Model systems for molecular recognition at interfaces: synthesis and characterisation of functionalised disulfides with hydrogen-bonding properties

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A series of symmetrical alkane disulfides bearing derivatives of barbituric acid and 2,4,5,6-tetraaminopyrimidine, respectively, as headgroups are synthesised, which can be used for the preparation of functionalised monolayers on gold.

Molecular recognition events at biological interfaces play a vital role in countless transport and regulation processes.[1,2] However, the complexity of biological membranes and the recognition processes involved makes direct examination difficult and still poses a substantial challenge for scientific research. Therefore, model systems have been developed to study interfacial recognition events under more amenable conditions. One such model system is based on self-assembled monolayers (SAMs) of alkane disulfides on gold, combining both simplicity and stability with a high degree of organisation.[3,4]

The formation of supramolecular structures in organic solution from barbituric acid and 2,4,6-triaminopyrimidine (TAP) or related derivatives was previously reported,[5,6] as was the formation of monomolecular films at the air–water interface.[7,8] The molecular recognition results from six hydrogen bonds per molecule between the complementary barbituric acid and TAP, lending a high degree of selectivity to these model systems. Recently, Motesharei and Myles used fluorescence spectroscopy to study the interaction of derivatised barbituric acid with monolayers on gold containing a specifically designed complementary receptor.[9]

This communication describes the synthesis of functionalised disulfides for the preparation of monolayers on gold and for probing molecular recognition events at solid–liquid interfaces between barbituric acid and TAP derivatives. A barbiturate-functionalised alkane disulfide **1** was synthesised, as were four different alkane disulfides functionalised with 2,4,5,6-tetraaminopyrimidine **2**–**5** (Fig. 1).† The corresponding SAMs were prepared on gold and their structures characterised by means of FTIR spectroscopy and contact angle measurements.

Disulfide **1** was prepared according to Scheme 1. Commercially available 4-hydroxybenzaldehyde **6** was protected as an imine by reacting it with aniline. Alkylation of the phenolic hydroxy group with 11-bromoundecan-1-ol gave the phenyl ether **7**. The imine was hydrolysed, the hydroxy group converted to the corresponding methanesulfonate, and the disulfide moiety was introduced in two steps *via* the S-alkyl thiosulfate, using first $Na_2S_2O_3$ and then thiourea–HCl, to afford disulfide **8**. The formation of barbiturate **1** was achieved by treating **8** with barbituric acid and pyridine under anhydrous conditions.

Compounds **2**–**5** were prepared from 11-bromoundecanoic acid, 16-hydroxyhexadecanoic acid, 4-(11-hydroxyundecyloxy)benzoic acid and 4-[4-(3-hydroxypropyl)phenyl]butyric acid **11**, respectively. 4-(11-Hydroxyundecyloxy)benzoic acid was synthesised from 4-hydroxybenzoic acid ethyl ester and 11-bromoundecan-1-ol using the same conditions as in Scheme 1 (step ii), followed by hydrolysis of the ester and **11** was synthesised in four steps according to Scheme 2 (steps i–iv). As depicted in Scheme 2 (steps v–ix) the ω-hydroxycarboxylic acids were then converted to the corresponding methanesulfonates, which as well as 11-bromoundecanoic acid, were treated with $Na_2S_2O_3$ and thiourea–HCl to afford bis(ω-carboxyalkyl)disulfides such as **12**. The amides, such as **5**, were formed by first reacting the carboxylic acid moieties with oxalyl chloride to afford the corresponding acid chlorides and, subsequently, treating these with a solution of 2,4,5,6-tetraaminopyrimidine in aqueous NaOH.

SAMs described here include pure monolayers of disulfides **1**–**5**, as well as mixed monolayers of disulfides **2**, **3** and **5**, respectively, with bis(11-hydroxyundecyl)disulfide in solution ratios of 1 : 1, 1 : 2, 1 : 5 and 1 : 10. However, the exact ratios of disulfides **2**, **3**, **5** and bis(11-hydroxyundecyl)disulfide chemi-

