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Cellulosics modified with slow-release reagents. Part I. Synthesis of triazine-anchored reagents for slow release of active substances from cellulosic materials

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Abstract

Novel tri-functional triazines for the modification of cellulosic fibers are prepared from cyanuric chloride. The compounds employ a monochlorotriazinyl (MCT) anchor group for fixation, an active substance showing slow release properties, and a reactivity tuner to facilitate release control. While the compounds are completely stable under dry conditions, the active substances are released simply by surrounding humidity. The reagents offer intriguing perspectives for the preparation of modified cellulosics for single-use application in fields such as healthcare, cosmetics, or personal hygiene.

Keywords: Slow release; Triazine anchors; Cellulose

1. Introduction

A modern way of drug administration is the use of *prodrugs*, which are mainly used if the application of the actual active substance is not possible or would be less effective [1]. Prodrugs are used for instance to transport the drug to special locations, such as certain organs [2], special tissues or cell types [3], to carry the drug through the cell membrane, to release it under special conditions, e.g. in a pH-selective manner [4], as well as to retard or prolong the drug release.

A recent trend in cellulose chemistry is the search for high-tech materials with special effects, such as antibacterial [5], UV-protecting [6], insect repellent, fire retarding [7], or even medical properties [8]. To date, the active substances have been covalently bound to the cellulose fiber using conventional fiber-agent bonding as employed in reactive dyeing and finishing [5,6a], or have been either simply incorporated into the fibers during the spinning process [6b] or added onto the fibers by soaking/drying cycles. The first approach, with stable agent-fiber covalent bonding, is not suitable for active substances which rely on volatility, e.g. insect repellancy, fragrance etc., or on availability in free form, e.g. physiologically or medically active compounds, for efficacy. A major drawback of the second approach—the incorporation into fibers—is the large amount of active substance needed compared to the relatively small amount which is eventually discharged from the fiber and free to act. The disadvantage of the soaking-and-drying application method is a nearly complete lack of control in terms of drug concentration, release time, and loss by simple washing. A radically alternative approach to the above is the use of reactive cyclodextrins. These cyclic oligosaccharides are able to form inclusion complexes with a variety of complex organic molecules, which are released over time from a textile surface. However, the release is not tunable and determined by rather ill-defined influencing factors.

In continuation of our studies on triazine-derived functionalization agents [9], we would like to communicate

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a novel approach which combines the concept of *prodrugs* with that of covalent functionalization of cellulose fibers. Synthesis and the slow-release properties of the novel reagents will be described; a detailed account of the application to cellulosic materials will be reported in due course.

2. Experimental

All chemicals were commercially available. Thin layer chromatography (TLC) was performed on silica gel 60 plates (5×10 cm, 0.25 mm) with fluorescence detection under UV light at 254 nm. NMR spectra were recorded with a Bruker Avance DPX instrument operating at 300.13 MHz for ^{1}H and 75.47 MHz for ^{13}C using tetramethylsilane as internal standard and $CDCl_3$ as the solvent, if not otherwise stated. Homo- and heteronuclear 2D NMR spectroscopy was performed with Bruker standard software. Chemical shifts are given in ppm, coupling constants in Hz. ^{13}C peaks were assigned by means of APT, HMQC and HMBC spectra, 'd.i.' denotes peaks of double intensity originating from two magnetically equivalent carbons.

