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Parameters Influencing the Release of Tertiary Alcohols from the Surface of "Spherical" Dendrimers and "Linear" Stylomers by Neighbouring-Group-Assisted Hydrolysis of 2-Carbamoylbenzoates

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Abstract: The influence of structural and physico-chemical parameters on the release of a volatile tertiary alcohol (2-methyl-1-phenyl-2-propanol) by neighbouring-group-assisted cyclisation of 2-carbamoylbenzoates at neutral pH was investigated by comparing the covalent-bond cleavage from the surface of linear, comblike poly(propylene imine) "stylomers" and their corresponding spherical, globular dendrimers. Determination of the kinetic rate constants for the stepwise intramolecular cyclisation of the 2-carbamoylbenzoate moiety by using HPLC showed that the polarity of the conjugates, and thus their solubility in the aqueous reaction medium, has a stronger influence on the rates of hydrolysis than the size (generation) or shape (linear or spherical) of the macromolecules. Furthermore, structural modifications in close proximity to the release unit, such as the presence of functionalities with catalytic activity, have a strong impact on the release efficiency of the active molecules. An understanding of the physico-chemical parameters determining the local environment of the covalent-bond cleavage site is therefore an important prerequisite to transfer the characteristics of small molecules to larger structures such as oligomers and polymers and thus to design efficient macromolecular conjugates for the controlled delivery of bioactive compounds.

Keywords: dendrimers · fragrances · kinetics · neighboring-group effects · stylomers

Introduction

Structural versatility combined with particular macroscopic properties make polymers[1] and polymer conjugates[2] interesting carrier materials to control the release of biologically active compounds. Due to their highly symmetric, branched, treelike structures,[3] some dendrimers can behave as unimolecular micelles[4] and have been investigated as macromolecular model compounds for the delivery of bioactive compounds.[5,6] With the loading capacity inside the dendrimers being quite limited, the removal of the outer shell,[7] which was originally developed to facilitate the release of encapsulated molecules, was adapted to release bioactive molecules from the dendrimer surface by stepwise covalent-bond cleavage.[8,9] Since, for steric reasons, a larger number of molecules can be attached to the dendrimer surface than could possibly be physically trapped within the dendritic branches, the release of bioactive compounds by covalent-bond cleavage from the dendrimer surface is particularly interesting for high-generation dendrimers. Redox reactions,[10–12] photofragmentations,[13–15] hydrolyses[16–19] and the action of enzymes or catalytic antibodies[20–23] were identified as the most common triggers for covalent-bond cleavage at the dendrimer surface. Besides drug delivery, this concept was also successfully used to control the release of fragrances.[18,23,24] Water is the most important solvent for all types of biological applications, and the release of the active compound must therefore proceed in aqueous media.

Neighbouring-group participation[25] or intramolecular catalysis[26] is a concept allowing the hydrolysis of carboxylic esters using an intermediate nucleophilic species in an intramolecular reaction pathway and is therefore suitable for the

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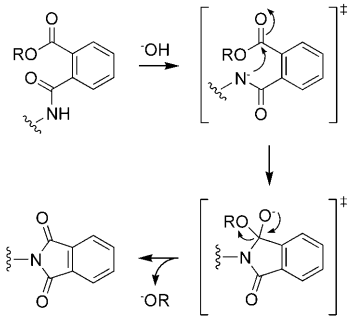
controlled release of bioactive alcohols by covalent-bond cleavage under mild reaction conditions.[24,27] Particularly interesting in this context are 2-carbamoylbenzoates, because they are easy to synthesise by reacting an activated benzoic acid derivative with a primary amine.[28–31] The release mechanism is pH dependent and based on the abstraction of a proton from the carbamoyl moiety under neutral or slightly basic conditions to form an intermediate nucleophile, as shown in Scheme 1.[18,30,31] The nucleophile then attacks the carbonyl group of the neighbouring ester group and releases the alcohol upon intramolecular cyclisation. Primary, secondary and even tertiary alcohols have successfully been released by using this concept, and besides monomeric or polymeric species, highly symmetric dendrimer-based 2-carbamoylbenzoates of fragrance alcohols have been prepared and analysed for their controlled-release properties.[18] The compounds were found to be stable in acidic aqueous media, but hydrolyse under neutral or slightly alkaline conditions to release the corresponding alcohol.



