Encapsulated Reagents

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Reagents with a Crystalline Coat

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Abstract: *Tetrakis(dimethoxyphenyl)adamantane (TDA) readily forms crystalline inclusion complexes with reactive, toxic, or malodorous reagents, such as benzoyl chloride, acetyl chloride, cyclohexyl isocyanide, phosphorus trichloride, and trimethylsilyl chloride. The crystals are stable and largely free of the problematic properties of the free reagents. When exposed to solvents such as DMSO or MeOH, the reagents react, and a large portion of the TDA precipitates. The TDA-coated reagents may lead to a safer way of storing, handling, and delivering reagents, and ultimately to synthetic protocols that do not require fume hoods.*

Taming reactive compounds until they are brought into contact with the desired reaction partner is one of the challenges of chemistry. The most common way of meeting this challenge is to keep reagents in tightly sealed glass containers. The container is only opened under a fume hood or in a glove box, and the reactive compound is transferred into the reaction vessel using appropriate procedures, which often involve a protective gas.[1] This approach is expensive as it requires a fully equipped laboratory. Furthermore, it is hazardous. If a container breaks during transport, storage, or handling, accidents can occur that have severe consequences for operators and the environment.

Reagents may be tamed by embedding them in an inert matrix. Examples of this approach include acetylene stored in gas bottles with inorganic matrices, white phosphorus encapsulated in self-assembled molecular containers,[2] alkali metals stored under mineral oil, and reactive hydrides in paraffin oil. However, heterogeneous slurries make it difficult to dispense reagents, and few homogenates of reagents[3] are available. The challenge of measuring out portions of inhomogeneous matrices can be overcome by embedding reactive compounds in crystalline matrices that form inclusion complexes of defined stoichiometry. For example, some inorganic reagents form stable co-crystals with inert salts, as in the case of the triple salt of persulfuric acid known as oxone.[4–6] However, even for inorganic salts, stable co-crystals that provide a reactive form of a reagent are the exception, not the rule.

For organic reagents, a generic crystalline matrix that acts as a formulation is lacking. Hemicarcerands are classical examples of molecules that can crystallize and form host–guest complexes[7] with organic molecules.[8] Cryptophanes are another class of compounds with designed cavities that encapsulate small molecules,[9] and so are metal–organic sponges.[10] Crystals of porous organic cages that absorb gases are also known,[11,12] and porous liquids are beginning to emerge,[13] but what would constitute a good crystalline matrix for formulating liquid reagents is unclear. While studying organic cores for matrix-forming DNA hybrids,[14–17] we observed that 1,3,5,7-tetrakis(2,4-dimethoxyphenyl)adamantane (TDA) readily includes small organic molecules in the unit cell of its crystal structures.[18] Even though a solvent-free crystalline form is known, TDA crystallizes with many different guest molecules. Herein, we show that TDA can act as a protective crystalline coat for reagents, enabling the formulation of reactive, malodorous, or toxic compounds, including inorganic reagents such as PCl_3. The crystalline formulation can mask problematic properties while delivering reactive compounds upon exposure to common organic solvents.

First, we optimized the three-step synthesis of TDA.[18] When one equivalent of toluenesulfonic acid was used in the final step of the reaction of adamantane tetraol and 1,3-dimethoxybenzene, and the temperature was lowered to 120 °C, the yield of TDA increased from 38 %[18] to 67 %, as detailed in the Supporting Information. We then screened a range of different compounds that are liquid at room temperature for their ability to form inclusion complexes with TDA. Mixtures of the liquid and TDA were heated until a solution formed, which was then allowed to cool to room temperature. A part of the unit cell of TDA crystals containing extremely malodorous 2,3,4-trimethylpyrazine as the inclusion compound is shown in Figure 1. Table 1 lists parameters of 15 representative X-ray crystal structures of inclusion complexes.

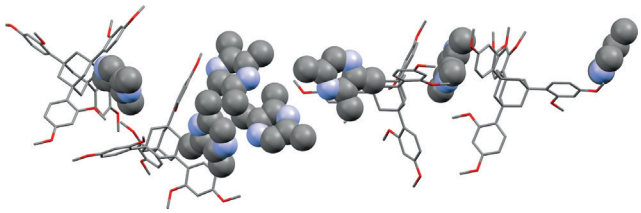

Figure 1. Structural details of the inclusion complex of TDA with 2,3,5-trimethylpyrazine, as observed in the X-ray crystal structure. C gray, N violet, O red. Hydrogen atoms omitted for clarity.