2.1. Preparation of slow release reagents **1–8**

2.1.1. Tocopheryl-morpholino-monochlorotriazine (**1**)

Procedure A. Cyanuric chloride (1.84 g, 0.1 mol) was dissolved in acetone (70 mL) and cooled to 5 °C. α-Tocopherol (4.31 g, 0.1 mol) and *sym*-collidine (1.30 g, 0.11 mmol) were dissolved in acetone (30 mL) and added dropwise to the cyanuric chloride solution. It was stirred at 5 °C for 5 h, then allowed to warm to r.t. over approximately 2 h giving a pale yellow solution and a white precipitate of collidinium hydrochloride. TLC control (ethyl acetate/*n*-hexane, v/v=3:7) showed a single strong band running ahead of vitamin E. Next day the precipitate was filtered off to give 1.01 g collidinium hydrochloride, after 4 days another 0.43 g were collected, and the acetone was removed in vacuo. The residue was slurried in water at pH 7 for 2 h at r.t. and then extracted repeatedly with ethyl acetate. Finally, the extract was washed with water to remove any residual collidine and cyanuric chloride residues, and the solvent was removed in vacuo after drying, to give 4.0 g of tocopheryl-dichlorotriazine (TDCT) as colourless slurry. ^{1}H NMR: δ 2.66–2.57 (m, 2H, H-4), 2.12 (s, 3H, H-5a), 1.98 (s, 3H, H-7a), 1.95 (s, 3H, H-8a), 1.90–1.75 (m, 2H, H-3), 1.26 (s, 3H, H-2a). ^{13}C NMR: δ 173.1 (C-O-Toc), 171.3 (C–Cl, d.i.), 150.0 (C-6), 141.5 (C-8a), 126.2 (C-5), 124.4 (C-7), 123.5 (C-8), 118.4 (C-4a), 75.4 (C-2), 37.5 (C-3), 28.0 (C-2a), 22.6 (C-4), 13.0 (C-5a), 11.9 (C-7a), 11.8 (C-8a). Resonances of the isoprenoid side chain are not listed, as they are not influenced by modification at the phenolic hydroxyl group.

Procedure B. Tocopheryl-dichlorotriazine (TDCT, 1.0 g, 1.73 mmol) was dissolved in dry *n*-hexane (20 mL) and morpholine (2.1 equiv.) in dry *n*-hexane was added at 0 °C (ice cooling) within 10 min whereby the temperature should not rise above 5 °C. After 30 min there was no TDCT left (TLC control, *n*-hexane/ethyl acetate, v/v=10:1). The precipitation of a white solid (morpholinium hydrochloride) was observed, which was removed by filtration. Then, the solvent was removed in vacuo and the crude product was purified by flash chromatography on silica gel (*n*-hexane/ethyl acetate, v/v=10:1) to give 0.53 g (49%) of tocopheryl-morpholino-monochlorotriazine (**1**, $C_{35}H_{55}ClN_4O_3$, M=615.31) as a colourless wax. ^{1}H NMR: δ 3.84 (t, ^{3}J=4.8 Hz, 2H, O-CH_A), 3.70 (t, ^{3}J=4.8 Hz, 2H, O-CH_B), 3.64 (m, 4H, N-CH_A and N-CH_B), 2.60 (t, ^{3}J=6.6 Hz, 2H, H-4), 2.11 (s, 3H, H-5a), 2.00 (s, 3H, H-7a), 1.96 (s, 3H, H-8a), 1.84–1.77 (m, 2H, H-3), 1.25 (s, 3H, H-2a). ^{13}C NMR: δ 172.0; 171.2; 166.2 (triazine), 149.6 (C-6), 142.4 (C-8a), 127.2 (C-5), 125.4 (C-7), 123.2 (C-8), 117.8 (C-4a), 75.5 (C-2), 66.8 (O–CH_2 in morpholine), 44.6 and 44.4 (N–CH_2 in morpholine), 37.7 (C-3), 28.4 (C-2a), 21.4 (C-4), 13.5 (C-5a), 12.6 (C-7a), 12.2 (C-8a).

2.1.2. Tocopheryl-methoxy-monochlorotriazine (**2**)

Procedure C. Methoxydichlorotriazine (1.80 g, 0.1 mol) was dissolved in acetone (70 mL) and cooled to 5 °C. α-Tocopherol (4.31 g, 0.1 mol) and *sym*-collidine (1.30 g, 0.11 mol) were dissolved in acetone (30 mL) and added dropwise to the methoxydichlorotriazine solution. It was stirred at 5 °C for 1 h, then allowed to warm to 40 °C, and stirred for another 2 h. After further stirring at r.t. for 24 h, addition of *n*-hexane (50 mL) and stirring for additional 2 h, the white precipitate of collidinium hydrochloride (1.52 g) was removed by filtration, and the acetone was removed in vacuo. The residue was slurried in water at pH 7 for 2 h at r.t. and then extracted repeatedly with ethyl acetate. Finally, the extract was washed with water to remove any residual collidine, and the solvent was removed in vacuo after drying, to give 4.00 g (71.4%) of **2** ($C_{32}H_{50}ClN_3O_4$, M=560.23) as a colourless wax. ^{1}H NMR: δ 3.52 (s, 3H, OMe), 2.60 (t, ^{3}J=6.6 Hz, 2H, H-4), 2.11 (s, 3H, H-5a), 2.00 (s, 3H, H-7a), 1.96 (s, 3H, H-8a), 1.84–1.77 (m, 2H, H-3), 1.25 (s, 3H, H-2a). ^{13}C NMR: δ 176.1; 170.1; 166.9 (triazine), 149.2 (C-6), 142.5 (C-8a), 127.0 (C-5), 125.4 (C-7), 123.1 (C-8), 117.9 (C-4a), 75.3 (C-2), 55.7 (OMe), 37.5 (C-3), 28.2 (C-2a), 21.2 (C-4), 13.2 (C-5a), 12.6 (C-7a), 12.3 (C-8a).

