Supplementary Information: On the atomic structure of cocaine in solution

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Neutron Diffraction with Isotopic Substitution

Isotopomeric samples measured by neutron diffraction are listed in Table 1. By measuring these isotopically distinct samples, EPSR was used to extract information about all interatomic interactions.

As explained in the main text, the data were collected on the SANDALS diffractometer located at the ISIS Facility (STFC, UK). The data were subsequently corrected using the software program Gudrun, which is based on the ATLAS package and is also available through the ISIS Facility and can be freely accessed via https://www.facebook.com/disord.matt. The SANDALS instrument is further equipped with a transition monitor, which allows for the sample composition to be checked with the theoretical value calcuated from the weighted scattering lengths (see Eq. 1 Main text). In each case the scattering from the samples in Table 1 was within $\sim$ 10% of their theoretical values and, on average, $\sim$ 5% away.

The measured neutron diffraction data ($F(Q)$) along with the EPSR fits are shown in the main text. The measured X-ray and neutron diffraction data in real space ($G(r)$) along with the EPSR fits to the data are shown in Fig 1.

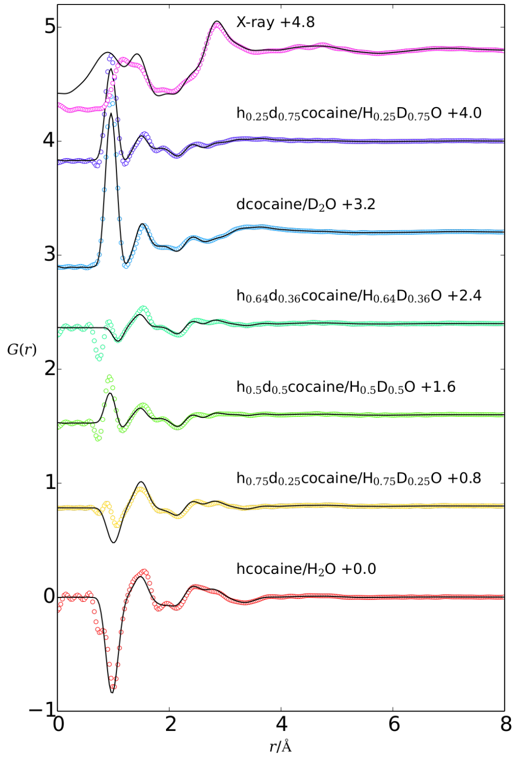

Fig. 1 Measured X-ray and neutron $F(Q)$ (colored lines) and EPSR fits to the data (black lines) in real space.

Empirical Potential Structure Refinement

As is described in the main text, EPSR is a reverse Monte Carlo technique, specifically designed for disordered materials, that models structure using experimental data as a di-

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Sample Name	Cocaine Hydrochloride	Water
1	hcocaine	H_2O
2	$h_{0.75}d_{0.25}$cocaine	$H_{0.75}D_{0.25}O$
3	$h_{0.5}d_{0.5}$cocaine	$H_{0.5}D_{0.5}O$
4	$h_{0.64}d_{0.36}$cocaine	$H_{0.64}D_{0.36}O$
5	dcocaine	D_2O
6	$h_{0.25}d_{0.75}$cocaine	$H_{0.25}D_{0.75}O$

Table 1 The components of the six samples measured by neutron diffraction. The molar ratio used was 1 cocaine hydrochloride: 65 water. Subscripts indicate isotopic proportions. hcocaine and dcocaine refer to cocaine molecules where the atom attached to the nitrogen is H or D, respectively. Sample 1 was also measured by X-ray diffraction.

