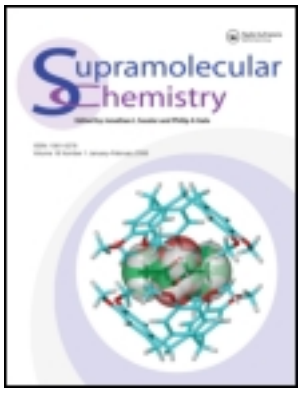


Supramolecular Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gsch20

Solubilising groups: a conceptual equivalent of protecting groups in organic synthesis

Velayutham Ravikumar [a], Andrea Fin [a], Naomi Sakai [a] & Stefan Matile [a]
[a] Department of Organic Chemistry, University of Geneva, Geneva, Switzerland

Available online: 31 Aug 2010

To cite this article: Velayutham Ravikumar, Andrea Fin, Naomi Sakai & Stefan Matile (2011): Solubilising groups: a conceptual equivalent of protecting groups in organic synthesis, Supramolecular Chemistry, 23:01-02, 69-73

To link to this article: http://dx.doi.org/10.1080/10610278.2010.510193

Supramolecular Chemistry
Vol. 23, Nos. 1–2, January–February 2011, 69–73

Taylor & Francis
Taylor & Francis Group

Solubilising groups: a conceptual equivalent of protecting groups in organic synthesis[†]

Velayutham Ravikumar, Andrea Fin, Naomi Sakai and Stefan Matile*

Department of Organic Chemistry, University of Geneva, Geneva, Switzerland

(*Received 18 June 2010; final version received 16 July 2010*)

In this brief essay, one of the most common and least appreciated challenge in the field is addressed. Few chemists, particularly supramolecular chemists, exist who are not all too familiar with solubility problems during the synthesis of new molecules. Solubility problems are inherent to the synthesis of molecules that are made to build supramolecular architectures because the same intermolecular interactions that cause the problem are later on essential for the final self-assembly of the system of interest. Naturally, many solutions exist for a problem that occurs so frequently. They are used as daily routine in many laboratories, the temporary attachment of hydrophobic bulk of various size and nature being the most common. However, contrary to the comparable situation with protecting groups, these solubilising groups are generally underappreciated, often communicated orally as one of those precious 'lab secrets' that nobody really takes serious but everybody really needs to get things running and reach the relevant part of the research project. Here, we briefly try to summarise latent concepts concerning solubilising groups, focusing particularly on questions concerning quantitative aspects and the removal of solubilising groups for self-assembly with pre-, post- or *in situ* desolubilisation, and provide a simple practical example with *tert*-butyldiphenylsilyl as an illustrative solubilising group.

Keywords: solubility; solubilising group; solubiliser; protecting group; organic synthesis; self-assembly

Introduction

The design of molecules that self-assemble into supramolecular functional systems usually requires strong intermolecular interactions, and thus usually results in poor solubility. No wonder, then, that the synthesis of these molecules often suffers from solubility problems (*1–19*). This conceptual dilemma is particularly acute when covalent chemistry is envisioned for the construction of functional architectures that operate at interfaces or on surfaces. For example, surface-initiated polymerisation of ordered, functional polymer brushes remains poorly explored because the high monomer concentrations needed to achieve significant polymerisation is often incompatible with the low solubilities imposed by the presence of organising molecular recognition motifs (*18*, *19*). This situation calls for solubilising groups or 'solubilisers' that can be put on at the beginning and taken off at the end of the synthesis of the building blocks or at best during the construction of the functional architectures.

In general, solubilising groups **S** are envisioned here as a general tool to accomplish the synthesis of the target molecule **D** from the starting material **A** that otherwise fails because of an intractable synthetic intermediate **C** (Figure 1). Namely, the reasonably soluble intermediate **B** is reacted with solubiliser **S** to give a further solubilised intermediate **BS**. Conversion of **B** into **C** now does not give an intractable material, but the solubilised intermediate **CS**, which can be easily isolated, purified and used for further reactions to ultimately give the solubilised target molecule **DS**. The removal of the solubilising group can be done at this point to produce the desired target molecule **D** that can then be used for the assembly of the final supramolecular system **E**. Because it occurs before the supramolecular synthesis, the removal of the solubilising group **S** at this point is referred to as pre-desolubilisation. Alternatively, the solubilising group **S** can be removed after the construction of a solubilised supramolecular system **ES** to afford the desired system **E** by a final post-desolubilisation step. As a third possibility, the *in situ* desolubilisation of the solubilised target molecule **DS** during the construction of the supramolecular system **E** by self-assembly, programmed assembly, covalent capture, surface-initiated polymerisation, self-organisation and self-repair appears most attractive as an additional tool to initiate and modulate supramolecular synthesis.