2.1.3. Pantothenoyl-morpholino-monochlorotriazine (**3**)

Procedure D. Morpholino-dichlorotriazine (2.35 g, 0.1 mol) was dissolved in acetone (20 mL) and panthothenic acid (2.40 g, 1.1 mmol) suspended in acetone (20 mL) was added. *sym*-Collidine (2.1 equiv.) in acetone (30 mL) was added dropwise at 5 °C whereby the temperature should not rise above 5 °C. The solution was allowed to warm to 40 °C, and stirred at this temperature for another 2 h. After further stirring at r.t. for 24 h, *n*-hexane (50 mL) was added. The solution was stirred for additional 2 h and the white

precipitate of collidinium hydrochloride was removed by filtration. The solvents were removed in vacuo, the residue was dissolved in ethyl acetate and washed with brine. After drying, the solvent was removed in vacuo to give **3** (2.74 g, 65.8%, $C_{16}H_{24}ClN_5O_6$, $M=417.85$) as a white powder. ^{13}C NMR: δ 173.2; 171.1; 166.3 (triazine), 173.1 (CON), 171.2 (COO), 73.7 (HC–OH), 67.2 (CH_2–OH), 66.6; 48.6 (morpholine), 35.4 (CH_2), 32.2 (CH_2), 30.5 (C), 19.5 (Me, d.i.).

2.1.4. Pantothenoyl-methoxy-monochlorotriazine (*4*)

The reagent was synthesized according to the above *procedure C*, employing pantothenic acid (2.40 g, 0.11 mol) instead of tocopherol. White powder (2.26 g, 62.4%, $C_{13}H_{19}ClN_4O_6$, $M=362.77$) ^{13}C NMR: δ 178.2; 172.1; 165.3 (triazine), 173.2 (CON), 171.2 (COO), 73.8 (HC–OH), 67.2 (CH_2–OH), 55.3 (O–Me), 35.6 (CH_2), 32.4 (CH_2), 30.5 (C), 19.4 (Me, d.i.).

2.1.5. Vanillyl-morpholino-monochlorotriazine (*5*)

The reagent was synthesized according to the above *procedures A and B*, employing vanillin instead of tocopherol, to give the product (2.75 g, 78.8%, $C_{15}H_{15}ClN_4O_4$, $M=350.76$) as white powder. In *procedure B* acetone was used instead of *n*-hexane. ^{13}C NMR: δ 190.3 (CHO), 172.2; 172.0; 167.1 (triazine), 161.3; 153.8; 129.2, 126.0; 123.1; 115.4 (^{Ar}C), 66.6; 48.6 (morpholine), 54.9 (O–Me).

2.1.6. Vanillyl-methoxy-monochlorotriazine (*6*)

The reagent was synthesized according to the above *procedure C*, employing vanillin instead of tocopherol, to give the product (2.49 g, 84.2%, $C_{12}H_{10}ClN_4O_3$, $M=295.68$) as white powder. ^{13}C NMR: δ 190.8 (CHO), 176.9; 173.1; 165.1 (triazine), 161.4; 153.6; 129.3, 126.0; 123.1; 115.4 (^{Ar}C), 55.3 (O–Me, triazine), 54.9 (O–Me).

2.1.7. (2,4,6-Trichlorophenyl)-morpholino-monochlorotriazine (*7*)

The reagent was synthesized according to the above *procedures A and B*, employing 2,4,6-trichlorophenol instead of tocopherol, to give the product (3.20 g, 81.1%, $C_{13}H_{10}Cl_4N_4O_2$, $M=396.06$) as white powder. In *procedure B* acetone was used instead of *n*-hexane. ^{13}C NMR: δ 173.0; 171.9; 165.7 (triazine), 147.0; 132.9; 131.2; 130.0 (^{Ar}C), 66.2; 48.1 (morpholine).

