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[10] X-ray crystallographic analysis was performed with a Rigaku AFC diffractometer (graphite monochromator, $Mo_{K\alpha}$ radiation). The structures were solved with PATTY and DIRDIF 94. (*R*),(*R*,*R*)-**2d**: $C_{62}H_{56}Cl_2N_2P_2Ru$, $M_r = 1063.06$, orange crystal, $0.1 \times 0.1 \times 0.1$ mm, monoclinic, space group *C*2 (no. 5), $a = 24.50(1)$, $b = 20.533(9)$, $c = 24.80(1)$ Å $\beta = 119.20(3)^\circ$, $V = 10908(10)$ Å^3, $Z = 8$, $\rho_{calcd} = 1.294$ g cm^{-3}, $\mu(Mo_{K\alpha}) = 4.84$ m^{-1}, $T = 296$ K. 9880 reflections were independent and unique, and 6220 with $I > 3.00\sigma(I)$ ($2\theta_{max} = 50^\circ$) were used for the solution of the structure. All hydrogen atoms were calculated from ideal geometries, fixed, and included in the calculation of the structural factor. $R = 0.034$, $Rw = 0.034$. (*R*),(*S*,*S*)-**2e**: $C_{62}H_{56}Cl_2N_2P_2Ru$, $M_r = 1063.06$, orange crystal, $0.1 \times 0.1 \times 0.2$ mm, monoclinic, space group *C*2 (no. 5), $a = 24.74(2)$, $b = 20.49(1)$, $c = 25.04(1)$ Å $\beta = 120.79(4)^\circ$, $V = 10908(11)$ Å^3, $Z = 8$, $\rho_{calcd} = 1.294$ g cm^{-3}, $\mu(Mo_{K\alpha}) = 4.84$ m^{-1}, $T = 296$ K. 12862 reflections were independent and unique, and 7807 with $I > 3.00\sigma(I)$ ($2\theta_{max} = 55^\circ$) were used for the solution of the structure. All hydrogen atoms were calculated from ideal geometries, fixed, and included in the calculation of the structural factor. $R = 0.034$, $Rw = 0.033$. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-101399. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
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[12] The turnover number (TON) is the number of moles of product per mole of catalyst. The turnover frequency (TOF) is the TON per hour or second.
[13] Reaction with the diastereomeric isomer (*R*),(*S*,*S*)-**2e**, either preformed or formed in situ, gave the *S* alcohol in 15 ± 2%.
[14] Various alkaline bases, such as KOH, $(CH_3)_2CHOK$, $(CH_3)_2CHONa$, $(CH_3)_3COK$, and K_2CO_3 can be used as cocatalysts. For reactions with a high S/C, acidic impurities should be carefully removed from substrates and solvents.
[15] Reaction of $[RuCl_2\{(S)\text{-TolBINAP}\}(dmf)_n]$ and (*S*,*S*)-DPEN in DMF at 50 °C (method B) gave a mixture of (*S*),(*S*,*S*)-**2d** and its *cis* isomer (^{31}P NMR, $\delta = 50.2$ (d, $J = 38.0$ Hz), 57.0 (d, $J = 38.0$ Hz)). Hydrogenation of **5g** with the *cis* isomer showed comparable reactivity to (*S*),(*S*,*S*)-**2d**, to give (*R*)-**6g** with 97% *ee*.
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Parallel Synthesis of Sialyl Lewis X Mimetics on a Solid Phase: Access to a Library of Fucopeptides**

Thomas F. J. Lampe, Gabriele Weitz-Schmidt, and Chi-Huey Wong*

In response to injury or inflammation the damaged tissue releases cytokines, which trigger the expression of P-selectin followed by E-selectin on the endothelium. The initial recognition of the tetrasaccharide sialyl Lewis X (sLe^x) of the terminal unit of surface glycoconjugates by the selectins leads to leukocyte "rolling" followed by protein – protein interactions (integrins CD 11/18, ICAM-1 ligand) and extravasation of leukocytes into the endothelium.[1] Thus, blocking the sLe^x/selectin interactions at an early stage of the inflammatory cascade, especially the P-selectin/ligand interactions, has been considered to be an effective way of treating acute and perhaps chronic inflammatory diseases.[2]