Like protecting groups (*20*), solubilising groups **S** require chemo-orthogonal chemistry. They have to resist reagents used during the synthesis but they can be attached and removed without affecting the rest of the molecules. Most efficient temporary (*1–11*) or permanent (*12–17*) solubilisers are branched, bent or bicyclic objects that function by disrupting 2D packings (*1–17*). Leading

*Corresponding author. Email: stefan.matile@unige.ch

[†]Presented in part at the fifth International Symposium on Macrocyclic and Supramolecular Chemistry (ISMSC-V), Nara, Japan, June 2010.

ISSN 1061-0278 print/ISSN 1029-0478 online

DOI: 10.1080/10610278.2010.510193
http://www.informaworld.com

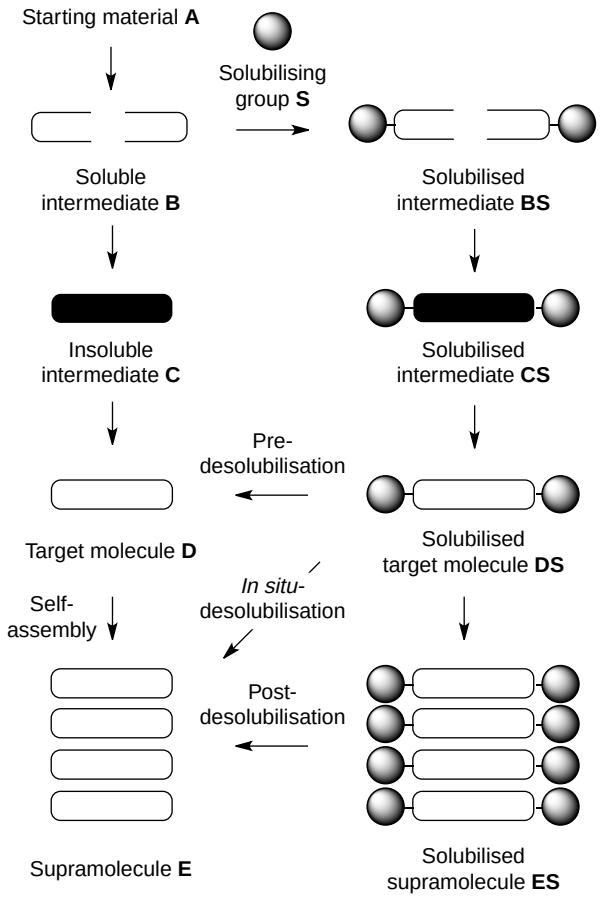


Figure 1. Solubilising groups are, similar to protecting groups, introduced at the beginning or during a multistep synthesis to overcome otherwise intractable solubility problems. Their removal at the end of the synthesis does not affect the rest of the molecules and can at best be used to trigger and control the assembly of supramolecular architectures.

examples include swallowtails in materials sciences (*12–16*). In peptide chemistry, the origin of the β-propensity (*21*) attributed to the β-branched valine or threonine is their ability to serve as permanent solubilisers of β-sheets (*2–8*, *21*).

As far as true solubilising groups **S** are concerned, that is temporary solubilisers that can be added and removed at will, branched alkyl groups in *tert*-butyl esters (*9*), *Boc* or silyl (*10*, *11*) groups have been proven useful. The removal of solubilising groups during rather than before self-assembly has received considerable recent attention as an elegant method to control the formation of supramolecular architectures (*1–8*). Successful examples include solubilising groups that can be removed with heat, light, enzymes and dynamic covalent chemistry.