2.1.8. (2,4,6-Trichlorophenyl)-methoxy-monochlorotriazine (*8*)

The reagent was synthesized according to the above *procedure C*, employing 2,4,6-trichlorophenol instead of tocopherol, to give the product (2.93 g, 86.0%, $C_{10}H_5Cl_4N_3O_2$, $M=340.98$) as white powder. ^{13}C NMR: δ 176.9; 172.4; 165.3 (triazine), 150.4; 140.0; 131.3; 130.0 (^{Ar}C), 55.6 (O–Me).

2.2. Derivatization of cellulose with slow-release reagents—example procedure

Preliminary experiments on derivatization of cellulose were carried out with a cellulosic pulp (*Eucalyptus urophylla*, prehydrolysis kraft) and the slow-release reagent tocopheryl-morpholino-monochlorotriazine (**1**) in a heterogeneous reaction. The pulp was swollen in 3% NaOH solution for different periods of time (1–24 h), filtered and squeezed. The derivatization reagent (0.1–5 mL of a 5% solution in ethanol) was added to 0.5 g of pulp. The pulp was heated to 80 °C in an oven for different times (5 min to 3 h). The derivatized cellulose was washed with cold water (3 times), ethanol (3 times) and diethyl ether (3 times). After drying in vacuo, the white samples were stored under exclusion of moisture.

Alkalization time and heating time were of no influence on the derivatization result, indicating the reaction to be complete after short alkalization and heating times, so that further extension did not improve the yield.

2.3. Slow release of reagents from the fiber material—preliminary results

The pulp derivatised with tocopheryl-morpholino-monochlorotriazine (**1**), containing approx. 1 mM of vitamin E, lost only 2% of the active substance upon dry storage at room temperature after 10 days. The release of the active substance, effected simply by storage under ambient atmosphere and a relative moisture content of about 70% was 23% after 1 day, 56% after 3 days and 100% after 14 days. The optimised experimental methods to study the slow release will be published elsewhere in due course.

3. Results and discussion

Cyanuric chloride readily reacts with nucleophiles in substitution reactions. Each nucleophilic substitution progressively reduces the reactivity of the remaining ring chlorine atoms, thereby allowing stepwise replacement to be carried out. The first chlorine reacts easily (0–5 °C) but the third one requires more forcing conditions (50–90 °C). This reactivity gradation has been widely exploited in the pesticide and reactive dye fields [10]. In the case of binding a monochlorotriazine (MCT) to the cellulose matrix, the cellulosic hydroxyl groups, catalyzed by the action of sodium hydroxide or other bases, act as nucleophiles in a conventional S_NAr reaction [11]. The newly established chemical bond between an MCT and cellulose is quite stable to normal wash-and-wear environments. This holds true for most aliphatic hydroxyls as well as primary and secondary amines. Such bonds are resistant to hydrolysis under near-neutral conditions and can be considered permanent. In contrast, bonds between a triazine and phenolic hydroxyls or carboxylic acids are relatively labile (more stable anions),

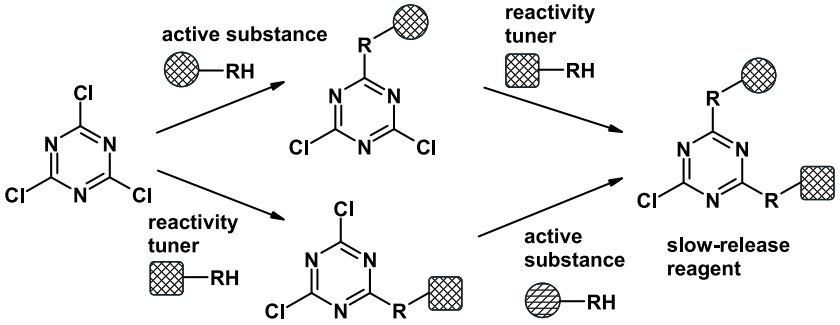

Fig. 1. Preparation of the slow-release reagents.

a fact, which has not received much attention so far, as permanent fixation of the triazine moieties is generally the desired effect. Phenoxy- and acyloxy-substituents in triazines are readily replaced in substitutions by hydroxyl, alkoxyl, or amino groups. This process proceeds also—albeit rather slowly—if atmospheric moisture is not carefully excluded during storage. The cleavage tendency in the case of acyloxy-substituted triazines can be especially high: specific triazines, such as dimethoxychlorotriazine [12], are even used as good leaving groups to 'activate' acids for esterification or amidation. In these cases, the acid reacts with the MCT derivative to give an acyloxy-triazine as an 'activated acid', which now can readily acylate an alcohol or amine to give esters or amides, respectively, as the triazinoxy moiety is a very good leaving group.