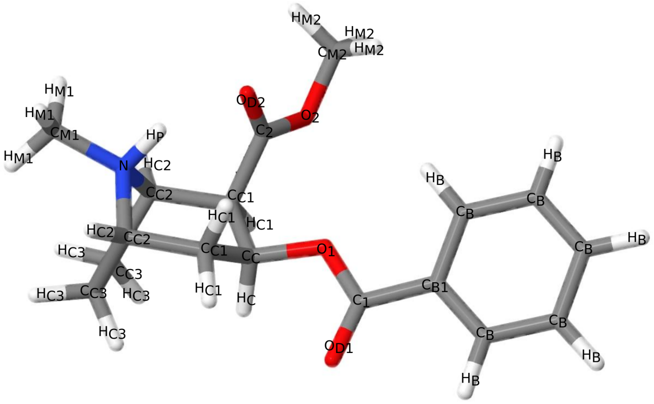

Fig. 2 The full labelling scheme for protonated cocaine.

rect constraint. Bonded interactions are defined by harmonic potentials, and intermolecular interactions are defined by Lennard-Jones potentials and point charges. $F(Q)$ is then calculated and compared with the measured data. Subsequently, non-bonded interactions are updated with a newly derived empirical potential until a structure is produced which results in a simulated $F(Q)$ that closely matches all of the measured $F(Q)$ data sets.

A summary of the parameters used for the atoms in EPSR, the labelling scheme for cocaine being depicted in Fig. 2, is shown in Table 2. Parameters for water molecules were taken from the SPC/E water model[1]. Parameters used for cocaine and Cl^- ions were generated in AMBER format with ANTECHAMBER[2,3] and converted to GROMACS format using the amb2gmx.pl script.[4]. Subsequently, collections of atoms were grouped together depending on the similarity of their charges. For example, benzene ring hydrogens, whose charges ranged from 0.145e-0.161e, were grouped together and collectively labelled as H_B. Sometimes atoms with similar parameters were not grouped together so that their individual behaviour could be understood, such as the carbonyl oxygens.

Atom Label	ε/KJ mol^{-1}	σ/Å	Charge/e
C_{B1}	0.4577	3.3997	-0.15360
C_B	0.4577	3.3997	-0.09720
H_B	0.0628	2.5996	0.15160
C_1	0.3598	3.3997	0.66970
O_{D1}	0.8786	2.9559	-0.53700
O_1	0.7113	3.0000	-0.44890
N	0.7113	3.2500	-0.71140
H_P	0.0657	1.0691	0.48980
C_{M1}	0.4577	3.3997	0.09110
H_{M1}	0.0657	1.9600	0.10100
C_2	0.3598	3.3997	0.64710
O_{D2}	0.8786	2.9599	-0.57700
O_2	0.7113	3.0000	-0.39390
C_{M2}	0.4577	3.3997	0.11970
H_{M2}	0.0657	1.9600	0.06970
C_C	0.4577	3.3997	0.16110
C_{C1}	0.4577	3.3997	-0.14305
C_{C2}	0.4577	3.3997	0.14600
C_{C3}	0.4577	3.3997	-0.10390
H_C	0.0657	2.4714	0.09470
H_{C1}	0.0657	2.6495	0.11737
H_{C2}	0.0657	1.9600	0.11920
H_{C3}	0.0657	2.6495	0.09400
Cl	0.4184	4.4010	-1.0000
O_w	0.65000	3.1660	-0.84760
H_w	0.0000	0.0000	0.42380

Table 2 The parameters used in the EPSR simulations of cocaine hydrochloride/water.

Verification of Cocaine Deuteration

As mentioned in the main text, how successfully the protonated form of cocaine had been deuterated was verified by measurement of cocaine dissolved in $CDCl_3$ using ^{1}H NMR. The relevant spectra are shown in Fig. 3.

This figure shows that H_P, which is the lone exchangeable proton and, for 100% successful deuteration, should not be visible in ^{1}H NMR, is significantly smaller in the deuterated cocaine spectrum. In fact, it is only 7% of the size of the H_P in the protonated cocaine spectrum. Although in NMR spectra that correspond to exchangeable protons can be difficult to integrate because of their broad shape, a high level of deuteration of this hydrogen has been achieved. Moreover, the fully deuterated sample (sample 5 in Table 1) had an experimental scattering cross section 97% of that which would be theoretically expected.