Scheme 1. Mechanism for the release of alcohols from 2-carbamoylbenzoates by neighbouring-group-assisted intramolecular cyclisation.

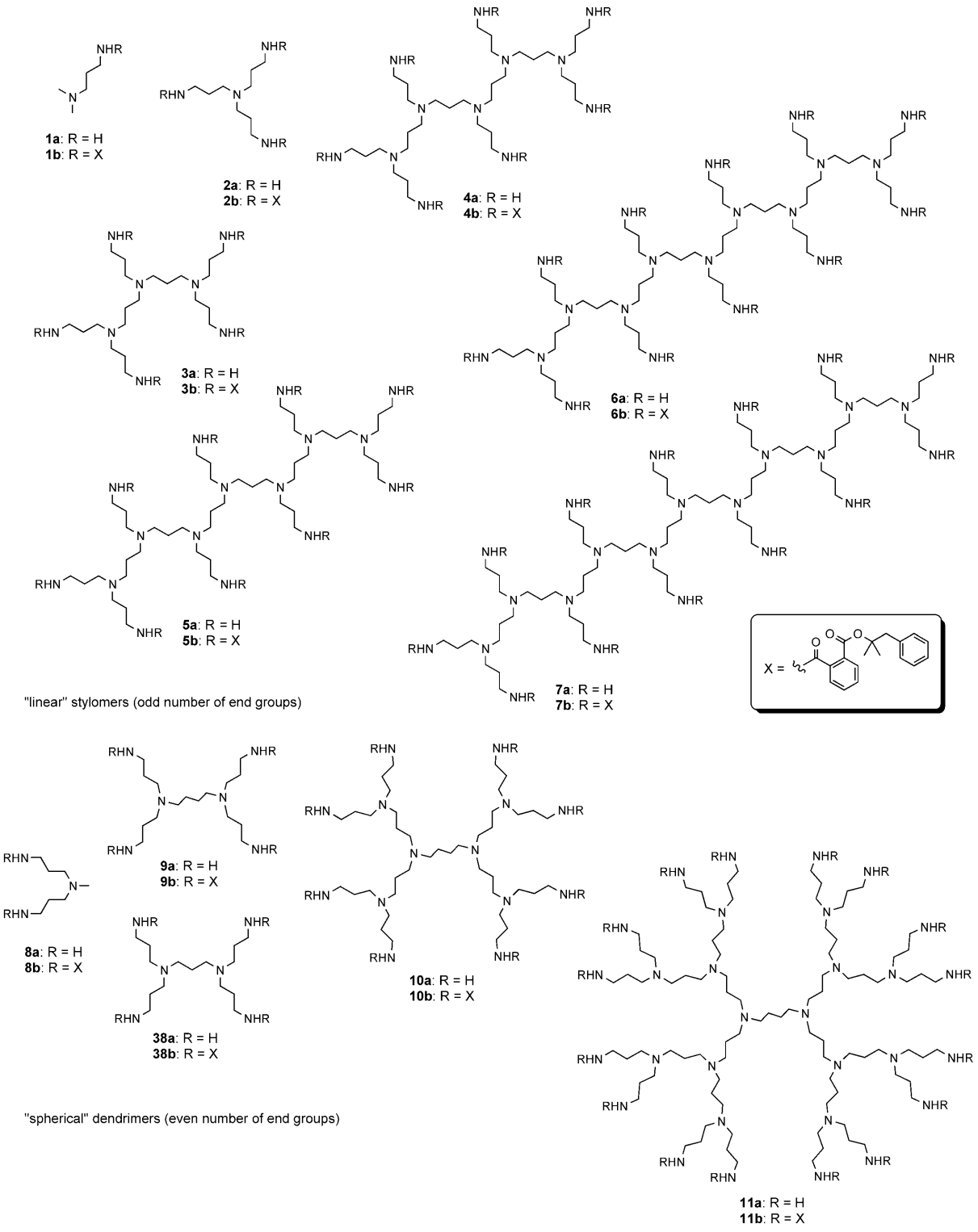
Abstract in French: *L'influence des paramètres structurels et physico-chimiques sur le relargage à pH neutre d'un alcool tertiaire volatil (2-méthyl-1-phényl-2-propanol) par cyclisation de 2-carbamoylbenzoates assistée par un groupe voisin a été étudiée. Les ruptures de liaisons covalentes depuis la surface de poly(propylene imines) en forme de peigne ("stylomères") d'une part et de leurs analogues sphériques et globulaires (dendrimères) correspondants d'autre part ont été comparées. La détermination par CLHP des constantes cinétiques pour la cyclisation intramoléculaire des unités 2-carbamoylbenzoate par étapes a montré que la polarité des conjugués, et par conséquent leur solubilité dans le milieu de réaction aqueux, a une influence plus forte sur les vitesses d'hydrolyse que la taille (génération) ou la forme (linéaire ou sphérique) des macromolécules. De plus, des modifications structurelles à proximité immédiate de l'unité de relargage telles que la présence de groupes fonctionnels avec une activité catalytique ont un fort impact sur l'efficacité de relargage des molécules actives. La compréhension des paramètres physico-chimiques qui déterminent l'environnement local du site de rupture de la liaison covalente est par conséquent une condition préalable importante lors du transfert de caractéristiques de petites molécules à des structures plus grandes telles que des oligomères et des polymères, et donc à la conception de conjugués macromoléculaires efficaces pour le relargage contrôlé de composés bioactifs.*