Naphthalenediimides (NDIs) are ideal for the self-assembly of π-stack surface architectures because they can change spectral and redox properties without global structural changes, their exceptional π-acidity assures

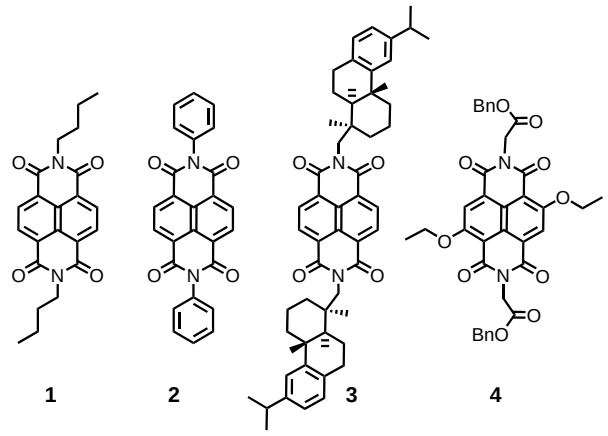


Figure 2. Some nasty simple NDIs (compare Table 1).

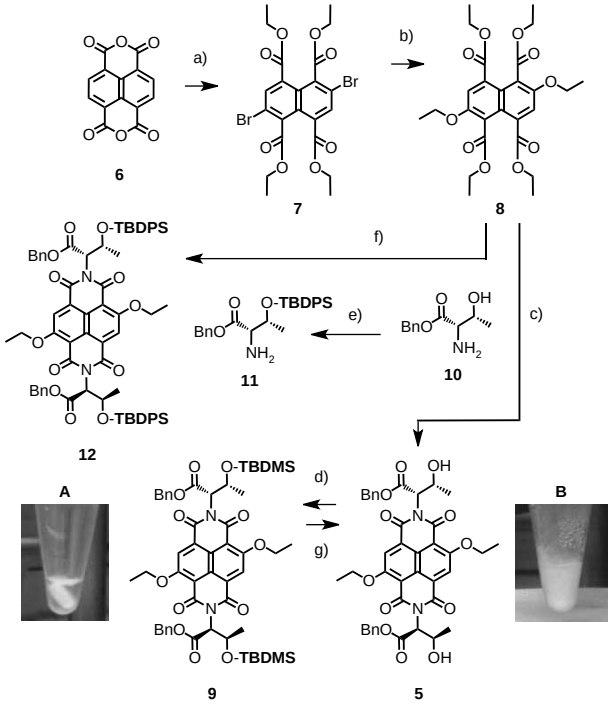
efficient π-stacking and their face-to-face π-stacks yield one of the few air-stable molecular *n*-semiconductors (*22–41*). Ideal for self-assembly, these unique characteristics can cause correspondingly serious problems during NDI synthesis. Systematic studies with aryl- and alkyl-substituted NDIs such as **1**–**3** have identified branched alkyl groups as the best solubilisers, although the observed effects were rather modest and solubilities remained in the low micromolar ranges in all solvents (Figure 2, Table 1) (*17*). Bulky and spherical groups such as *tert*-butyl and *tert*-butyldiphenylsilyl (TBDPS) groups have been essential as temporary solubilisers to succeed in the synthesis of pores with internal NDI clamps (*2–9*).

The solubility of the simple yellow NDI fluorophore **4** with two alkoxy substituents in the core is clearly better than that of NDIs **1**–**3** without core substituents (Table 1). However, solubility of up to 10 mM in halogenated solvents only was insufficient for a key intermediate in the synthesis of artificial photosystems (*33–39*). Considering this challenging molecule as a meaningful example, we here report that the introduction of solubilising groups allows, without much effort, to transform a quite intractable molecule into a molecule with solubility in

Table 1. Solubility in different solvents.[a]

	Compd[b]	$CHCl_3$	CH_2Cl_2	Toluene	THF	CH_3CN
1	**1**	0.05	0.05	0.02	0.03	0.02
2	**2**	0.04	0.05	0.02	0.03	0.02
3	**3**	0.07	0.08	0.04	0.04	0.05
4	**4**	10	6	<1	<1	<1
5	**5**	810	325	<4	10	<4
6	**9**	1100	920	1100	790	1100
7	**12**	940	660	470	235	550
8	**15**	470	470	410	450	380

[a] Concentrations at saturation in mM, data for **1**–**3** are from Ref. (*17*). No significant solubility was observed in other solvents such as hexane or methanol.
[b] See Figure 2 and Schemes 1 and 2 for structures.