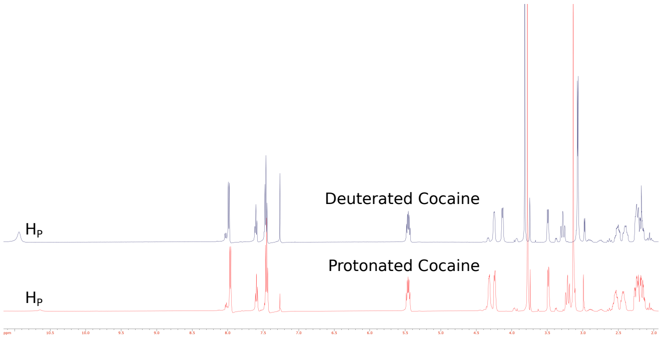

Fig. 3 ^{1}H NMR spectra of deuterated (blue) and protonated (red) cocaine dissolved in $CDCl_3$.

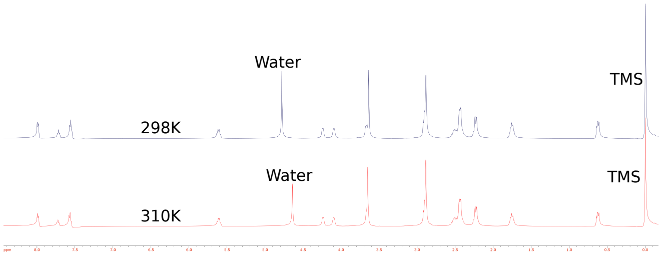

Fig. 4 ^{1}H NMR spectra of protonated cocaine dissolved in D_2O at a concentration of 55mM (1 mole cocaine:1000 moles water) at temperatures of 298K (blue) and 310K (red). TMS was used as a standard. H_P is not visible due to exchange with the water deuteriums.

The Effect of Temperature on Structure

In order to confirm that performing neutron diffraction measurements at a temperature of 298K did not mean a different stucture was measured to that which exists at more physiologically relevant temperatures, ^{1}H NMR measurements were performed for cocaine dissolved in D_2O at a concentration of 55mM for temperatures of 298K and 310K. These spectra are shown in Fig. 4, where TMS was used as a standard.

Fig. 4 indicates that there is no change in structure in this temperature range. The only change in chemical shift is a small shift observed for the water peak.

Orthonormal Coordinate Systems Assigned to Cocaine

Fig. 5 displays the orthonormal coordinate systems that were assigned to fragments of the cocaine molecule in order for the distribution of water molecules about cocaine to be analysed using ANGULA.

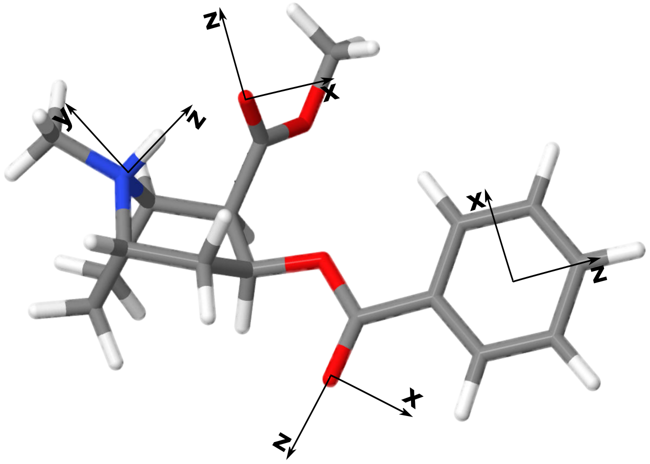

Fig. 5 The coordinate systems assigned to the cocaine molecule in ANGULA.

