

# ELECTRONIC SUPPLEMENTARY INFORMATION

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## **A Digital Workflow from Crystallographic Structure to Single Crystal Particle Attributes for Predicting the Formulation Properties of Terbutaline Sulphate**

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### Abstract

The utility of synthonic modelling approach in understanding of organic salt materials (inhalation drug) at molecular scale by following a pathway from a molecule, intermolecular packing, crystal morphology, notably possibilities of calculated surface energy and hence predicted surface properties is presented in the main paper and in this supplementary material some additional information is provided. This comprises:

S1. Electronic charge

S2. Synthon analysis for strongest terbutaline-terbutaline cations, sulfate –sulfate anions in crystal lattice

S3. Analysis of the Surface Chemistry of the Habit Planes

S4. Visualization of preferred binding position of probe molecules (ethyl acetate, chloroform and toluene) on TBS crystal surfaces

S5. Adsorption Isotherms for the probes used in inverse gas chromatography

S6. Comparing the calculated lattice energy using Tripos forcefield and the enthalpy of sublimation for anhydrous sodium dodecyl sulfate (to validate the Tripos force field which can be used to calculate lattice energy for sulfate salt).

### S1. Partial atomic charges calculated from MOPAC

Atom	Atomic charges	Atom	Atomic charges
S1	2.8182	H19	0.1070
O1	-1.1332	H20	0.0917
O2	-1.1588	C13	-0.0666
O3	-1.2283	C14	-0.1355
O4	-1.2369	C15	0.1221
C1	-0.0668	C16	-0.2199
C2	-0.1636	C17	0.1224
C3	0.1696	C18	-0.2305
C4	-0.2307	O8	-0.2239
C5	0.1050	O9	-0.2421
C6	-0.1828	C19	0.0807
O5	-0.2243	O10	-0.3095
O6	-0.2578	C20	-0.0727
C7	0.0891	N2	0.0153
O7	-0.2643	C21	-0.0167
C8	-0.1344	C22	-0.1974
N1	0.0074	C23	-0.1955
C9	-0.0202	C24	-0.1820
C10	-0.1819	H21	0.1461
C11	-0.1975	H22	0.1345
C12	-0.1852	H23	0.1197
H1	0.1697	H24	0.2090
H2	0.1339	H25	0.2054
H3	0.1178	H26	0.1392
H4	0.2785	H27	0.2246
H5	0.2069	H28	0.1007
H6	0.0667	H29	0.1106
H7	0.1616	H30	0.2045
H8	0.1123	H31	0.2846
H9	0.1826	H32	0.0762

H10	0.1911	H33	0.1419
H11	0.2263	H34	0.0777
H12	0.1006	H35	0.0800
H13	0.0959	H36	0.0929
H14	0.1091	H37	0.0787
H15	0.0805	H38	0.0820
H16	0.0936	H39	0.0778
H17	0.1088	H40	0.1288
H18	0.0799		

## S2. Synthons analysis

The strongest repulsions within the crystal structure were found to be between the sulfate anions.