Scheme 1. (a) 1. Dibromoisocyanuric acid; 2. EtI, EtOH, K_2CO_2, 35% (*34*); (b) NaOEt, 73% (*37*); (c) 1. KOH, iPrOH, 80°C, 48 h, 2. **10**, AcOH–DMF 1:1, microwave, 120°C, 30 min, 40%; (d) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 0°C, 30 min, 76%; (e) TBDPSCl, DBU, MeCN, 0°C to rt, 12 h, 57%; (f) 1. KOH, iPrOH, 80°C, 48 h, 2. **11**, AcOH–DMF 1:1, microwave, 130°C, 30 min, 4% and (g) HCl–THF 1:1, rt, 12 h, A, reaction mixture at the beginning, B, reaction mixture after 12 h.

molar concentrations in many solvents. The removal of the solubilising groups in NDI **5** is shown to occur with coinciding precipitation, an *in situ* desolubilisation process considered as ideal for the assembly of ordered surface architectures, which is controlled directly by chemical transformations (Scheme 1).

Results and discussion

To explore the efficiency of small and branched permanent solubilisers common in β-sheets (*2–8*, *21*), the glycine tails in NDI **4** were first replaced by the bioinspired threonine tails in **5** (Scheme 1). The bromination of dianhydride **6** with dibromoisocyanuric acid followed by the transformation into the tetraester **7** with ethyliodide has been described (*37*, *40*). Nucleophilic aromatic core substitution with ethanolate to give tetraester **8** was also accomplished following previously established procedures (*37*, *40*). After basic ester hydrolysis, threonine **10** was introduced in excellent 40% yield by adapting the recent elegant microwave-assisted conditions from the Sanders group (*41*). Compared to the insoluble glycine analogue **4**, the introduction of permanent threonine solubilisers in NDI **5** increased solubility in chloroform 80 times. A similar 50-fold increase was found in methylenechloride, whereas the solubility in other solvents remained poor (Table 1, entry 5 vs. 4).

The branched *tert*-butyldimethylsilyl (TBDMS) group was tested first as the solubilising group of NDI **5**. Silylation of the secondary alcohols was accomplished with TBDMS-triflate and 2,6-lutidine as a base in unproblematic 76% yield. The obtained NDI **9** was soluble in molar concentrations not only in chloroform but also in solvents such as toluene or acetonitrile, where NDI **5** was very poorly soluble. Compared to the original NDI **4**, the introduction of permanent solubilisers in **5** as well as removable solubilising groups in **9** converted a nearly intractable compound into a pleasant one with roughly molar solubility in all meaningful solvents.

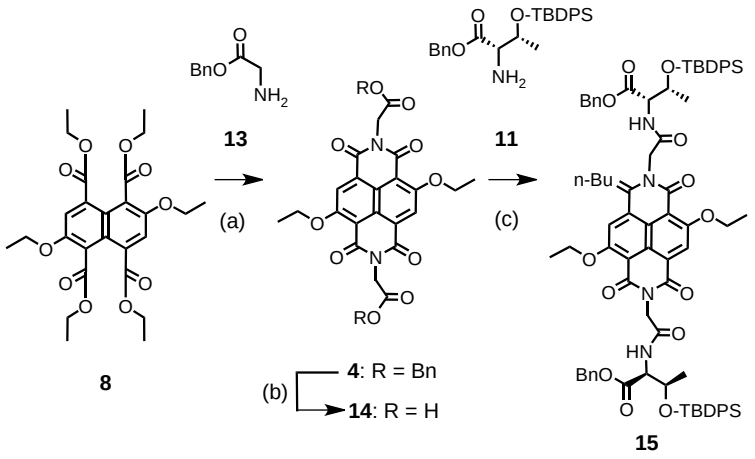
Direct introduction of silylated threonine into hydrolysed naphthalene **8** was possible using TBDPS instead of more acid-labile TBDMS. Diimide formation with amine **11** was possible under microwave irradiation, but the yellow NDI **12** was isolated in trace amounts only. This demonstrated that silylation is better done after rather than before diimide formation.

