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Solubilizing Groups - A Conceptual Equivalent of Protecting Groups in Organic Synthesis[†]

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In this brief and mildly provocative note, one of the most ordinary, best known and least appreciated challenge in the field is addressed, superficially, and not for the first time. Few chemists, particularly supramolecular chemists, exist that 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 solubilizing groups are generally underappreciated, often communicated orally as one of those precious "lab secrets" nobody really cares but everybody really needs to get things running and reach the relevant part of the research project. Here, we briefly try to summarize latent concepts concerning solubilizing groups, focusing particularly on questions concerning quantitative aspects and removal of solubilizing groups for self-assembly with pre-, post- or *in-situ* desolubilization, and provide a simple practical example with TBDPS as illustrative solubilizing group.

Keywords: Solubility; solubilizing group; solubilizer; protecting group; organic synthesis; self-assembly; supramolecular systems

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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.[1-7] 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 polymerization of ordered, functional polymer brushes remains poorly explored because the high monomer concentrations needed to achieve significant polymerization is often incompatible with the low solubilities imposed by the presence of organizing molecular recognition motifs.[7] This situation calls for solubilizing groups or "solubilizers" that can be attached at the beginning and removed at the end of the synthesis of the building blocks or at best during the construction of the functional architectures.

In general, solubilizing groups **S** are envisioned here as a general tool to accomplish the synthesis of target molecule **D** from starting material **A** that otherwise fails because of an intractable synthetic intermediate **C** (Figure 1). Namely, the reasonably soluble intermediate **B** is reacted with solubilizer **S** to give a further solubilized intermediate **BS**. Reaction of **B** to **C** now doesn't give intractable material but the solubilized intermediate **CS**, which can be easily isolated, purified and used for further reactions to ultimately give the solubilized target molecule **DS**. Removal of the solubilizing 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 supramolecular synthesis, removal of the solubilizing group **S** at this point is referred to as pre-desolubilization. Alternatively, the solubilizing group **S** can be removed after the construction of a solubilized supramolecular system **ES** to afford the desired system **E** by a final post-desolubilization step. As a third possibility, the in-situ desolubilization of the solubilized target molecule **DS** during the construction of the supramolecular system **E** by self-assembly, programmed assembly, covalent capture, surface-

initiated polymerization, self-organization and self-repair appears most attractive as additional tool to initiate and modulate supramolecular synthesis.

Like protecting groups,[8] solubilizing groups **S** require chemoorthogonal chemistry. They have to resist reagents used during the synthesis but can be attached and removed without affecting the rest of the molecule. Most efficient temporary[1-4] or permanent[5,6] solubilizers are branched, bent or bicyclic objects that function by disrupting two-dimensional packings.[1-4] Leading examples include swallowtails in materials sciences.[5] In peptide chemistry, the origin of the β-propensity[9] attributed to the β-branched valine or threonine is their ability to serve as permanent solubilizers of β-sheets.[2,9]

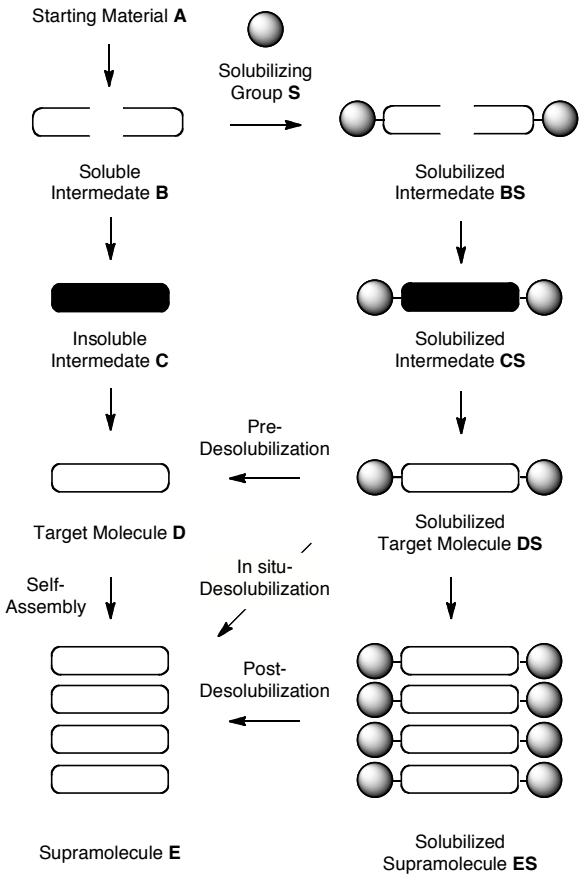


FIGURE 1. Solubilizing groups are, similar to protecting groups, introduced at the beginning or during a multistep to overcome otherwise intractable solubility problems. Their removal at the end of the synthesis does not affect the rest of the molecules and can at best be use to trigger and control the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