For the delivery of volatiles, it has been shown that the release from polymer conjugates is considerably slower than that from the corresponding monomeric, low-molecular-weight analogues, thus indicating a strong stabilising effect of the polymer structure.[24,29,32] For the understanding of the structural and physico-chemical parameters influencing the release kinetics from polymeric structures, it is desirable to find suitable model systems that can easily be analysed. As dendrimers, with their globular, micellar structures, are not necessarily representative model compounds for linear polymers, we decided to prepare "linear", comblike poly(propylene imine) "stylomers"[33] **1a**–**7a** as analogues of the corresponding "spherical", globular dendrimers **8a**–**11a**. After functionalisation with 2-carbamoylbenzoates, the release of 2-methyl-1-phenyl-2-propanol (**12**) as a typical tertiary fragrance alcohol was investigated as a function of the size and structure of the respective "linear" derivatives **1b**–**7b** (with an odd number of 2-carbamoylbenzoate units) and "spherical" compounds **8b**–**11b** (bearing an even number of 2-carbamoylbenzoate moieties).[18] In the case of the smaller molecules of each series (e.g., **1b**–**3b**, **8b** and **9b**) the topology of the molecules should be quite similar; a more pronounced effect related to either a "linear" or "spherical" shape of the macromolecules might only be expected for the larger structures.