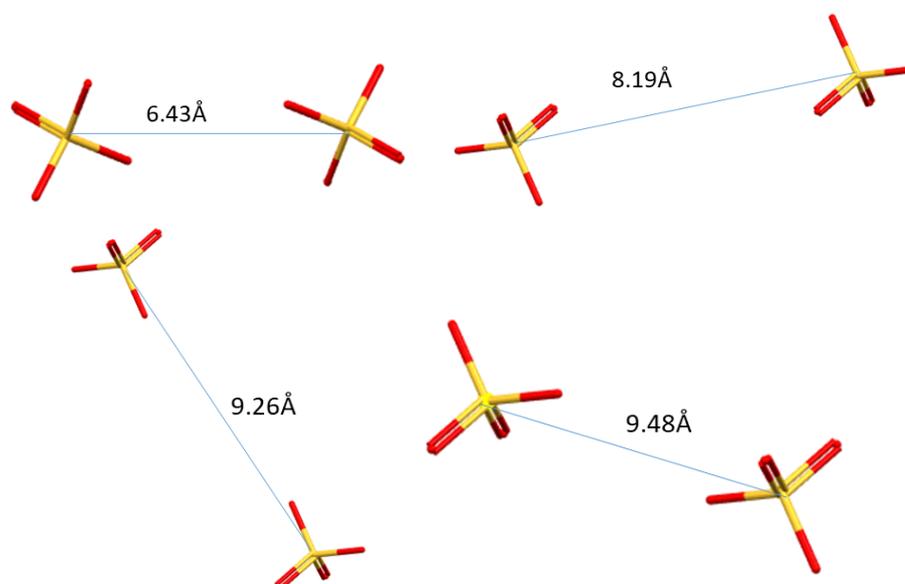
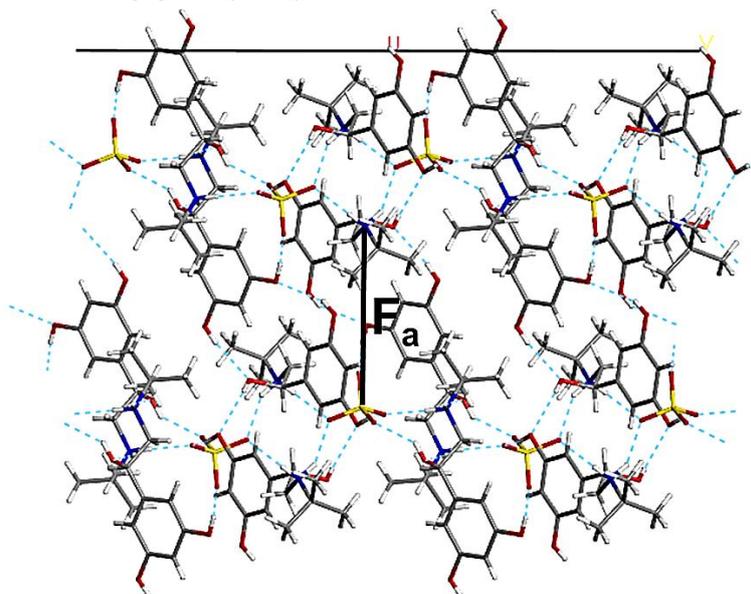


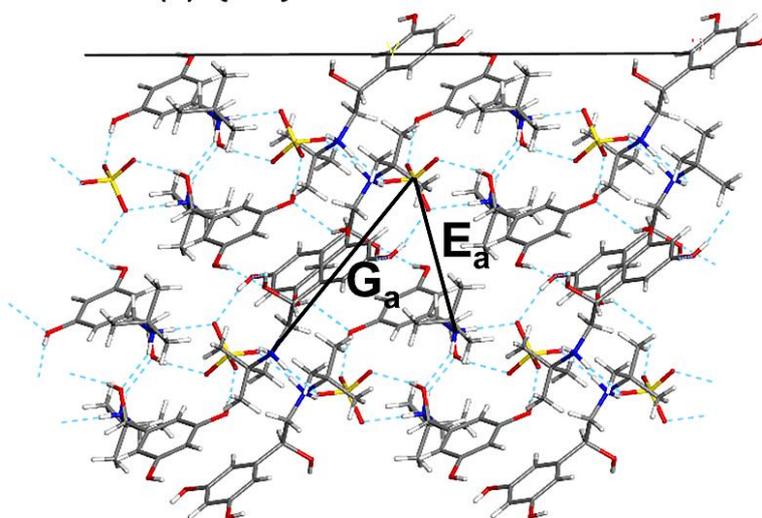
Figure S1. Molecular orientation of the top 4 repulsive synthons, indicating that the major repulsions were between the sulfate ions. All distances are quoted between sulfur atoms.