Torsional Angle Distribution

Fig. 6 shows the distribution of selected torsional angles of the cocaine molecules in the EPSR simulation box. The torsional angle distributions shown were chosen as they correspond to fragments of the cocaine molecule able to rotate.

$\phi_{O_1-C_1-C_{B1}-C_B}$ indicates that the benzene ring of cocaine is generally found within 50^0 of being in the plane of O_1. In contrast, $\phi_{CC-O_1-C_1-C_{B1}}$ shows that the piperidine ring is usually at 30^0 relative to the plane of the benzene ring. This torsional angle distribution implies that cocaine rarely folds back on itself, such that water correlations with the benzene ring are not as a result of associations of water with other parts of the cocaine molecule. A similar distribution of angles is seen for the second methyl group. The angular distribution corresponding to this second methyl group places CM_2 above the ester linkage. $\phi_{C_C-C_{C1}-C_2-O_2}$ is $\sim 100^0$ and $\phi_{C_{C2}-C_{C1}-C_2-O_2}$ is $\sim 125^0$, which results in O_{D2} facing H_P.

The Most Probable Nearest Neighbor Water Molecule

In order to plot the position and orientation of the most probable nearest neighbor water molecule of H_P, a 2D contour map of the the nearest neighbor water molecules of H_P was first plotted. This contour map, shown in Fig. 7 A, shows the relative positions of the origins (center of masses - CM) of the sets of axes assigned to this fragment of the cocaine molecule (see Fig. 5) and the water molecules in polar coordinates. From the contour map of the nearest neighbor water molecules around H_P, the area of the highest density of nearest neighbor water molecules was then selected. Contour maps corresponding to this area were then plotted showing the angles between the

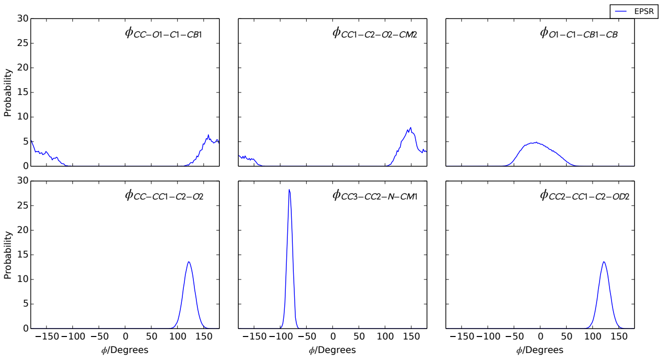

Fig. 6 Selected torsional angles of the cocaine molecules in the EPSR simulation box.

sets of axes assigned to cocaine and water (Euler angles), as shown in Fig. 7 B. Consequently, the most probable angles between the sets of axes, and hence the relative orientation of water molecules, was extracted. Feeding these values into a plotting program, along with the position of the peak of the RDF for the selected area of density of nearest neighbor water molecules, allows Fig. 7 C to be plotted.

Water-water RDFs

Fig. 8 shows RDFs for the interactions between water molecules in the system. Corresponding RDFs extracted from an EPSR simulation of pure water[5] are shown for comparison. As can be seen from Fig. 8, the water structure is largely unaffected by the addition of cocaine molecules, the position and form of the peaks in the cocaine/water system being broadly consistent with those of pure water.