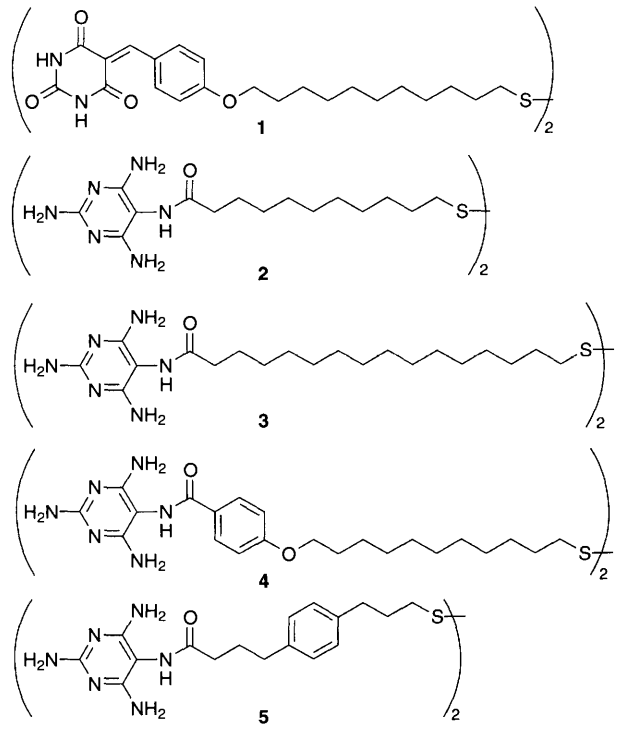
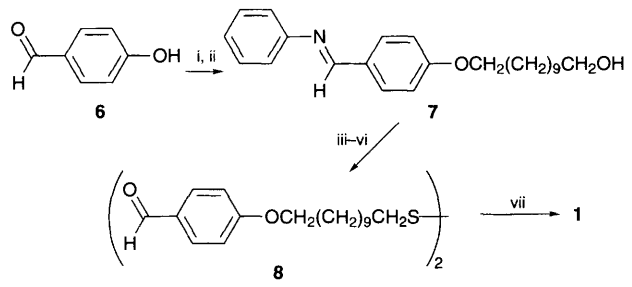


Fig. 1 Molecular structures of functionalised disulfides **1**–**5**



Scheme 1 *Reagents and conditions*: i, aniline, EtOH, 75%; ii, $BrCH_2(CH_2)_9CH_2OH$, K_2CO_3 KI (cat.), 4-methylpentan-2-one, reflux, 86%; iii, HCl aq., THF, 91%; iv, $MeSO_2Cl$, NEt_3, THF, 0 °C, 76%; v, $Na_2S_2O_3$, H_2O, EtOH, reflux; vi, thiourea, HCl aq., EtOH, reflux, 69%; vii, barbituric acid, pyridine, $CHCl_3$, reflux, 47%

sorbed to the gold surface were not determined. The introduction of bis(11-hydroxyundecyl)disulfide serves to separate the relatively bulky TAP moieties on the gold surface. The SAMs were formed by immersion of thin gold-film coated glass slides into EtOH solutions containing either the corresponding functionalised disulfide alone or both the disulfide and bis(11-hydroxyundecyl)disulfide.‡

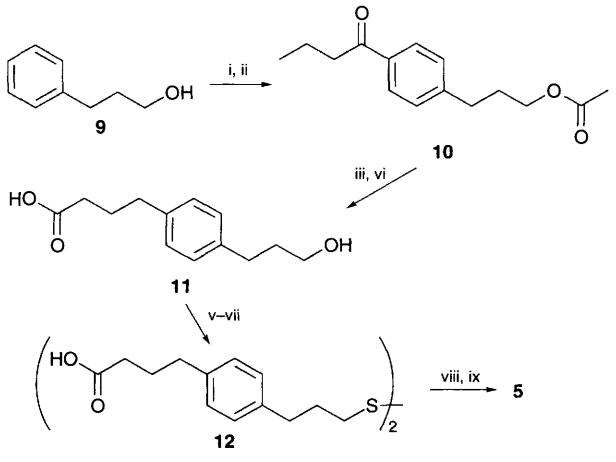
Grazing-angle FTIR spectroscopy§ has proved a useful technique for obtaining information as to whether the packing of alkane chains is solid- or liquid-like, as determined from the peak positions of the asymmetric (ν_{as}) and symmetric (ν_s) C–H stretching modes of the methylene groups.[10] Unlike straight-chain alkane disulfides [$\nu_{as}(CH_2)$ = 2919 cm^{-1}, $\nu_s(CH_2)$ = 2851 cm^{-1}, for hexadecane disulfide], which pack in a crystal-like structure, bis(11-hydroxyundecyl)disulfide [$\nu_{as}(CH_2)$ = 2925 cm^{-1}, $\nu_s(CH_2)$ = 2854 cm^{-1}] was found to self-assemble in a liquid-analogous phase, which is more suitable as a model system for molecular recognition at a biological surface.

SAMs obtained for disulfides **1** [$\nu_{as}(CH_2)$ = 2921, 2924¶ cm^{-1}, $\nu_s(CH_2)$ = 2853, 2854¶ cm^{-1}], **2** [$\nu_{as}(CH_2)$ = 2923 cm^{-1}, $\nu_s(CH_2)$ = 2852 cm^{-1}], **4** [$\nu_{as}(CH_2)$ = 2928 cm^{-1}, $\nu_s(CH_2)$ = 2855 cm^{-1}] and **5** [$\nu_{as}(CH_2)$ = 2923 cm^{-1}, $\nu_s(CH_2)$ = 2856 cm^{-1}] all showed a liquid-analogous phase, with the exception of disulfide **3** [$\nu_{as}(CH_2)$ = 2918 cm^{-1}, $\nu_s(CH_2)$ = 2849 cm^{-1}], which is probably due to the increase in chain length favouring tighter packing within the alkane chain region. It can be inferred that end groups such as barbiturate or TAP, which are bulky relative to the cross section area of the alkane chains viewed along their long axis, favour less tight packing and a liquid-analogous phase results.