## S3. Analysis of the Surface Chemistry of the Habit Planes

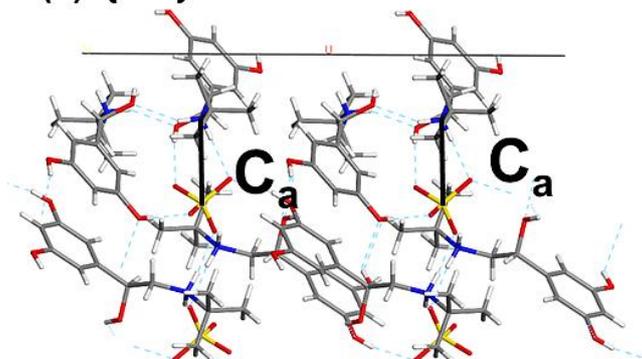
(a) {010}



(b) {100}



(c) {001}



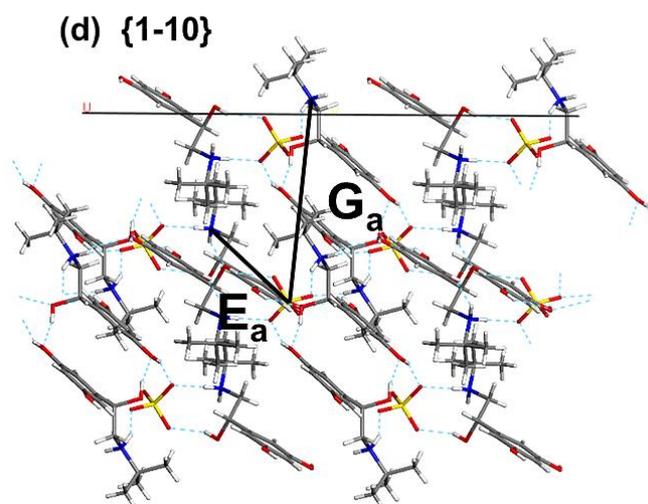


Figure S2. Molecular packing diagrams based upon the crystallographic structures: (a) molecular orientation at the  $\{010\}$  face with the strong synthons  $F_a$  marked as contributing to  $E_{ATT}$ ; (b) molecular orientation of the  $\{100\}$  surface with synthons  $E_a$  and  $G_a$  marked as contributing to  $E_{ATT}$ ; (c) molecular orientation of the  $\{001\}$  surface with synthons  $C_a$  marked as contributing to  $E_{ATT}$ ; and (d) molecular orientation of the  $\{1\bar{1}0\}$  surface with synthons  $E_a$ ,  $F_a$  and  $G_a$  contributing to the attachment energy ( $E_{ATT}$ ). Note that in this  $\{1\bar{1}0\}$  projection the  $F_a$  synthon is obscured by other molecules in the structure and hence is not easy to visualise.

#### **S4. Preferred binding position of probe molecules on TBS crystal surfaces**

The molecular orientations of the strongest interactions found from the SystSearch of an acetone, ethyl acetate, chloroform and toluene molecule (displayed in a ball and stick model) at the  $\{010\}$  surface,  $\{100\}$  surface,  $\{001\}$  surface and  $\{1\bar{1}0\}$  surface of TBS crystals (displayed in a stick model) were visualised using the Mercury software.