Although sLe^x is being clinically evaluated for the treatment of reperfusion injury, it must be administered by injection at high doses, as it binds the selectins weakly and is orally inactive and unstable in the blood. However, the structure of sLe^x has served as a useful guide for designing simpler and better low molecular weight compounds as

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selectin antagonists.[3] On the basis of the crystal structure of E-selectin, NMR studies of the conformations of sLe^x in solution and bound to E-, P-, and L-selectin,[5] and structure/activity studies on sLe^x derivatives and mimetics,[6] the essential functional groups and their spatial arrangement required for binding of the sLe^x epitope to the selectins have been elucidated. By using this recognition model, numerous structurally diverse low molecular weight sLe^x mimetics have been prepared (Figure 1).[3, 7] Some of them exhibit an affinity towards the selectins equal to or higher than that of sLe^x.

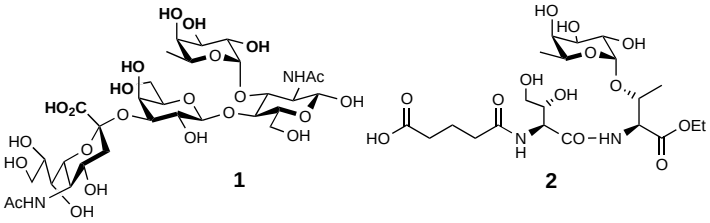
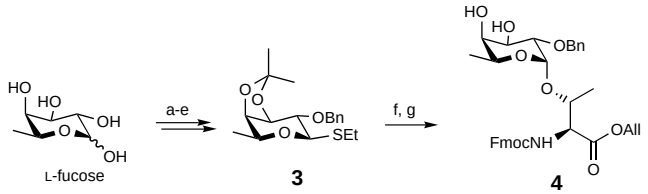


Figure 1. The tetrasaccharide sialyl Lewis X (**1**) and the fucopeptide **2** as an oligosaccharide mimic.

Recently, interest in solid-phase syntheses has increased dramatically, since they allow combinatorial chemistry to be performed for the discovery of biologically active compounds and for optimization of lead structures.[8] In particular, the parallel synthesis of individual compounds on solid phases is considered to be a promising approach to rapid optimization of previously identified lead structures. Here we report on our efforts to develop new strategies for the parallel and/or combinatorial synthesis of a substance library of *O*- and *C*-fucosylpeptides structurally related to **2**, which is nearly as active as sLe^x towards E-selectin.[7a]

Fucose, which contains the three hydroxyl groups required for recognition of sLe^x by E-selectin, was retained as the only carbohydrate moiety in the mimic, while GlcNAc was replaced by L-threonine and its derivatives. Anchoring the fucose–GlcNAc surrogate through its 3,4-*cis*-diol unit[9] enables the bidirectional elongation of the glycosylated amino acid while bound to the solid support. *N*-terminal elongation allows the elaboration of optimal substitutions for the galactose and sialic acid residues. *C*-terminal modifications[10] can be used to install additional functionalities that interact with new groups in selectins.[7b, 11] The use of Fmoc–peptide chemistry and the application of an orthogonal protective-group strategy (R^1 = All, R^2 = Fmoc, R^3 = Bn; for abbreviations, see legends to schemes), as well as the reversible immobilization of the 3,4-*cis*-diol moiety of fucose by a highly acid labile linker group, enable the rapid and bidirectional assembly of fucosylpeptides.