The tetraaryladamantane crystallized in three different crystal systems. Aside from monoclinic and triclinic systems,[18] a hexagonal system was observed for the first time. Stoichiometries between 2:1 and 4:7 were measured, and partially disordered guest molecules were common. Compounds such as pyridine, piperidine, morpholine, acetyl chloride, and furfural were included in near-stoichiometric

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Table 1: Data of the X-ray crystal structures of TDA with organic inclusion compounds.

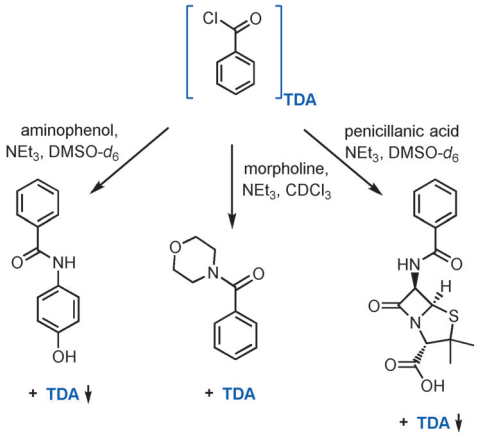
Entry	Crystal system	Space group	Unit cell [Å^3]	Inclusion guest	TDA/guest	$R1$[a]
1	monoclinic	$C2/c$	16254	piperidine	1:1	0.0671
2		$P21/c$	7553	styrene	2:1	0.0448
3			7585	anisole		0.0443
4			7611	*N*,*N*-dimethylaniline		0.0609
5			7512	1-vinylimidazole		0.0541
6			7532	benzoyl chloride		0.0539
7			7598	benzoyl chloride[b]		0.0549
8		$P21/n$	7533	dimethylsulfoxide		0.0535
9			7548	pyrrolidine		0.0515
10	triclinic	$P\bar{1}$	4097	pyridine	4:5	0.0529
11			9597	2,3,5-trimethylpyrazine	4:7	0.0629
12			7745	morpholine	4:3	0.0519
13			3829	acetyl chloride		0.0488
14			3992	furfural		0.0609
15	hexagonal	$P65$	11870	trimethylphosphate	2:1	0.0652

[a] Final R indices [$I > 2\sigma(I)$]. [b] Crystallized from *n*-decane as inert solvent.

quantities despite their different sizes. The malodorous guests 2,3,5-trimethylpyrazine and alkyl isocyanides gave co-crystals that, after washing, were odor-free and stable. This was also true for lachrymatory and reactive compounds that hydrolyze in air, such as acyl chlorides.

Figure 2 shows our approach for producing a crystalline formulation of benzoyl chloride, together with the X-ray crystal structure. A mixture of 100 mg TDA and 100 µL reagent was heated and allowed to crystallize upon cooling (Figure 2b). The resulting crystalline sample was washed with cyclohexane and dried. An individual crystal gave the structure shown in Figure 2b. We propose the use of brackets with "TDA" in subscript as a short-hand notation for the crystal-encapsulated reagents. The stability of $[BzCl]_{TDA}$ when stored in a conventional snap-cap glass vial at room temperature was monitored by visual inspection and ^{1}H NMR spectroscopy (see the Supporting Information, Figure S1). Little degradation was apparent within four months of storage on the bench without an inert gas or tight sealing. Furthermore, $[BzCl]_{TDA}$ stored at 55 °C did not show any signs of decomposition, and the first transition detectable by differential scanning calorimetry (DSC) started at 110 °C (Figures S2 and S3). When stored in a water-saturated atmosphere, 80 % of the reagent in $[BzCl]_{TDA}$ was still intact after three days whereas free benzoyl chloride was fully hydrolyzed under the same conditions within one day (Figures S4–S7).

We then tested whether the crystal-coated benzoyl chloride still possessed its reactivity. Scheme 1 shows reactions of $[BzCl]_{TDA}$ with aminophenol, morpholine, and 6-aminopenicillanic acid (6-APA), substrates typically used in pharmaceutically oriented syntheses. The conversion of the substrate upon



Scheme 1. Reactions of $[BzCl]_{TDA}$ with nucleophiles.