## S4.1 Acetone

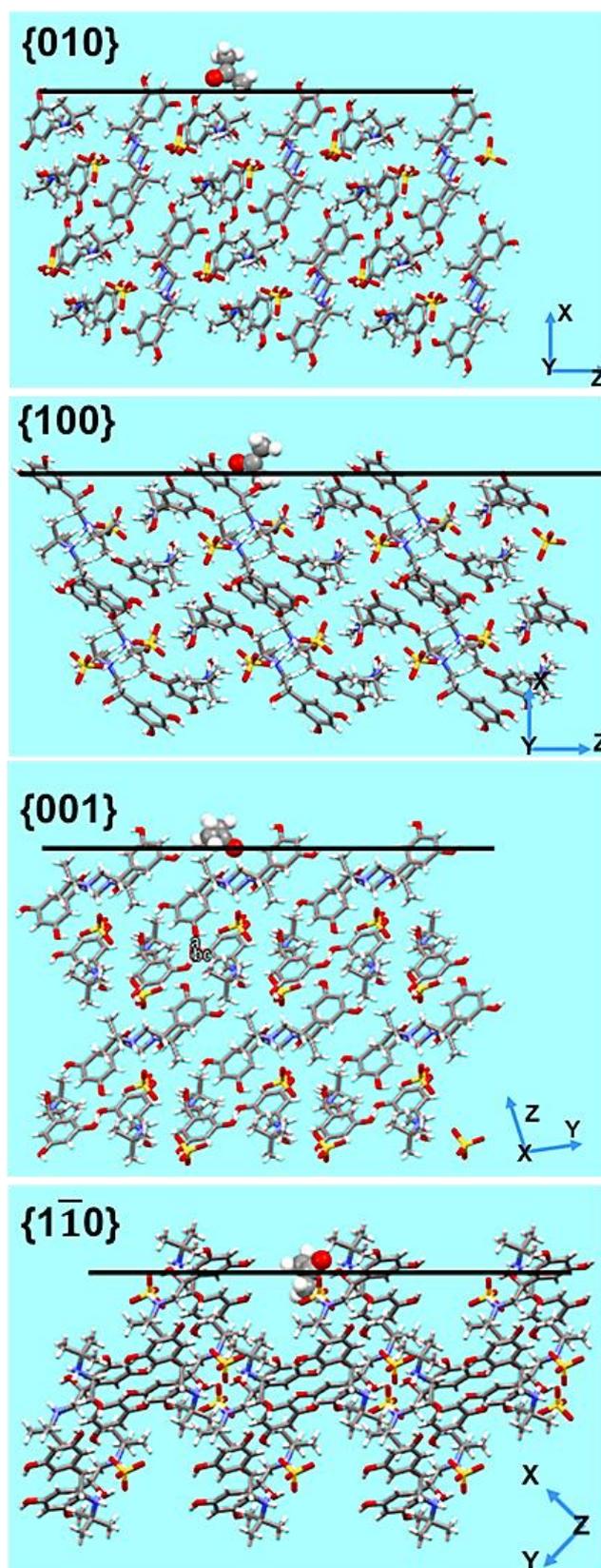


Figure S3. Preferential binding position of an acetone molecule at the TBS crystal surfaces.