The synthesis of orthogonally protected α-fucoside **4** is depicted in Scheme 1. L-Fucose was converted into ethylthiofucoside

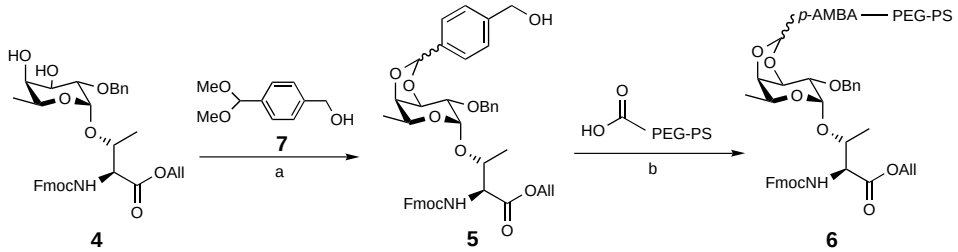


Scheme 1. a) Ac_2O, 4-DMAP, pyridine, 0→20 °C; b) EtSH, $BF_3 \cdot Et_2O$, 0→20 °C (60%, two steps); c) NaOMe (cat.) in MeOH, 20 °C; d) 2,2-dimethoxypropane, cat. p-TsOH · H_2O, CH_2Cl_2, 20 °C (94%, two steps, α/β = 1:7); e) NaH, BnBr, TBAI (cat.), THF (84%, 100% β); f) Fmoc-Thr-OAll, $CuBr_2$/TBAI, CH_2Cl_2, DMF; g) aqueous AcOH, (80%, 1% TFA). All = allyl, Bn = benzyl, 4-dmap = 4-(dimethyamino)pyridine, Fmoc = 9-fluorenylmethyloxycarbonyl, TBAI = tetrabutylammonium iodide, TFA = trifluoroacetic acid, Thr = threonine, Ts = toluenesulfonate.

3 (five steps, 47% overall yield) by standard methods. By using CuI_2/$[Bu_4N]I$,[12] Fmoc-protected L-threonine allyl ester was glycosylated with **3** to give selectively the α anomer ($\alpha/\beta \approx 9/1$). Cleavage of the acetonide with 80% aqueous acetic acid containing 1% TFA followed by column chromatography gave fucoside **4** as the pure α anomer (64% yield, two steps).

Treatment of the diol **4** with the dimethyl acetal **7** and a catalytic amount of p-TsOH · H_2O gave a diastereomeric mixture of benzylidene acetals **5** (Scheme 2). The bifunctional linker **7** was easily derived from commercially available 4-formylbenzoic acid by formation of the dimethyl acetal and reduction of the acid group (62%, two steps). By using a moderate excess (2.1 equiv) of the alcohol **5** and DIC/4-DMAP activation, **5** was immobilized nearly quantitatively (0.24 mmol g^{-1}) on a carboxyl-functionalized poly(ethylene glycol) graft copolymer resin(PEG-PS) to give **6**.[13] The loading was determined by photometric analysis of the cleaved Fmoc groups and gravimetrically by means of the product released from the resin with aqueous acetic acid (80% + 2% TFA). The diol **4** was liberated quantitatively without any detectable cleavage of the acid-sensitive α-fucosidic bond. Thus, the combination of the *para*-acyloxymethylbenzylidene acetal (*p*-AMBA) anchor group and PEG-PS solid support achieved maximal loading, recovery of excess reagent, appropriate swelling of the solid support, desirable stability of the acetal linkage during synthesis, and selective cleavage by a weak acid.

Starting with 0.8 mmol resin-bound **6**, we conducted a parallel synthesis of sLe^x mimetics **8** on a preparative scale (Scheme 3). At branching points of the synthesis, the material



Scheme 2. Immobilization of fucoside **4** on a carboxyl-functionalized PEG-PS resin by anchor group **7**. a) **7**, p-TsOH (cat.), CH_2Cl_2, 20 °C; b) DIC, 4-DMAP (cat.), CH_2Cl_2, 20 °C, 18 h, 100% (0.24 mmol g^{-1}). p-AMBA = p-(acyloxymethyl)benzylidene acetal anchor group, DIC = diisopropylcarbodiimide, PEG-PS = poly(ethylene glycol) graft copolymer; for other abbreviations, see legend to Scheme 1.