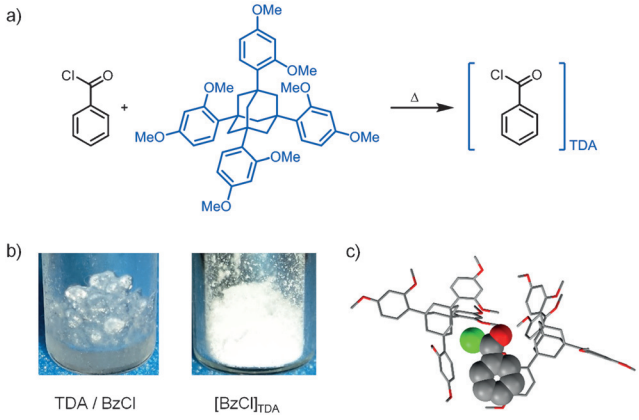


Figure 2. a) Encapsulating benzoyl chloride in TDA crystals. b) Photographs of the crude crystal sample obtained after heating 50 mg TDA and 50 µL benzoyl chloride (left) and the encapsulated reagent after washing and drying (right). c) A part of the unit cell of $[BzCl]_{TDA}$ crystals showing two molecules of TDA and one molecule of benzoyl chloride.

exposure to the encapsulated reagent was monitored in situ by NMR spectroscopy. In chloroform as a solvent in which TDA is well-soluble, the benzoylation was instantaneous, with full conversion in less than 1 min (Figures S15 and S16). Figure 3 shows ^{1}H NMR spectra of benzoyl chloride, its TDA-encapsulated form, and the reaction mixture with 6-APA. The latter benzoylation was performed in DMSO, a solvent in which TDA does not dissolve well. Here, the reaction was significantly slower (Figure S19), probably owing to slow release of the reagent. Interestingly, with $[BzCl]_{TDA}$, a cleaner reaction occurred than when the benzoylated penicillin[19] was synthesized with free BzCl in the same solvent (Figure 3d). Both in this reaction mixture and in the one involving aminophenol, the solution darkened quickly when the reaction was performed with free BzCl. We suspect that the cleaner conversion with $[BzCl]_{TDA}$ is due to protection from hydrolysis during handling and slow release.

A favorable property of the reaction in DMSO is that 70–80 % of the TDA precipitates from the solution, so that a large

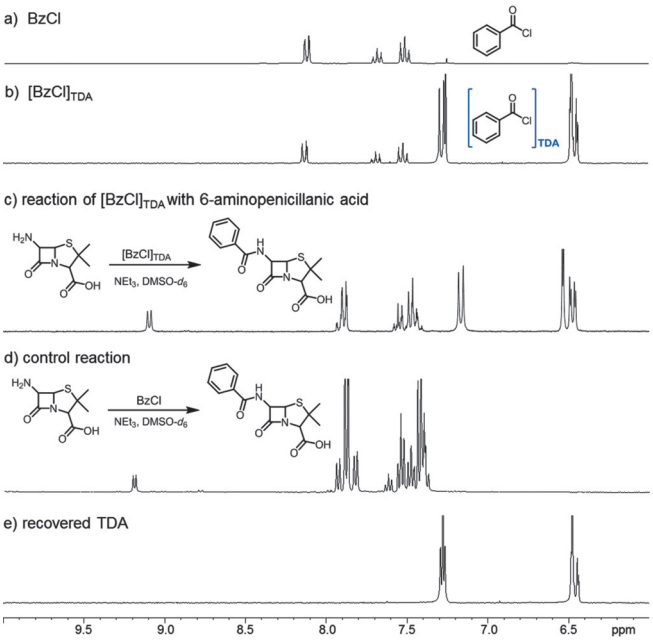


Figure 3. ^{1}H NMR (300 MHz) spectra of a) BzCl, b) $[BzCl]_{TDA}$, c) the reaction solution of 6-APA with $[BzCl]_{TDA}$, d) the control reaction (all in DMSO-d_6), and e) recovered TDA dissolved in $CDCl_3$.

Table 2: TDA crystals with encapsulated reagents, as analyzed by NMR spectroscopy.

