ by 180 °given that the axes on water have this symmetry. The distribution of orientations indicate that although the preferential orientation is somewhat broad, it is highly likely that a single water molecule will form two hydrogen bonds on prilocaine. The distances used were the maxima for $g_{OHw}(r)$ and $g_{N2Hw}(r)$.

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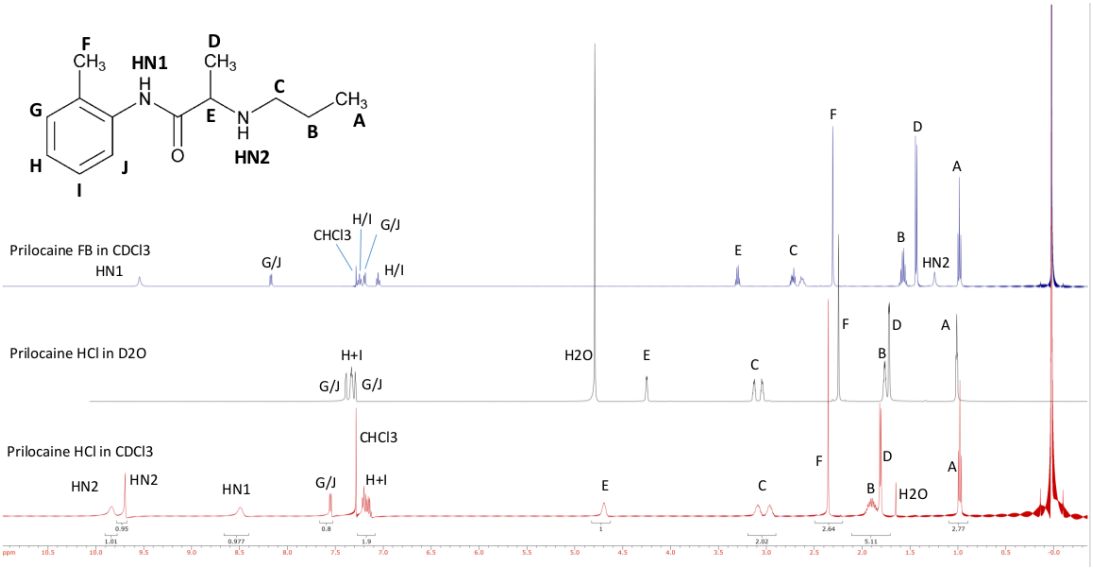

Fig. 1 (top) PLC in d-$CHCl_3$, (middle) HPLC in D_2O (the H_{Nx} peaks are suppressed from the rapid exchange with water) and (bottom) HPLC in d-$CHCl_3$.

	HPLC			PLC		
Atom Label	ε (kJ mol^{-1})	σ (Å)	q (e)	ε (kJ mol^{-1})	σ (Å)	q (e)
HB	0.0628	2.600	0.1540	0.0628	2.600	0.1540
HC2	0.0657	1.960	0.1190	0.0657	1.960	0.1060
HC3	0.0657	1.960	0.1030	0.0657	1.960	0.1000
HC4	0.0657	2.650	0.0692	0.0657	2.650	0.0652
HC5	0.0657	2.650	0.0620	0.0657	2.650	0.0580
HM2	0.0657	2.650	0.0830	0.0657	2.650	0.0770
HMB	0.0657	2.650	0.0494	0.0657	2.650	0.0454
HN1	0.0657	1.070	0.3330	0.0657	1.070	0.2000
HN2	0.0657	1.070	0.4670	0.0657	1.070	0.4000
C1	0.3600	3.400	0.6470	0.3600	3.400	0.5800
C2	0.4580	3.400	0.0365	0.4580	3.400	0.0365
C3	0.4580	3.400	0.1040	0.4580	3.400	0.1000
C4	0.4580	3.400	-0.1050	0.4580	3.400	-0.1350
C5	0.4580	3.400	-0.1020	0.4580	3.400	-0.1340
CB	0.3600	3.400	-0.1130	0.3600	3.400	-0.1230
CBM	0.3600	3.400	-0.0943	0.3600	3.400	-0.0993
CBN	0.3600	3.400	0.0116	0.3600	3.400	0.0106
CMB	0.4580	3.400	-0.0628	0.4580	3.400	-0.0684
CM2	0.4580	3.400	-0.1320	0.4580	3.400	-0.1320
N1	0.7110	3.250	-0.4190	0.7110	3.250	-0.4600
N2	0.7110	3.250	-0.7616	0.7110	3.250	-0.8000
O	0.8790	2.960	-0.6000	0.8790	2.960	-0.6000
Cl	0.4184	4.401	-1.0000			

Table 1 The prilocaine parameters used in the EPSR simulations of the samples.