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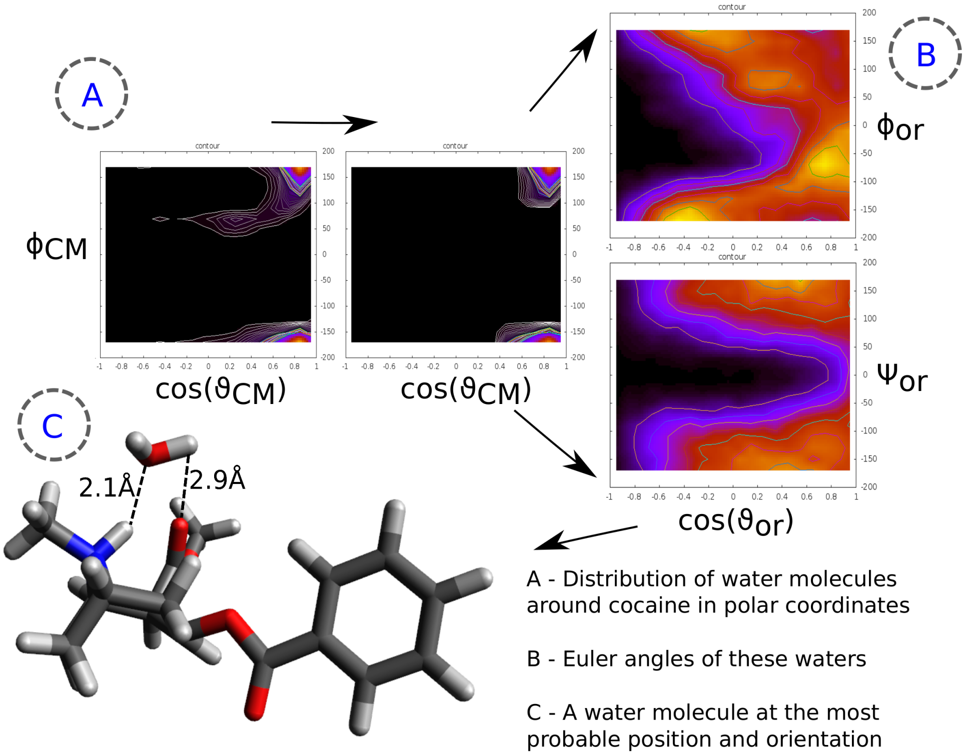

A - Distribution of water molecules around cocaine in polar coordinates

B - Euler angles of these waters

C - A water molecule at the most probable position and orientation

Fig. 7 A flow chart showing the process by which the orientation and position of the most probable nearest neighbor water molecule of H_P was extracted.

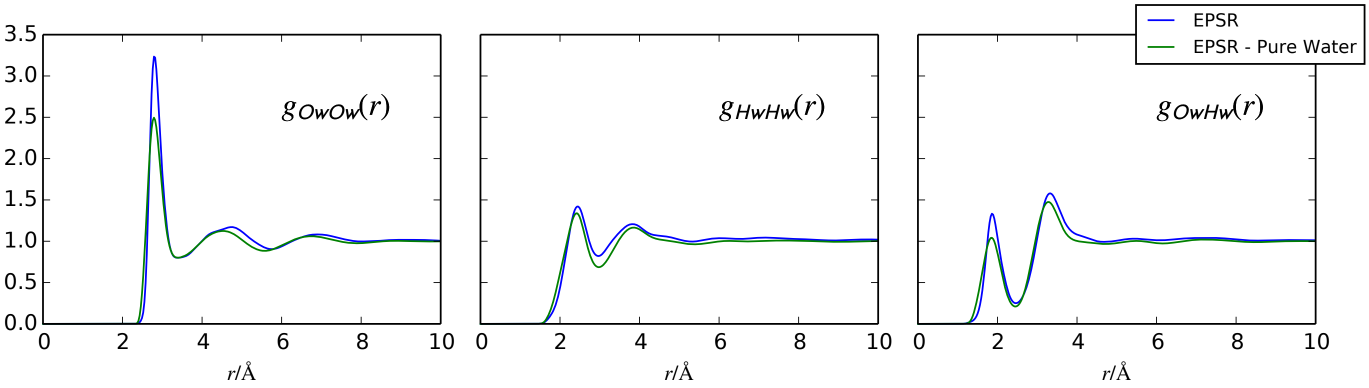

Fig. 8 RDFs for the interactions between water molecules extracted from EPSR simulations of cocaine hydrochloride dissolved in water (blue) and pure water[5] (green).