Entry	Inclusion guest	TDA/reagent molar ratio
1	AcCl	4:3
2	$(CH_3O)_2P(O)H$	1:1
3	4-$(CF_3)C_6H_4COCl$	1:2
4	BzCl	2:1
5	PCl_3	1:1[a]
6	TMSCl	3:4
7	Me_2Cl_2Si	3:1
8	*i*PrNC	3:2
9	*t*BuNC	3:2
10	CyNC	1:2

[a] Determined by elemental analysis. Cy = cyclohexyl, TMS = trimethylsilyl.

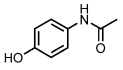
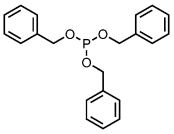
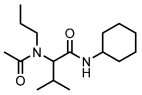
portion of the crystal-forming matrix can be recovered by filtration at the end of the reaction. For the benzoylation of aminophenol and morpholine, 87% and 98% of TDA was recovered during work-up. In either case, the yields of isolated products were slightly higher than for the reactions with free BzCl (see the Supporting Information).

We then tested the encapsulation of other reactive, toxic, and/or strongly malodorous compounds in TDA by the same thermal crystallization method. Here, the loading of the crystals with the reagent was determined by NMR spectroscopy. It was found that TDA also forms inclusion complexes with such reagents as dimethyl phosphite, PCl_3, and three different alkyl isocyanides (Table 2).

Table 3 lists substrates and products of different synthetic transformations with reagents that were encapsulated according to our new method. TDA-formulated acetyl chloride gave 4-acetaminophenol (paracetamol), and tribenzyl phosphite was cleanly formed from crystal-coated phosphorous trichloride. The control reaction with free PCl_3 gave more of the hydrolysis side product (Figure S8). Formulated cyclohexyl isocyanide, $[CyNC]_{TDA}$, readily underwent an Ugi four-component reaction (Ugi 4CR). The latter reaction was carried out in CD_3OD. Near-quantitative recovery of TDA was achieved by filtering off the precipitate at the end of the reaction.

In conclusion, we have reported a method for encapsulating reagents in organic crystals that masks their reactivity and odor and makes them easy to handle and dispense. Some reactions occur more smoothly with the formulation, and the increase in stability can reduce hydrolytic side reactions. Encapsulation may also prevent toxic chemicals from escaping into the environment during transport and handling. Previously, catalysts have been stabilized by encapsulation in non-crystalline matrixes,[20,21] including wax capsules for air-sensitive catalyst mixtures.[22] This allowed for synthetic transformations without a glove box. With TDA reagent formulations and solvents such as DMSO, some synthetic transformations may not even require a fume hood.

Table 3: Selected reactions with TDA-encapsulated reagents.

Reagent	Reaction	Solvent	Product	Recovered TDA [%][a]
$[AcCl]_{TDA}$	acylation	DMSO		70–90
$[PCl_3]_{TDA}$	phosphitylation	$CDCl_3$		—[b]
$[CyNC]_{TDA}$	Ugi 4CR	CD_3OD		99

[a] From the reaction mixture itself. [b] TDA is well soluble in this solvent.

Experimental Section

Encapsulation: A TDA sample (100 mg, 147 μmol) in a glass vial was treated with benzoyl chloride (100 μL, 87 μmol), and the resulting mixture was heated on a hot plate (130 °C) until a homogeneous solution formed. The hot plate was switched off, and the sample was allowed to cool for 30 min while still on the plate, leading to a crystalline sample. The sample was centrifuged, and any remaining supernatant was aspirated. The crystals were washed with cyclohexane (4 × 500 μL) and dried under a flow of nitrogen. An experiment starting from 2 g TDA and 2.2 mL benzoyl chloride gave similar results.

Benzoylation of 6-aminopenicillanic acid: A sample of 6-aminopenicillanic acid (5 mg, 23 μmol) in DMSO-d_6 (400 μL) containing triethylamine (3.8 μL, 27.7 μmol, 1.2 equiv) was treated with TDA-encapsulated benzoyl chloride (25 mg $[BzCl]_{TDA}$, 23 μmol BzCl) at

20 °C. The slurry was shaken for 45 min, followed by centrifugation, harvesting of the precipitate (15 mg, 22 μmol, 70 % recovered TDA), and analysis of the supernatant by NMR spectroscopy.

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Keywords: adamantane · controlled release · encapsulated reagents · synthetic methods · X-ray diffraction

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