Similar results were obtained for mixed monolayers. The asymmetric and symmetric C–H stretching modes were observed within the ranges 2922–2924 and 2851–2855 cm^{-1}, respectively, indicating a liquid-analogous phase for all mixed monolayers, including those of **3**. For disulfides **2** and **3**, the peak intensity of the modes associated with the TAP end group was found to decrease with increasing amount of bis(11-hydroxyundecyl)disulfide in solution. For disulfide **5**, however, the intensity remained almost constant, indicating that the SAMs do not contain the corresponding proportion of bis(11-hydroxyundecyl)disulfide, possibly due to the fact that mixing straight-chain alkane disulfides with disulfides containing an aromatic system in the hydrophobic region is unfavourable.

Contact angle measurements using *n*-hexadecane showed continuous wetting on all monolayers. Advancing contact angles measured with water were in the range 50–59° for disulfides **1**, **2**, **4**, **5** and 77° for disulfide **3**, in accord with values expected for a liquid-like monolayer with polar end groups and a more solid-like monolayer, respectively.[10] The contact angles for the mixed monolayers, containing both the TAP-functionalised disulfides **2**, **3**, **5** and bis(11-hydroxyundecyl)disulfide, did not vary significantly from those obtained for the pure monolayers.

In summary, by employing SAMs of functionalised disulfides, a range of model systems has been established which are stable and easy to prepare and can be used for the examination of interfacial molecular recognition processes. To this end, experiments utilising FTIR, surface plasmon resonance (SPR), atomic force microscopy (AFM) and quartz crystal microbalance (QCM) measurements are currently underway to observe the molecular recognition processes, and will be reported later.



Scheme 2 *Reagents and conditions*: i, acetic anhydride, pyridine, 82%; ii, PrCOCl, $AlCl_3$, 1,2-dichloroethane, 0 °C, 86%; iii, sulfur, morpholine, 140 °C; iv, KOH aq., EtOH, reflux, 14%; v, $MeSO_2Cl$, NEt_3, THF, 0 °C, 71–99%; vi, $Na_2S_2O_3$, H_2O, EtOH, reflux; vii, thiourea, HCl aq., EtOH, reflux, 66–88%; viii, oxalyl chloride, THF; ix, 2,4,5,6-tetraaminopyrimidine, NaOH aq., 11–14%

Footnotes

† All new compounds were characterised by FTIR, NMR, MS and microanalysis. We estimate that, due to the method of preparation, the products contain less than 5% of a species where only one headgroup was converted to the corresponding barbiturate or amide.

‡ *Preparation of the gold surface.* Microscope slides as supplied by manufacturer were cleaned thoroughly (NOCHROMIX®/sulfuric acid) and precoated with 6 nm of chromium followed by 130 nm of gold, both evaporated at a pressure of 5×10^{-6} mbar from a resistively heated tungsten boat.

Preparation of the monolayers. Gold-coated slides were immersed into a freshly made anhydrous ethanolic solution of the corresponding disulfide (10^{-4} mol dm^{-3} or saturated) or into a freshly made mixed anhydrous ethanolic solution of the corresponding disulfide (10^{-4} mol dm^{-3} or saturated) and bis(11-hydroxyundecyl)disulfide (1, 2, 5 or 10×10^{-4} mol dm^{-3}) at 55 °C for at least 12 h. The samples were then rinsed with anhydrous ethanol and dried under a stream of nitrogen.

§ The angle of incidence was 81° for all FTIR measurements.

¶ SAMs obtained from DMF solution.

References

1 J.-M. Lehn, *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 89.
2 M. Ahlers, W. Müller, A. Reichert, H. Ringsdorf and J. Venzmer, *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 1269.
3 R. G. Nuzzo and D. L. Allara, *J. Am. Chem. Soc.*, 1983, **105**, 4481.
4 P. Fenter, A. Eberhardt and P. Eisenberger, *Science*, 1994, **266**, 1216.
5 J.-M. Lehn, M. Mascal, A. DeCian and J. Fischer, *J. Chem. Soc., Chem. Commun.*, 1990, 479.
6 J. A. Zerkowski, C. T. Seto, D. A. Wierda and G. M. Whitesides, *J. Am. Chem. Soc.*, 1990, **112**, 9025.
7 R. C. Ahuja, P.-L. Caruso, D. Möbius, W. Paulus, H. Ringsdorf and G. Wildburg, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 1033.
8 T. M. Bohanon, S. Denzinger, R. Fink, W. Paulus, H. Ringsdorf and M. Weck, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 58.
9 K. Motesharei and D. C. Myles, *J. Am. Chem. Soc.*, 1994, **116**, 7413.
10 A. Ulman, *An Introduction to Ultrathin Organic Films*, Academic Press, San Diego, 1991 and references therein.

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