In the present case, the tri-functional cyanuric chloride was used as starting material to prepare slow release reagents to be bound to cellulosic fibers. This requires one chlorine remaining on the triazine, which will then be replaced by the cellulosic hydroxyl to establish the permanent link to the fiber. A second prerequisite is the non-permanent binding of the active substance to the triazine, replacing the second chlorine. As phenols and carboxylic acids are non-permanently bound, the present concept of slow-release was focused on these two classes of substances. The third chlorine was reacted with a so-called 'reactivity tuner' i.e. a moiety with an aliphatic hydroxyl or a primary/secondary amino group that is permanently attached to the triazine, see Fig. 1. This reactivity tuner influences the rate at which the active substance is released.

It seemed reasonable to assume that the reactivity tuner exerted electronic effects on the carbon carrying the active substance, altering the electron density there and thus the rate of nucleophilic displacement. However, computations at a high level of theory (density functional, B3LYP/6-311+G**) have shown that the electronic effects are too small to account for the observed reactivity differences, so that steric effects are likely to be the decisive factor instead.

The order of introduction of reactivity tuner and active substance is exchangeable for phenols. Once the phenol has been attached to the triazine, it is usually stable enough to survive the reaction with the reactivity tuner without being cleaved off. However, it is always recommended to attach the reactivity tuner first and then the active substance in the second step, since this way side reactions can be avoided from the beginning (Fig. 1). In the case of carboxylic acids, this order is even essential, since the triazine—carboxylic acid bond is too labile to survive the reaction conditions needed for attaching the reactivity tuner.

The slow-release reagent is fixed onto cellulosic fibers in the same manner as standard MCT dyes. Even though cleavage of the active substance during fixation cannot be excluded, this process is minimal due to the short contact times with the alkaline reaction medium. Once the triazine—fiber bond is established, the active substance is the only cleavable moiety attached to the triazine. Since the active substance is released in its genuine form, no issues concerning toxicological problems or unknown pharmacognosy will arise. After cleavage, the triazine with the reactivity tuner remains bound to the fiber matrix, the active substance having been replaced by a hydroxyl originating from surrounding moisture (Fig. 2).

Eight slow release reagents have been prepared, employing the lipophilic vitamin E (α-tocopherol) [13], the hydrophilic vitamin B5 (pantothenic acid) [14], the phenol vanillin—which can readily be detected by its characteristic odour, and the antibacterial agent and disinfectant 2,4,6-trichlorophenol (Fig. 3). Methanol and morpholine were used as reactivity tuners. The selection of the active substances was done to demonstrate the broad applicability

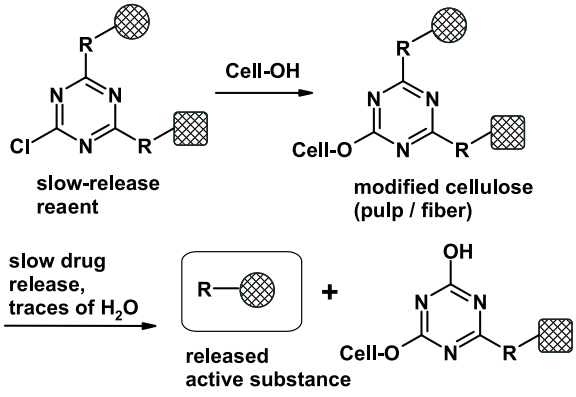

Fig. 2. Fixation of the reagents onto cellulose and slow release of the active substances.