## S4.2 Ethyl acetate

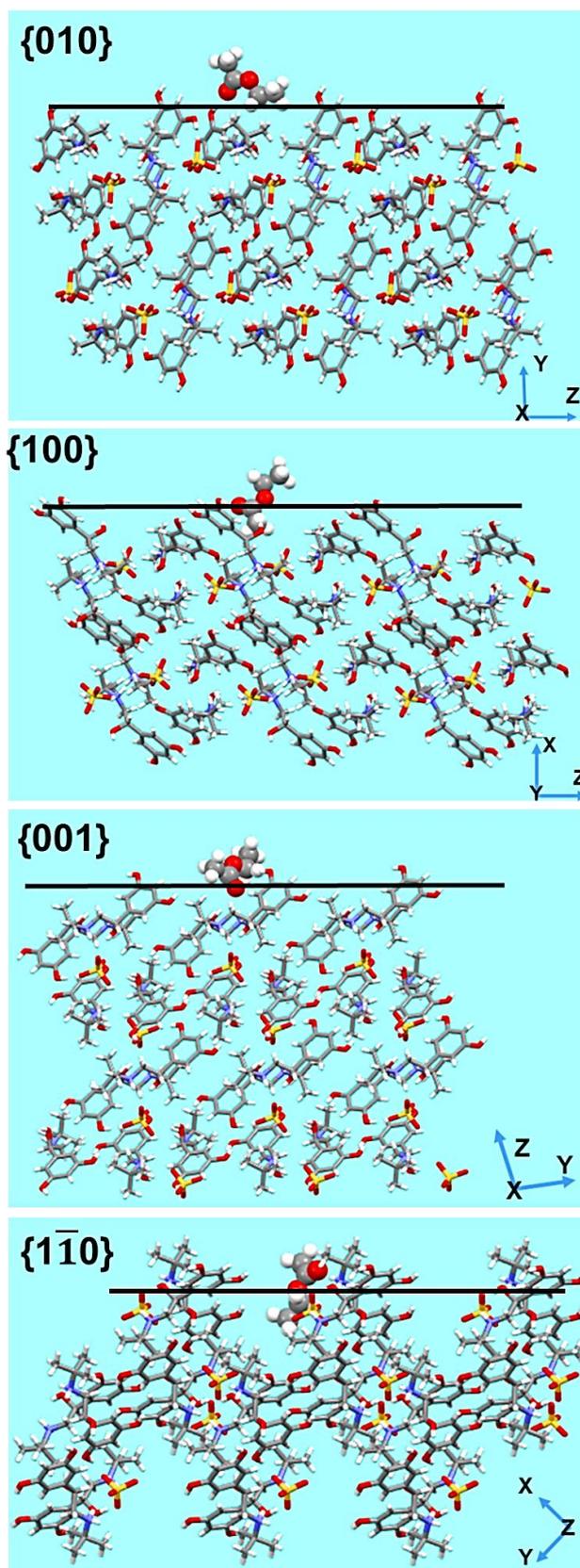


Figure S4. Preferential binding position of an ethyl acetate molecule at the TBS crystal surfaces.