Atom Label	ε (kJ mol^{-1})	σ (Å)	q (e)
Cm	0.2761	3.500	0.1450
Om	0.7113	3.120	-0.6830
Hm	0.1255	2.500	0.0400
Hmo	0.0000	0.000	0.4180
Ow	0.6500	3.166	-0.8476
Hw	0.0000	0.000	0.4238

Table 2 The parameters used in the EPSR simulations for the solvents. The first 4 atom types on methanol, Ow and Hw on water.

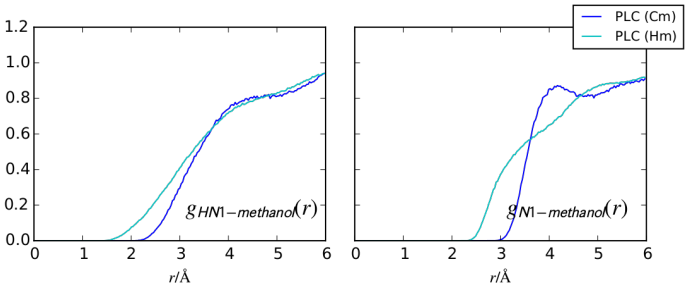

Fig. 2 $g(r)$s and SDMs for methanol OH interactions around N1 in the prilocaine methanol/water system

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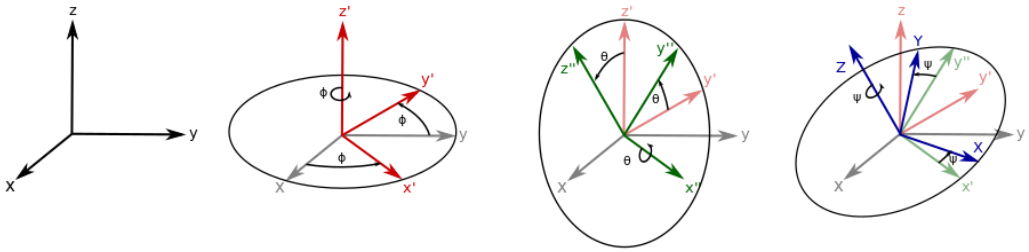

Fig. 3 Euler angle definitions used for ANGULA anlysis in main text

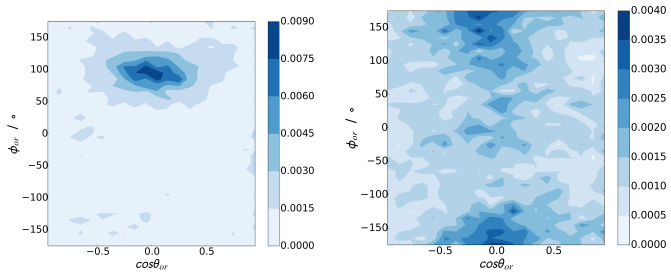

Fig. 4 Euler angle probability density maps for nearest neighbour methanol molecules underneath the methylphenyl ring. Left: ($cos\theta_{or}$, ϕ_{or}), right: ($cos\theta_{or}$, ψ_{or}).

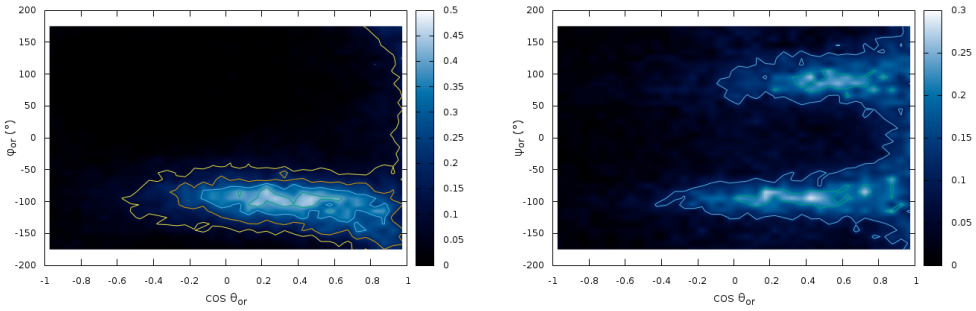

Fig. 5 Euler angle probability density maps for water around N2, plotted using the reference system from the amine nitrogen (N2) for PLC in methanol/water solution. Left: ($cos\theta_{or}$, ϕ_{or}), right: ($cos\theta_{or}$, ψ_{or}).