TBDPS–NDI **12** was very well soluble in all meaningful solvents (Table 1, entry 7). However, the solubility never reached molar concentrations and was consistently a bit lower than that of TBDMS–NDI **9**. This result suggested that alkyl solubilisers are preferable over aryl solubilisers, even if the volume of the solubilising object is clearly smaller.

The effect of the solubilising TBDPS-threonine **11** was slightly weaker if it is attached to the original glycine NDI **4** (Scheme 2). Thanks to the high reactivity of the primary amine in glycine benzylester **13**, NDI **4** was accessible nearly quantitatively from tetraester **8** without the need of microwaves. Deprotection and coupling of diacid **14** with TBDPS-threonine **11** gave the solubilised NDI **15**.

Contrary to the original glycine-NDI **4**, direct attachment of permanent threonine plus temporary TBDPS solubilisers made NDI **15** compatible with all meaningful solvents (Table 1, entry 4 vs. 8). The NDIs **15** and **12** with and without glycine spacer had similar solubility, the former being slightly inferior in most solvents but clearly better in THF (Table 1, entries 7 and 8).

To explore the possibility to couple the removal of solubilising groups with the self-assembly of functional systems, the overall most convincing TBDMS-solubilised NDI **9** was incubated with HCl–THF at an ambient temperature (Scheme 1A). Within 12 h, a yellow pigment precipitated (Scheme 1B). The spectroscopic and analytical data of the yellow powder were identical with the desolubilised NDI **5**. This result confirmed that the removal of bulky silyl-solubilising groups can, in principle, be coupled with the self-assembly of functional



Scheme 2. (a) 1. KOH, iPrOH, 80°C, 21 h, 2. **13**, AcOH, 80°C, 54 h, 97%; (b) TFA, HBr–AcOH, 6 h, 98% and (c) **11**, HATU, TEA, DMF, rt, 12 h, 72%.

systems and at best be of use to control formation kinetics and micro-/nanostructures of their supramolecular architectures.

Conclusion

The bottom line is that solubility problems during multistep synthesis can be solved with simple and rational approaches and without affecting the properties of the final target molecule. Similar to protecting groups, solubilising groups are introduced at the beginning or during the synthesis of molecules that self-assemble into functional systems. Their removal at the end of the synthesis does not affect the rest of the molecule and can at best trigger and control self-assembly. Here, silyl solubilising groups are shown to reversibly transform nearly intractable building blocks for functional systems into well-behaved molecules that are soluble at molar concentrations in all meaningful solvents. Their removal can be coupled and presumably control the self-assembly of functional systems. Studies in this direction are ongoing to explore whether or not covalent chemistry approaches can ultimately compete with the routinely and successfully used supramolecular methods to build functional systems without solubility problems (e.g. denaturants, detergents, micelles, liposomes, polyion–counterion complexes, host–guest complexes (cyclodextrins) and so on) (*42*, *43*).

Solubilising groups are not the future of supramolecular chemistry. However, they have the potential to solve the best known and least appreciated challenge in the field for good. This would be very helpful for the community and could have a very broad impact, providing facile access to supramolecular functional systems that are intractable today because of simple solubility problems. A systematic survey of the existing literature to identify and classify existing solubilising groups according to their nature, solubilising power, compatibility with structural motifs and solvents, attachment and removal chemistry as well as chemo-orthogonality could already provide a book of the practical value of the protecting group 'bible' by Green and Wuts (*20*). Many directions are conceivable for future research on solubilising groups, reaching from fundamental systematic screening exercises of highest importance to more innovative adventures with *in situ* desolubilisation to build today's 'intractable' supramolecular architectures.

Experimental section

Complete experimental details can be found in the Supporting Information, available online.