### S4.3 Chloroform

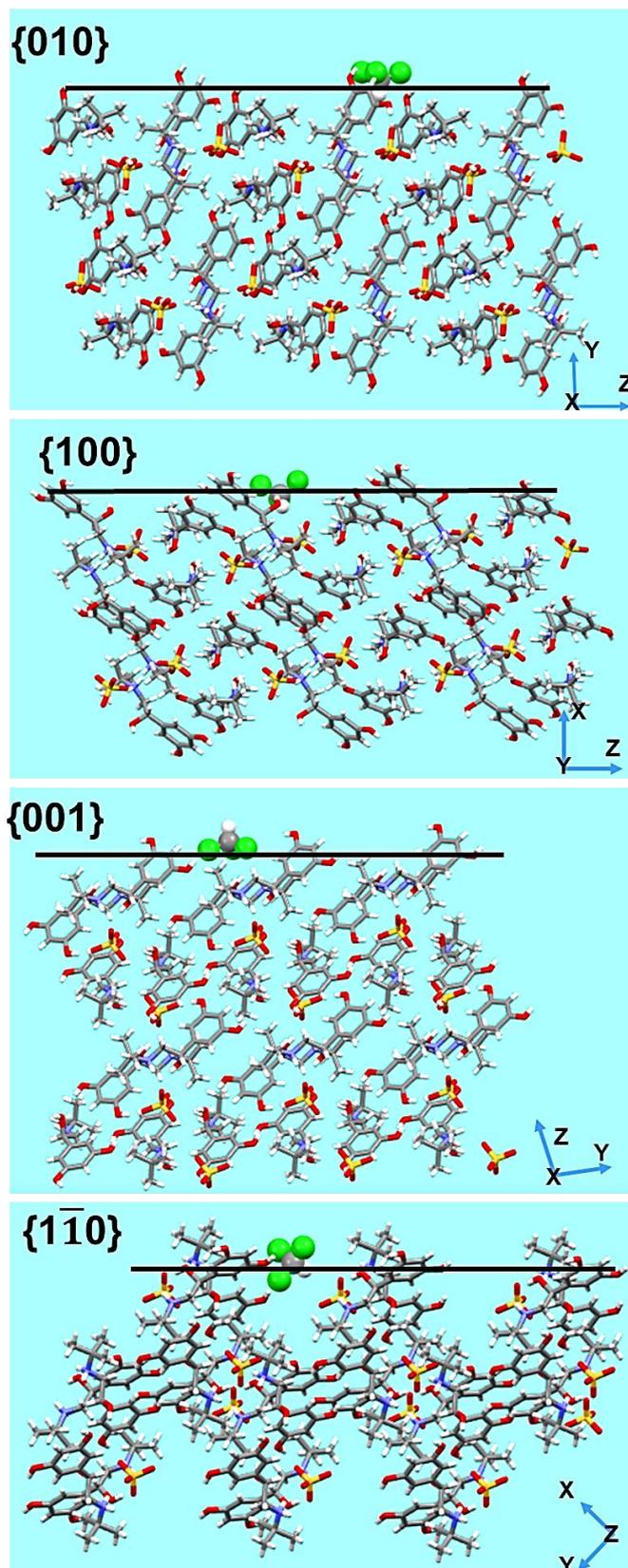


Figure S5. Preferential binding position of a chloroform molecule at the TBS crystal surfaces.

## S4.4 Toluene

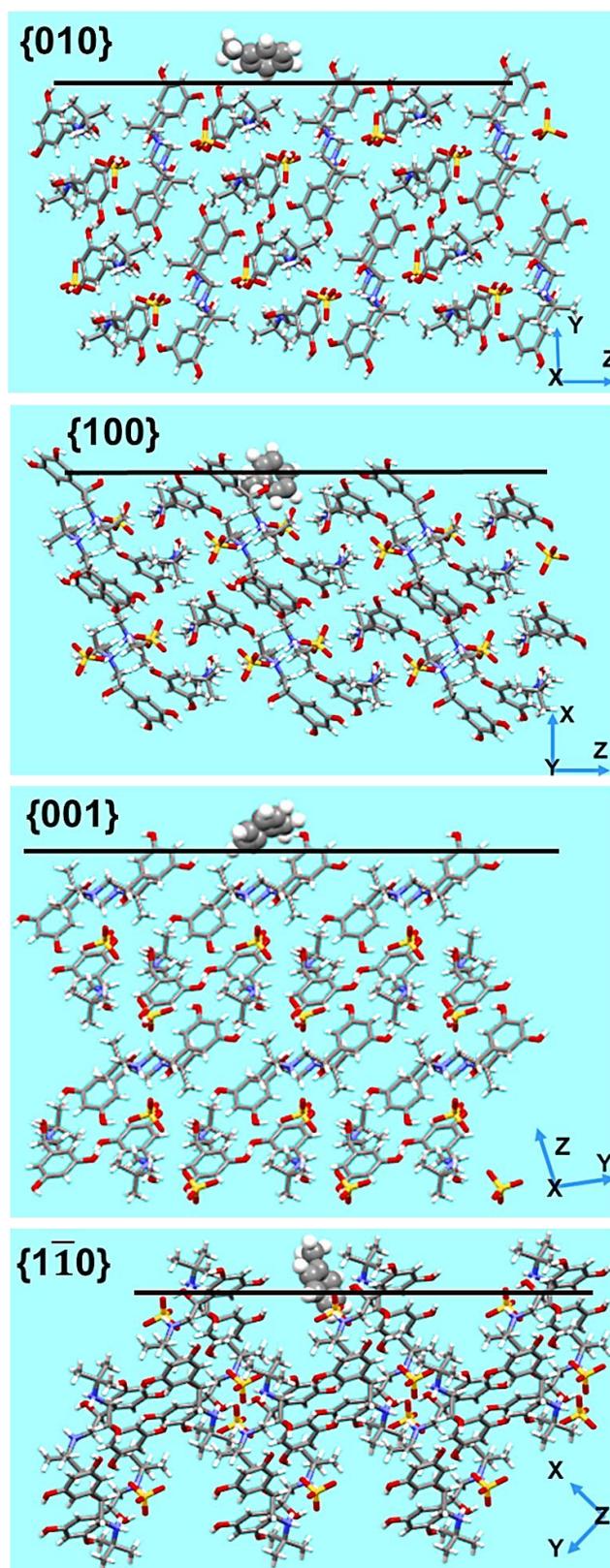


Figure S6. Preferential binding position of a toluene molecule at the TBS crystal surfaces.