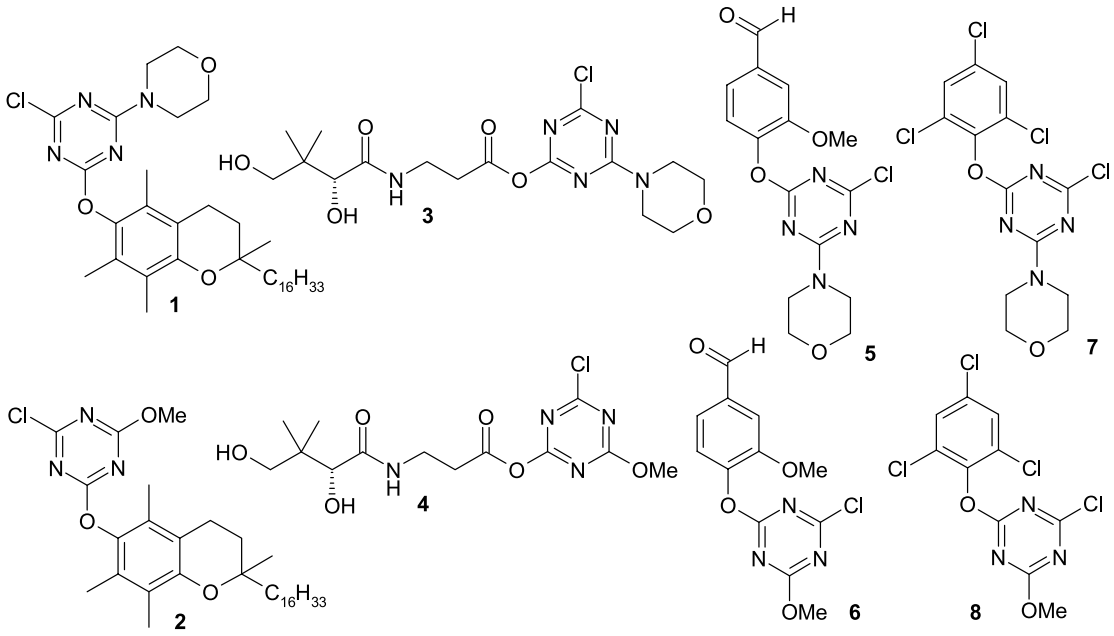

Fig. 3. Synthesized slow-release reagents **1**–**8**.

of the approach. Noticeably, it is not limited to medically active substances which are slowly liberated (cf. **1**–**4**). Also odorants (cf. **5**–**6**), antibacterials (cf. **7**–**8**)—or compounds with other effects—can be temporarily attached to fibers via the slow release reagents.

Tests on the pure reagents have established their stability and slow-release characteristics, i.e. the reagents were studied before binding onto cellulose. In all cases, loss of active substances under dry storage was negligible. Upon storage under moist conditions, the reagent showed half-lives of 2–4 days, meaning that the reagent had released approx. 50% of the active substance after these times (Table 1). Comparison of methoxyl and morpholino groups, as reactivity tuners, showed a 50% acceleration for the former. After 14 days under moist conditions (rel. humidity ca. 80%), the release was complete in all cases.

Preliminary studies on cellulose modified with tocopheryl-morpholino-monochlorotriazine to a surface load of 360 μmol/g gave similar results (see Section 2). While the dry stability was excellent (2% loss of active substance after 10 days at r.t.), under moist conditions 23% of the active substance was released in 24 h, and 56% after 3 days. As in the case of non-bound reagents, 100% of the active substance was cleaved from the triazine after 14 days.

Table 1
Slow release characteristics of reagents **1**–**8**

Reagent	Dry storage[a]	Moist storage[b]	'Half-time'[c]
1	1.2	24	3 days
2	3.4	30	2 days
3	0.8	19	4 days
4	1.5	32	2 days
5	n.d.	28	2–3 days
6	n.d.	36	2 days
7	1.8	22	2–3 days
8	2.8	31	2 days

[a] Amount of active substance released upon dry storage at r.t. in the dark over 5 days.

[b] Amount of active substance released under moist conditions (r.t., 24 h, 100-fold molar excess of H_2O relative to reagent).

[c] Estimated time for release of 50% of active substance under moist conditions.

4. Conclusions

Eight slow-release reagents have been prepared from cyanuric chloride. The reagents carry an active substance, e.g. a medicinally active compound, an odorant, or a bactericide, attached via a phenolic or carboxylic acid function, which show slow-release properties. The slow release is activated by contact with (atmospheric) moisture, and the reagents are stable when stored under dry conditions. The rate of release is influenced by the second substituent on the triazine, which acts as a reactivity tuner with regard to the slow-release compound, but itself remains permanently linked to the triazine. The reagents are fixed onto cellulosic fibers according to standard conditions used for triazine dyes. The broad applicability of the slow-release approach was demonstrated by selecting four active substances from quite different fields.

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