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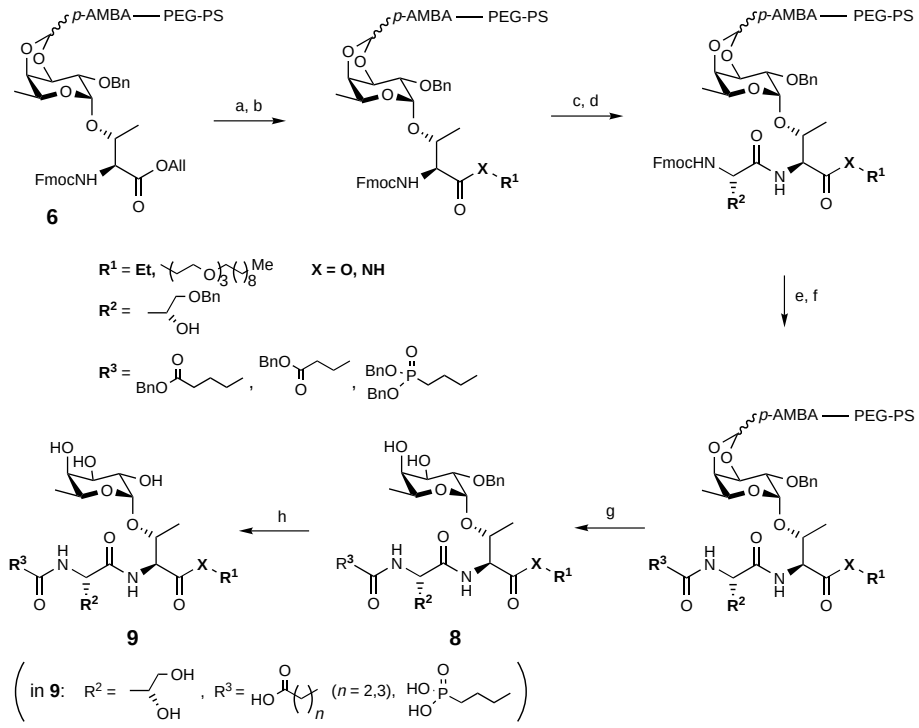


Scheme 3. a) $[Pd(PPh_3)_4]$ (cat.), dimedone, THF, 20 °C, 18 h; b) R^1OH, 2,6-dichlorobenzoyl chloride, pyridine, CH_2Cl_2/DMF (1/1), 20 °C, 18 h; or R^1NH_2, HBTU, HOBT, NMM, CH_2Cl_2/DMF (1/1), 20 °C, 4.5 h; c) DMF/morpholine (1/1), 20 °C, 1 h; d) $FmocNHCHR^2CO_2H$, HBTU, HOBT, NMM, DMF, 20 °C, 4 h; e) DMF/piperidine (3/2), 20 °C, 10 min; f) R^3CO_2H, HBTU, HOBT, NMM, DMF, 20 °C, 4 h; g) aqueous AcOH (80 %, 2 % TFA), 20 °C, 2 × 18–22 h; h) H_2, 10 % Pd/C, EtOH/THF/H_2O, 20 °C, 3–4 h. HBTU = 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, HOBT = 1-hydroxybenzotriazole, NMM = *N*-methylmorpholine; for other abbreviations, see legend to Scheme 1.

was divided into equal parts in the dry state. Allyl cleavage[14] with Pd° and dimedone as a scavenger liberated the C-terminus of the fucosyl–threonine conjugate, which was subsequently modified. Esterification was best accomplished with a large excess of alcohol and activation by a mixed anhydride,[15] and amide bonds were formed by standard methods of peptide synthesis. Our model studies revealed that C-terminal functionalization on solid phase proceeds with high yield and no racemization. A peptide synthesis consisting of removal of the Fmoc groups, amino acid coupling, and cleavage of the benzylidene acetal anchor groups under weakly acidic conditions afforded the protected fucosylpeptides **8** in high yields (Table 1). Diketopiperazines and compounds formed by cleavage of the α-fucosidic bond were not detected on analysis of the crude cleavage products by mass spectrometry. To obtain homogeneous materials for biological evaluation, fucosylpeptides **8** were purified by chromatography on silica gel. Yields of **8** range from 47 to 65 % (based on the initial loading); this corresponds to an average yield of 90–94 % per step. Removal of the benzylic protecting groups by catalytic hydrogenation afforded the mimetics **9**.