Acknowledgements

We thank D. Jeannerat, A. Pinto and S. Grass for NMR measurements, the Sciences Mass Spectrometry (SMS) platform at the Faculty of Sciences, University of Geneva, for mass spectrometry services and the University of Geneva and the Swiss NSF for financial support.

References

(1) Yamada, H.; Okujima, T.; Ono, N. *Chem. Commun.* **2008**, *44*, 2957–2974.
(2) Williams, R.J.; Smith, A.M.; Collins, R.; Hodson, N.; Das, A.K.; Ulijn, R.V. *Nat. Nanotechnol.* **2009**, *4*, 19–24.
(3) Kühnle, H.; Börner, H.G. *Angew. Chem., Int. Ed.* **2009**, *48*, 6431–6434.
(4) Yang, Z.; Liang, G.; Ma, M.; Gao, Y.; Xu, B. *Small* **2007**, *3*, 558–562.
(5) Um, S.H.; Lee, J.B.; Park, N.; Kwon, S.Y.; Umbach, C.C.; Luo, D. *Nat. Mater.* **2006**, *5*, 797–801.
(6) Mutter, M.; Chandravarkar, A.; Boyat, C.; Lopez, J.; Dos Santos, S.; Mandal, B.; Mimna, R.; Murat, K.; Patiny, L.; Saucede, L.; Tuchscherer, G. *Angew. Chem., Int. Ed.* **2004**, *43*, 4172–4178.