As far as true solubilizing groups **S** are concerned, that is temporary solubilizers that can be added and removed at will, branched alkyl groups in tert-butyl esters,[3] Boc or silyl[4] groups have been proven useful. The removal of solubilizing groups during rather than before self-assembly has received considerable recent attention as elegant method to control the formation of supramolecular architectures.[1,2] Successful examples include solubilizing 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 efficient π-stacking, and their face-to-face π-stacks are one of the few air-stable molecular *n*-semiconductors.[10-15] 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 best solubilizers, although the observed effects were rather modest and solubilities remained in the low micromolar ranges in all solvents (Figure 2, Table 1).[6] Bulky and spherical groups such as tert-butyl and tert-butyldiphenylsilyl (TBDPS) groups have been essential as temporary solubilizers to succeed in the synthesis of pores with internal NDI clamps.[2,3]

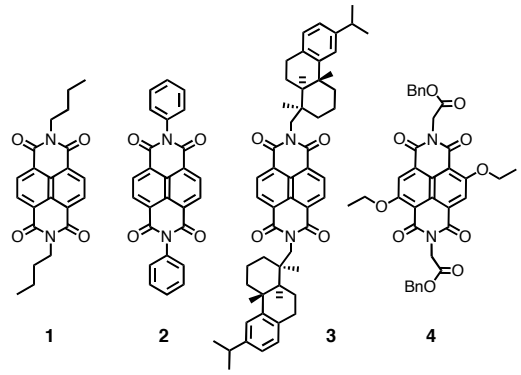


FIGURE 2. Some nasty simple NDIs (compare Table 1).

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 solvent only was insufficient for a key intermediate in the synthesis of artificial photosystems.[15] Considering this challenging molecule as a meaningful example, we here report that the introduction of solubilizing groups allows, without much effort, to transform a quite intractable molecule into a molecule with solubility in molar concentrations in many solvents. Removal of the solubilizing groups in NDI **5** is shown to occur with coinciding precipitation, an in-situ desolubilization that is ideal for the assembly of ordered surface architectures that is controlled directly by chemical transformations (Scheme 1).

RESULTS AND DISCUSSION

To explore the efficiency of small and branched permanent solubilizers common in β-sheets,[2,9] 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.[16,15e] Nucleophilic aromatic core substitution with ethanolate to give tetraester **8** was also accomplished following previously established procedures.[16,15e] After basic ester hydrolysis, threonine **10** was introduced in excellent 40% yield by adapting the recent elegant microwave-assisted conditions from the Sanders group.[17] Compared to the insoluble glycine analog **4**, the introduction of permanent threonine solubilizers in NDI **5** increased solubility in chloroform 80-times. A similar 50-fold

increase was found in methylenechloride, whereas solubility in other solvents remained poor (Table 1, entry 5 vs 4).

The branched tert-butyldimethylsilyl (TBDMS) group was tested first as solubilizing 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 solubilizers in **5** as well as solubilizing groups in **9** converted a nearly intractable compound into a pleasant one with roughly molar solubility in all meaningful solvents.

Table 1. Solubility in different solvents.[a]

	cpds[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 6. No significant solubility was observed in other solvents such as hexane or methanol. [b]See Figure 2 and Schemes 1 and 2 for structures.

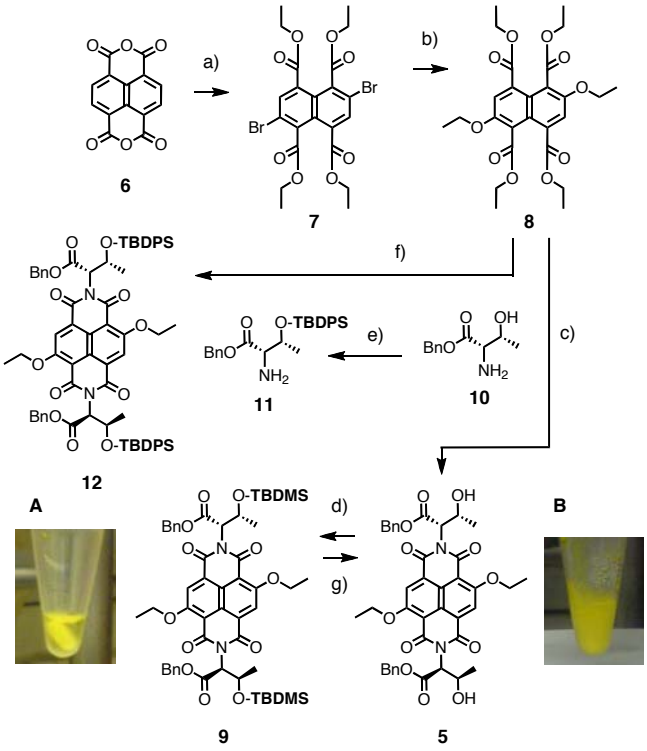
Direct introduction of silylated threonine into hydrolyzed naphthalene **8** was possible using TBDPS instead of more acid labile TBDMS. Diimide formation with amine **11** was possible under microwave irradiation, but the yellow NDI **12** was isolated in trace amounts only. This demonstrated that silylation 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 weaker than that of TBDMS-NDI **9**. This result suggested that alkyl solubilizers are preferable over aryl solubilizers, even if the volume of the solubilizing object is clearly smaller.