Fucosylpeptides **9a–h** were tested against E- and P-selectins in a cell-free assay system.[16] With polyvalent sLe^a attached to a polyacrylamide[16a] in the E-selectin binding assay, all members of the fucosylpeptide library showed only moderate binding affinities, whereby phosphonate fucopeptide **9h** was the most active ($IC_{50} = 0.7$ mM). While the biological activity of the fucopeptides towards E-selectin decreased with increasing chain length of the C-terminal residue (XR^1), the opposite was observed in the P-selectin assay: Binding affinity generally increased significantly on addition of a tris(ethylene glycol) decyl ether residue (ester or amide linkage). The ester derivative **9c** binds 53 times more strongly than the ethyl derivative **9a**. An increase of biological activity is also observed for the corresponding amide **9d**, which binds 100 times more strongly than **9a**. The influence of the N-terminal residue R^3 on binding to P-selectin seems to be limited; the phosphonate fucopeptide **9h** ($IC_{50} = 17\,\mu$M) has the highest activity. Comparing the values for the two selectins shows that fucosylpeptides **9d** ($\approx$100-fold) and **9h** (almost 200-fold) inhibit P-selectin significantly more strongly than E-selectin.

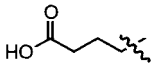
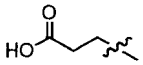
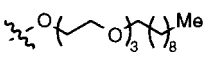
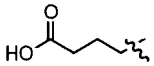
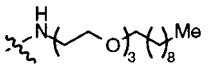
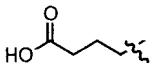
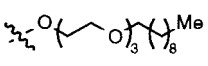
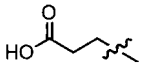
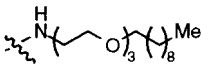
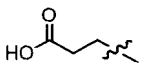
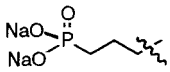
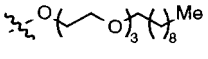
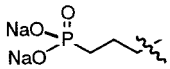
We have developed a new synthetic strategy for the parallel synthesis of fucopeptides as sLe^x mimetics on a solid phase. Linking the sugar through a highly acid sensitive 1,2-diol protecting and anchoring group (*p*-AMBA) enables variable functionalization of the N- and C-termini of glycopeptides. This provides access to a library of sLe^x mimetics by parallel or combinatorial synthesis and allows rapid optimization of the biological activity of a known lead structure. Some members of the fucopeptide library exhibit high selectivity and activity against P-selectin in cell-free assay systems. Work is in progress to test the versatility of *p*-AMBA based immobilization methodology in other synthetic areas involving 1,2- and 1,3-diol units, for example, the synthesis of complex oligosaccharides on solid phases.

Experimental Section

Immobilization of **5**: Carboxyl-functionalized resin (3.85 g, 0.26 mmol g^{-1}, corresponding to 1.0 mmol of functional groups) was dried for several hours under high vacuum. Then 4-DMAP (12.2 mg, 0.1 mmol), DIC (1.5 mmol), and a solution of alcohol **5** (1.545 g, 2.1 mmol) in dry CH_2Cl_2 (16 mL) were added, and the suspension was gently shaken for 14 h at room temperature. The reaction mixture was transferred into a peptide synthesis vessel, filtered, and the resin washed thoroughly with dry CH_2Cl_2 and dried under high vacuum to give 4.32 g of material. The combined filtrate was concentrated in vacuo, and unchanged alcohol **5** (740 mg, 1.0 mmol, 48 %) was recovered after purification by column chromatography on silica gel. Cleavage of the Fmoc groups from the dry resin followed by photometric analysis revealed a loading of $\approx$0.24 mmol g^{-1} ($\approx$1.04 mmol on resin, 100 % functionalization).

Fmoc cleavage and amino acid coupling: After swelling in DMF and removal of excess DMF, the resin was suspended in DMF/morpholine (1/1, 0.6 mL per 100 mg dry resin) and shaken for 1 h at room temperature (step c, Scheme 3) or suspended in DMF/piperidine (3/2) and shaken for 10 min at room temperature (step e, Scheme 3). After washing with dry

Table 1. Structures, yields, and biological activities of the sLe^x mimics **8** and **9**.