(7) Hu, B.-H.; Messersmith, P.B. *J. Am. Chem. Soc.* **2003**, *125*, 14298–14299.
(8) Winkler, S.; Wilson, D.; Kaplan, D.L. *Biochemistry* **2000**, *39*, 12739–12746.
(9) Sakai, N.; Majumdar, N.; Matile, S. *J. Am. Chem. Soc.* **1999**, *121*, 4294–4295.
(10) Tanaka, H.; Litvinchuk, S.; Tran, D.-H.; Bollot, G.; Mareda, J.; Sakai, N.; Matile, S. *J. Am. Chem. Soc.* **2006**, *128*, 16000–16001.
(11) Tanaka, H.; Bollot, G.; Mareda, J.; Litvinchuk, S.; Tran, D.-H.; Sakai, N.; Matile, S. *Org. Biomol. Chem.* **2007**, *5*, 1369–1380.
(12) Adam, D.; Schuhmacher, P.; Simmerer, J.; Haussling, L.; Siemensmeyer, K.; Etzbach, K.H.; Ringsdorf, H.; Haarer, D. *Nature* **1994**, *371*, 141–143.
(13) Boden, N.; Bushby, J.R.; Clements, J.; Movaghar, B.; Donovan, K.J.; Kreouzis, T. *Phys. Rev. B* **1995**, *52*, 13274–13280.
(14) Bao, Z.N.; Lovinger, A.J.; Dodabalapur, A. *Adv. Mater.* **1997**, *9*, 42–44.
(15) van de Craats, A.M.; Warman, J.M. *Adv. Mater.* **2001**, *13*, 130–133.
(16) Wescott, L.D.; Mattern, D.L. *J. Org. Chem.* **2003**, *68*, 10058–10066.
(17) Erten, S.; Posokhov, Y.; Alp, S.; Icli, S. *Dyes Pigm.* **2005**, *64*, 171–178.
(18) Edmondson, S.; Osborne, V.L.; Huck, W.T.S. *Chem. Soc. Rev.* **2004**, *33*, 14–22.
(19) Snaith, H.J.; Whiting, G.L.; Sun, B.; Greenham, N.C.; Huck, W.T.S.; Friend, R.H. *Nano Lett.* **2005**, *5*, 1653–1657.
(20) Green, T.W.; Wuts, P.G.M. *Protective Groups in Organic Synthesis*, 3rd ed., Wiley: New York, 1999.
(21) Sazaki, T.; Lieberman, M. In *Comprehensive Supramolecular Chemistry*; Murakami, Y., Ed.; Elsevier: Oxford, 1996; Vol. 4, pp 193–243.
(22) Würthner, F.; Ahmed, S.; Thalacker, C.; Debaerdemaeker, T. *Chem. Eur. J.* **2002**, *8*, 4742–4750.
(23) Thalacker, C.; Roger, C.; Würthner, F. *J. Org. Chem.* **2006**, *71*, 8098–8105.
(24) Röger, C.; Würthner, F. *J. Org. Chem.* **2007**, *72*, 8070–8075.
(25) Gabutti, S.; Schaffner, S.; Neuburger, M.; Fischer, M.; Schäfer, G.; Mayor, M. *Org. Biomol. Chem.* **2009**, *7*, 3222–3229.
(26) Blaszczyk, A.; Fischer, M.; von Hänisch, C.; Mayor, M. *Helv. Chim. Acta* **2006**, *89*, 1986–2005.
(27) Chaignon, F.; Falkenstrom, M.; Karlsson, S.; Blart, E.; Odobel, F.; Hammarström, L. *Chem. Commun.* **2007**, *42*, 64–66.
(28) Chopin, S.; Chaignon, F.; Blart, E.; Odobel, F. *J. Mater. Chem.* **2007**, *17*, 4139–4146.
(29) Jones, B.A.; Facchetti, A.; Wasielewski, M.R.; Marks, T. *J. Am. Chem. Soc.* **2007**, *129*, 15259–15278.
(30) Bhosale, S.V.; Jani, C.H.; Langford, S. *J. Chem. Soc. Rev.* **2008**, *37*, 331–342.
(31) Pantos, G.D.; Wietor, J.L.; Sanders, J.K.M. *Angew. Chem., Int. Ed.* **2007**, *46*, 2238–2290.
(32) Gabriel, G.J.; Iverson, B.L. *J. Am. Chem. Soc.* **2002**, *124*, 15174–15175.
(33) Sakai, N.; Mareda, J.; Vauthey, E.; Matile, S. *Chem. Commun.* **2010**, *46*, 4225–4237.
(34) Dawson, R.E.; Hennig, A.; Weimann, D.P.; Emery, D.; Gabutti, S.; Montenegro, J.; Ravikumar, V.; Mayor, M.; Mareda, J.; Schalley, C.A.; Matile, S. *Nat. Chem.* **2010**, *2*, 533–538.
(35) Sakai, N.; Bhosale, R.; Emery, D.; Mareda, J.; Matile, S. *J. Am. Chem. Soc.* **2010**, *132*, 6923–6925.
(36) Bhosale, R.; Perez-Velasco, A.; Ravikumar, V.; Kishore, R.S.K.; Kel, O.; Gomez-Casado, A.; Jonkheijm, P.; Huskens, J.; Maroni, P.; Borkovec, M.; Sawada, T.; Vauthey, E.; Sakai, N.; Matile, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 6461–6464.
(37) Kishore, R.S.K.; Kel, O.; Banerji, N.; Emery, D.; Bollot, G.; Mareda, J.; Gomez-Casado, A.; Jonkheijm, P.; Huskens, J.; Maroni, P.; Borkovec, M.; Vauthey, E.; Sakai, N.; Matile, S. *J. Am. Chem. Soc.* **2009**, *131*, 11106–11116.
(38) Litvinchuk, S.; Tanaka, H.; Miyatake, T.; Pasini, D.; Tanaka, T.; Bollot, G.; Mareda, J.; Matile, S. *Nat. Mater.* **2007**, *6*, 576–580.
(39) Bhosale, S.; Sisson, A.L.; Talukdar, P.; Fürstenberg, A.; Banerji, N.; Vauthey, E.; Bollot, G.; Mareda, J.; Röger, C.; Würthner, F.; Sakai, N.; Matile, S. *Science* **2006**, *313*, 84–86.
(40) Kishore, R.S.K.; Ravikumar, V.; Bernardinelli, G.; Sakai, N.; Matile, S. *J. Org. Chem.* **2008**, *73*, 738–740.
(41) Pengo, P.; Pantoş, G.D.; Otto, S.; Sanders, J.K.M. *J. Org. Chem.* **2006**, *71*, 7063–7066.
(42) Butterfield, S.M.; Miyatake, T.; Matile, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 325–328.
(43) Lipshutz, B.H.; Ghorai, S. *Aldrichimica Acta* **2008**, *41*, 59–72.