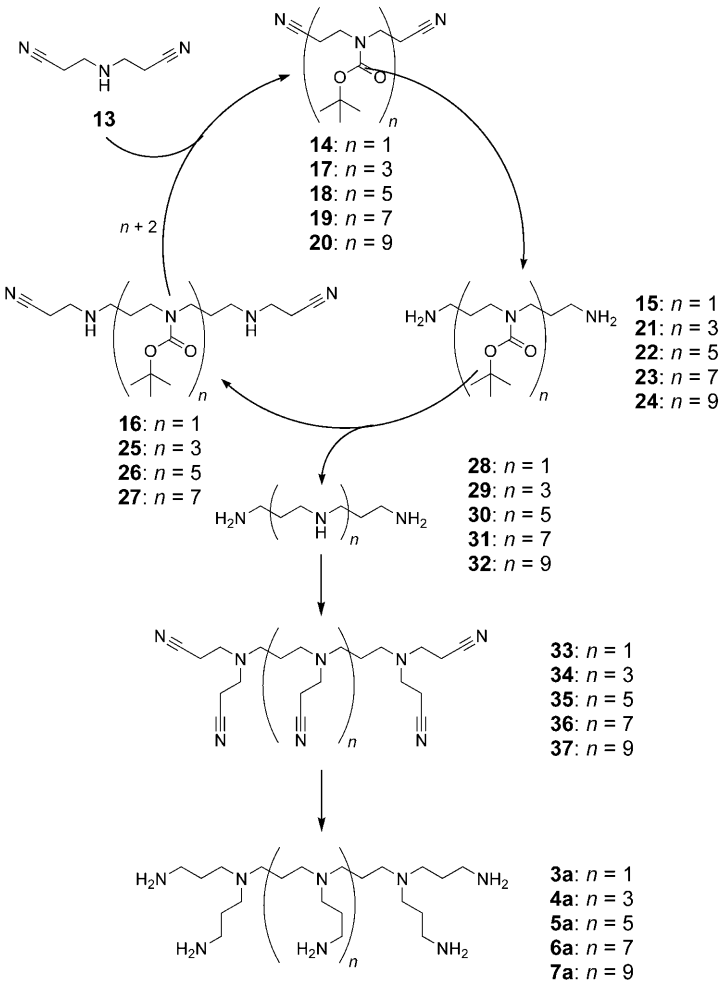
Despite a considerable number of reported cleavage reactions, the influence of the dendrimer structure on the release rates of bioactive compounds has mainly been investigated as a function of the total size of the dendrimers (generation-dependent or generation-independent release).[11–13,17–23] Other aspects, such as the topology of the macromolecules (linear or spherical), their polarity and solubility (as modified by the presence of surfactants) as well as the nature of the local environment in proximity to the release unit, which are important for practical applications, have only been considered in isolated cases[19,21] and will thus be the subject of the present work.

Results and Discussion

Synthesis: Whereas compounds **1a**, **2a** and **8a**–**11a** are commercially available, poly(propylene imine) stylomers **3a**–**7a** had to be synthesised. Inspired by the preparation of the corresponding dendrimers **9a**–**11a**,[34,35] and the synthesis of spermine-type polyamines,[36–39] we proceeded by using a cyclic, stepwise reaction procedure as depicted in Scheme 2. The key steps of the repetitive reaction sequence comprise Michael addition of propenenitrile (acrylonitrile) to the primary amino functions followed by hydrogenation of the nitrile groups.



3,3′-Iminodipropanenitrile (**13**) was selected as the starting material for the preparation of **3a**–**7a**. To achieve a linear rather than a spherical growth of the structures, the secondary amine functions within the principal chain were protected with *tert*-butoxycarbonyl (Boc) groups. Reaction of **13** with di-*tert*-butyl dicarbonate gave dinitrile **14**,[36] which was reduced to the corresponding primary diamine **15** with hydrogen (8 bar) in the presence of Raney nickel as the catalyst.[36] 1,4-Addition of **15** to acrylonitrile in methanol at room temperature afforded dinitrile **16** with an extended chain length of two units with respect to its precursor **13** (Scheme 2).[36] Under mild reaction conditions (room



Scheme 2. Cyclic reaction procedure for the preparation of "linear" poly(propylene imine) oligomers **3a**–**7a**.

temperature), acrylonitrile selectively reacts with primary amines to give the monoaddition product. To functionalise the secondary amines, higher temperatures and a slight excess of acrylonitrile are required.

Each cycle contains three reaction steps, namely, protection of the secondary amino functions, reduction of the nitrile groups, and 1,4-addition of the primary diamines to acrylonitrile to increase the size of the oligomers by two units (n+2; Scheme 2). Repeating the consecutive reaction steps several times gave fully protected nitriles **17**–**20**, the corresponding primary diamines **21**–**24** and partially protected nitriles **25**–**27**.