8 or **9**[a]	Yield of **8**[b]	Yield of **9**[c]	XR^1	R^3[d]	E-selectin IC_{50} [mM][e]	P-selectin IC_{50} [mM][e]
a	62	88	OEt		0.8	3.0
b	65	97	OEt		4.0	0.66
c	47	76			3.2	0.057
d	58	67			4.1	0.030
e	49	81			1.8	0.059
f	51	95			3.2	0.256
g	65	94	OEt		0.7	> 1.0
h	55	90			4.1	0.017

[a] In this series R^2 remains constant, and Fmoc-protected γ-benzyloxy-L-*allo*-threonine[17] was used as amino acid building block. [b] Yields based on purified fucopeptides **8**. [c] Yields based on purified **9** after fractional precipitation of crude hydrogenation products from MeOH/Et_2O (**9a**–**f**), ion-exchange chromatography (**9g** and **9h**) and lyophilization from H_2O. [d] The substituents shown refer to **9**; compounds **8** contain the corresponding benzylated substituents. [e] The activities were measured according to the procedure described previously with sLe^a–polyacrylamide conjugate. The values are an average of three measurements, ±10%.; IC_{50} for sLe^x = 0.8 mM towards E-selectin and > 3 mM towards P-selectin).[16a]

DMF (6×, 1 mL per 100 mg dry resin), a pre-stirred (5–10 min) solution of the acids used for coupling (3 equiv for step d and 6 equiv for step f, Scheme 4), HOBT, NMM, and HBTU (1.6 equiv, 2.2 equiv and 1.05 equiv, based on the amount of acid) in dry DMF (0.2–0.25 M in acid) was added to the resin. After shaking for 4–4.5 h at room temperature, the coupling reaction was terminated by filtration, and the resin was washed with DMF and CH_2Cl_2 (6× each).

Cleavage from the resin: A suspension of resin in aqueous AcOH (80%, 0.9 mL per 100 mg dry resin) containing 2% TFA was shaken for 18–22 h at room temperature. After filtration and washing three times with AcOH (80%), the cleavage procedure was repeated. The filtrate was concentrated in vacuo, and residual AcOH and H_2O were removed by coevaporating twice with dry toluene. The colorless to slightly yellow oil or solid was purified by column chromatography on silica gel to afford material that was homogeneous according to HR-MS, ^1H, and ^{13}C NMR spectroscopy.

9b: colorless hygroscopic solid; ^1H NMR (500 MHz, D_2O): $\delta = 4.95$ (d, $J =$ 3.5 Hz, 1H), 4.68 (brs, 1H), 4.54 (d, $J = 7.2$ Hz, 1H), 4.44 (q, $J \approx 6.1$ Hz, 1H), 4.22 (dq, $J = 10.6$, 7.2 Hz, 1H), 4.12 (dq, $J = 10.6$, 7.2 Hz, 1H), 3.97 (m, 1H), 3.74–3.69 (m, 5H), 3.60 (dd, $J = 12.1$, 6.4 Hz, 1H), 2.62–2.52 (m, 4H), 1.24 (t, $J = 7.1$ Hz, 3H), 1.15 (brd, $J \approx 6.4$ Hz, 6H); HR-MS: *m/z* calcd for $C_{20}H_{34}O_{13}N_2Cs$: 643.1115 $[M+Cs]^+$, found: 643.1139. **9d**: colorless hygroscopic solid; ^1H NMR (500 MHz, D_2O): $\delta = 4.94$ (d, $J = 3.7$ Hz, 1H), 4.53 (d, $J = 9.0$ Hz, 1H), 4.44 (brs, 1H), 4.41 (d, $J = 6.3$ Hz, 1H), 3.89–3.87 (m, 1H), 3.75–3.52 (m, 16H), 3.43 (t, $J = 6.7$ Hz, 2H), 3.31–3.36 (m, 2H), 2.29 (t, $J \approx 7.1$ Hz, 2H), 2.24 (t, $J = 7.4$ Hz, 2H), 1.81 (t, $J \approx 7.3$ Hz, 2H), 1.55–1.50 (m, 2H), 1.28–1.21 (m, 14H), 1.18 (d, $J = 6.1$ Hz, 3H), 1.14 (d, $J =$ 6.4 Hz, 3H), 0.83 (brt, $J \approx 6.6$ Hz, 3H); HR-MS: *m/z* calcd for $C_{35}H_{65}O_{15}N_3Cs$: 900.3470 $[M+Cs]^+$, found: 900.3498. **9e**: colorless hygroscopic solid; ^1H NMR (500 MHz, D_2O): $\delta = 4.94$ (d, $J = 3.5$ Hz, 1H), 4.70 (brs, 1H), 4.58 (d, $J = 7.2$ Hz, 1H), 4.42–4.35 (m, 2H), 4.18–4.16 (m, 1H), 3.97–3.96 (m, 1H), 3.74–3.55 (m, 16H), 3.42 (t, $J = 6.5$ Hz, 2H), 2.64–2.53 (m, 4H), 1.53 (brs, 2H), 1.30–1.23 (m, 14H), 1.17 (d, $J = 6.1$ Hz, 3H), 1.15 (d, $J = 6.4$ Hz, 3H), 0.85 (brt, $J \approx 6.5$ Hz, 3H); HR-MS: *m/z* calcd for $C_{34}H_{62}O_{16}N_2Cs$: 887.3154 $[M+Cs]^+$, found: 887.3184.