## S5. IGC data

Adsorption isotherms produced from the adsorbed amount of the probes as a function of the partial pressure in the iGC-SEA, over the range of targeted surface coverages 0.5%-13 %.

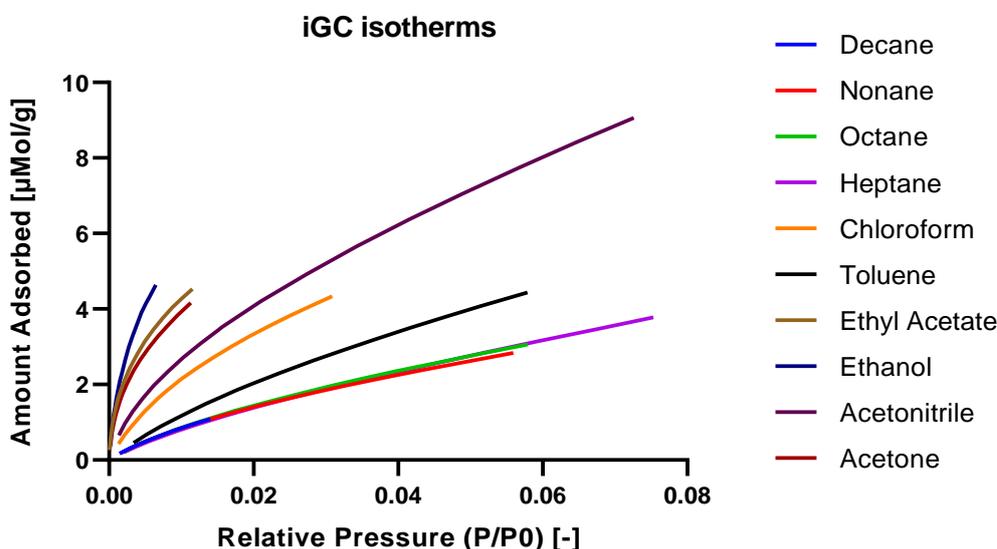


Figure S7. Adsorption Isotherms for the probes used in inverse gas chromatography

## S6. Comparing the calculated the lattice energy using Tripos forcefield and the enthalpy of sublimation for anhydrous sodium dodecyl sulfate

In this calculation the atomic coordinates were taken from the crystal structure (CSD reference code VECYOR01) <sup>1</sup>. The partial charges were used from the previous publication <sup>2</sup>. The later paper reports a molar dissolution enthalpy in water for SDS of 7.63 kcal/mol, the molar enthalpies of hydration for dodecyl sulfate anion of 67.0 kcal/mol and sodium cation of 98.5 kcal/mol. An enthalpy of sublimation for SDS, assuming ideal solutions, can be estimated as  $7.63 + 0.5 \cdot (67.0 + 98.5) = 90.4$  kcal/mol (mole of salt).

The lattice energy was calculated to be -93.2 kcal/mol on the same basis (with the coulombic contribution -81.7 kcal/mol and van der Waals contribution -11.5 kcal/mol).

The data showed that there is a good agreement between the enthalpy of sublimation and the calculated lattice energy using Tripos force for anhydrous sodium dodecyl sulfate.

## References

1. L. Smith, R. Hammond, K. Roberts, D. Machin and G. McLeod, *Journal of Molecular Structure*, 2000, **554**, 173-182.
2. L. A. Smith, G. B. Thomson, K. J. Roberts, D. Machin and G. McLeod, *Crystal growth & design*, 2005, **5**, 2164-2172.