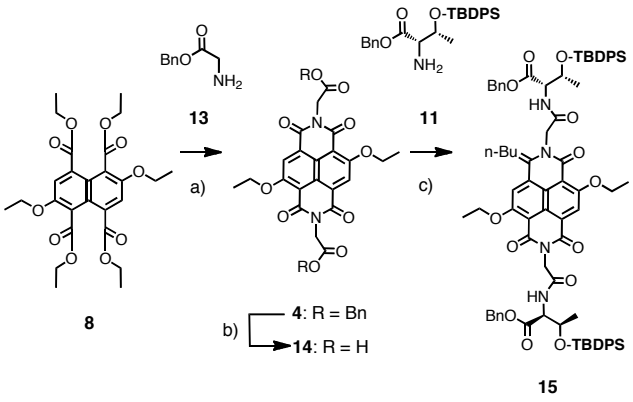
The effect of the solubilizing TBDPS-threonine **11** was slightly weaker if it is attached to the original glycine NDI **4** (Scheme 2). Thanks to the high reactivity of the primary amine in glycine benzylester **13**, NDI **4** was accessible nearly quantitatively from tetraester **9** under harsh conditions but without the need of microwaves. Deprotection and coupling of diacid **14** with TBDPS-threonine **11** gave the solubilized NDI **15**.

Contrary to the original glycine-NDI **4**, direct attachment of permanent threonine plus temporary TBDPS solubilizers made NDI **15** compatible with all meaningful solvents (Table 1, entry 4 vs 8). The NDIs **15** and NDI **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 solubilizing groups with the self-assembly of functional systems, the overall most convincing TBDMS-solubilized NDI **9** was incubated with HCl/THF at 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 desolubilized NDI **5**. This result confirmed that removal of bulky silyl solubilizing groups can in principle be coupled with the self-assembly of functional systems and at best be of use to control formation kinetics and micro-/nanosturctures of their supramolecular architectures.



SCHEME 1. a) 1. Dibromoisocyanuric acid; 2. EtI, EtOH, K_2CO_2, 35%.[15b] b) NaOEt, 73%.[15e] c) 1. KOH, iPrOH, 80 ºC, 48 h, 2. **10**, AcOH/DMF 1:1, microwave, 120 ºC, 30 min, 40%. d) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 0 ºC, 30 min, 76%. e) TBDPSCl, DBU, MeCN, 0 ºC to rt, 12 h, 57%. f) 1. KOH, iPrOH, 80 ºC, 48 h, 2. **11**, AcOH/DMF 1:1, microwave, 130 ºC, 30 min, 4%. g) HCl/THF 1:1, rt, 12 h, A: reaction mixture at the beginning, B: reaction mixture after 12 h.



SCHEME 2. a) 1. KOH, iPrOH, 80 ºC, 21 h, 2. **13**, AcOH, 80 ºC, 54 h, 97%. b) TFA, HBr/AcOH, 6 h, 98%. c) **11**, HATU, TEA, DMF, rt, 12 h, 72%.

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, solubilizing 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 solubilizing 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).[18,19]

Solubilizing 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 existing literature to identify and classify existing solubilizing groups according to their nature, solubilizing power, compatibility with structural motifs and solvents, attachment and removal chemistry as well as chemoorthogonality could already provide a book of the practical value of the protecting group "bible" by Green and Wuts.[8] Many directions are conceivable for future research on solubilizing groups, reaching from fundamental systematic screening exercises of highest importance to more innovative adventures with in-situ desolubilization to build today's "intractable" supramolecular architectures.

EXPERIMENTAL SECTION

Complete experimental details can be found in the Supporting Online Information.

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