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Complex Fluids Based on the Flexible One-Dimensional Mineral Polymers $[K(MPS_4)]_\infty$ (M = Ni, Pd): Autofragmentation to Concave, Cyclic $(PPh_4)_3[(NiPS_4)_3]$**

Julien Sayettat, Lucy M. Bull, Jean-Christophe P. Gabriel, Stéphane Jobic, Franck Camerel, Anne-Marie Marie, Marc Fourmigué, Patrick Batail,* Raymond Brec,* and René-Louis Inglebert

In memory of Jean Rouxel

The discovery of the lyotropic nematic phase of $LiMo_3Se_3$ in *N*-methylformamide,[1] a rare example of a liquid crystal based on a mineral core, was achieved 70 years after the pioneering work of the German physicist H. Zocher.[2] This event, soon followed by the study of the nematic behavior of V_2O_5 ribbons[3] and smectic clays[4] in water, has aroused acute interest in the development of solution-phase chemistry of charged, all-inorganic molecules. The motivation for such investigations is the prospect of unraveling the organic/inorganic interfacial chemistry and physics of unprecedented anisotropic fluids based on one- and two-dimensional, charged, extended mineral polymers.[5, 6]

The solid-state chemistry of transition metal chalcogenides[7] is abound with low-dimensional motifs, such as $^1_\infty[Mo_3Se_3]^-$. Their dimensionality arises from the balance between the strong covalent character of the transition metal–chalcogen bonds within the negatively charged chains or slabs and their effective ionic screening by alkali metal cations.[8, 9] A recent example is the series of transition metal chalcogenide phosphates $KMPS_4$ (M = Ni, Pd) with infinite anionic chains $^1_\infty[MPS_4]^-$.[10] Here we demonstrate 1) that $KMPS_4$ compounds are soluble in polar organic solvents such as dimethylformamide (DMF) and dimethyl sulfoxide (DMSO), and form complex fluids made up of flexible inorganic polymers; 2) that $[(NiPS_4)_3]^{3-}$—an unprecedented, concave trimetallic thiophosphate molecular trianion adopting pseudo-C_{3v} symmetry—is formed in DMF at room temperature from the autofragmentation and rearrangement of $^1_\infty[NiPS_4]^-$; and 3) that it is possible to follow the dissolution and fragmentation processes with mass spectrometry, solution-state ^{31}P NMR spectroscopy, and transmission electron microscopy (TEM). Thus, the contrasting behavior and stability of the Ni and Pd phases can be revealed.

In accordance with their highly anisotropic bonding, $KNiPS_4$ and $KPdPS_4$ are soluble in polar organic solvents

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