All transformations within the cyclic procedure proceeded with high efficiency, and could therefore be carried out on a multigram scale (up to 100 or 200 g). The hydrogenation reaction required large amounts of the Raney nickel catalyst; for small-scale reactions (1–10 g) two weight equivalents of catalyst with respect to the quantity of the dinitrile to be reduced were used, on a larger scale (80–100 g) one equivalent was found to be sufficient. The best results were obtained by using a mixture of ethanol and aqueous ammonia as solvent. The isolated products (80–99 % yield) were slightly blue, presumably due to the presence of traces of nickel complexes. The crude compounds were used for the following reaction step, except in the case of the products obtained after Boc protection, which were purified by using column chromatography. The purification slightly decreased the yields for this reaction (80–90 %), but allowed the removal of the nickel complexes before the next hydrogenation step.

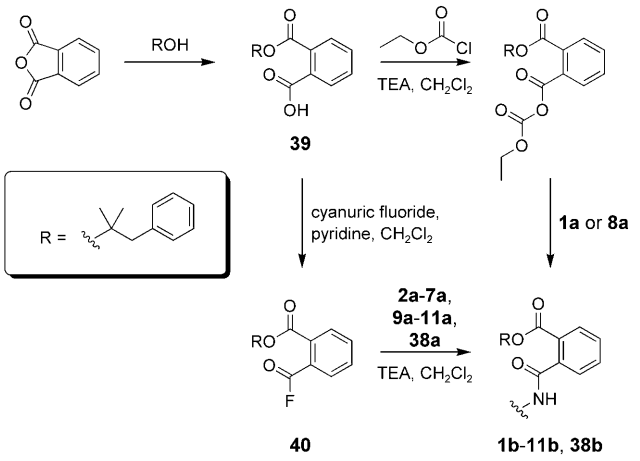
Stylomers **3a**–**7a** were then obtained in three steps from Boc-protected primary diamines **15** and **21**–**24**, respectively, which were removed from the cyclic reaction procedure (Scheme 2). As the first step, the Boc-protecting groups were removed by treatment with trifluoroacetic acid (TFA), followed by exchange of trifluoroacetate anions on a basic anion-exchange resin (Dowex 1X8). Linear amines **28**–**32** were obtained in moderate-to-good yields (30–96 %), which decreased with increasing molecular size. Functionalisation of **28**–**32** with 2–3 equivalents of acrylonitrile at 80–120 °C in water afforded nitriles **33**–**37**. The increase in temperature allowed addition to the secondary amines and afforded the target compounds in 60–80 % yield. Finally, target amines **3a**–**7a** were obtained from nitriles **33**–**37** by catalytic hydrogenation in alkaline ethanol/water using Raney nickel as the catalyst (for further details, please refer to the Supporting Information).

The limited solubility of the nitriles and the removal of the remaining NaOH after the reaction are the two major problems encountered in the isolation of large quantities of the pure multiamines. NaOH was removed by saturating the aqueous phase and then the supernatant oil phase containing the multiamine was removed by using a pipette. Interestingly, the large multiamines were obtained in higher yields than their smaller analogues.

With the hydrogenation being less and less efficient for an increasing number of nitrile functions, "linear" tridecaamine **7a** was the largest stylomer we could prepare on a reasonable scale. Although we managed to isolate small quantities of the corresponding pentadecaamine under similar reaction and work-up conditions, its purification was quite complicated.

The use of **13** as the starting material resulted in stylomers **3a**–**7a** with an odd number of primary amine groups, as compared with dendrimers **9a**–**11a**, which all have an even number of amino functional groups at their surface. Even-numbered stylomers can principally be obtained with the same reaction sequence using propane-1,3-diamine as the starting material.[36] In this work, we only prepared compound **38a**[40] with four primary amine functions as the propane-1,3-diamine analogue of the even-numbered butane-1,4-diamine dendrimer **9a**, as well as its corresponding carbamoylbenzoate derivative **38b**.

The size of the molecule influences the ease of further functionalisation. Amines **1a** and **8a** could easily be functionalised with the mixed anhydride obtained by reaction of the corresponding monosubstituted phthalates (benzene-1,2-dicarboxylates) **39** with ethyl chloroformate to give amides **1b** and **8b** (Scheme 3). However, this reaction did not occur



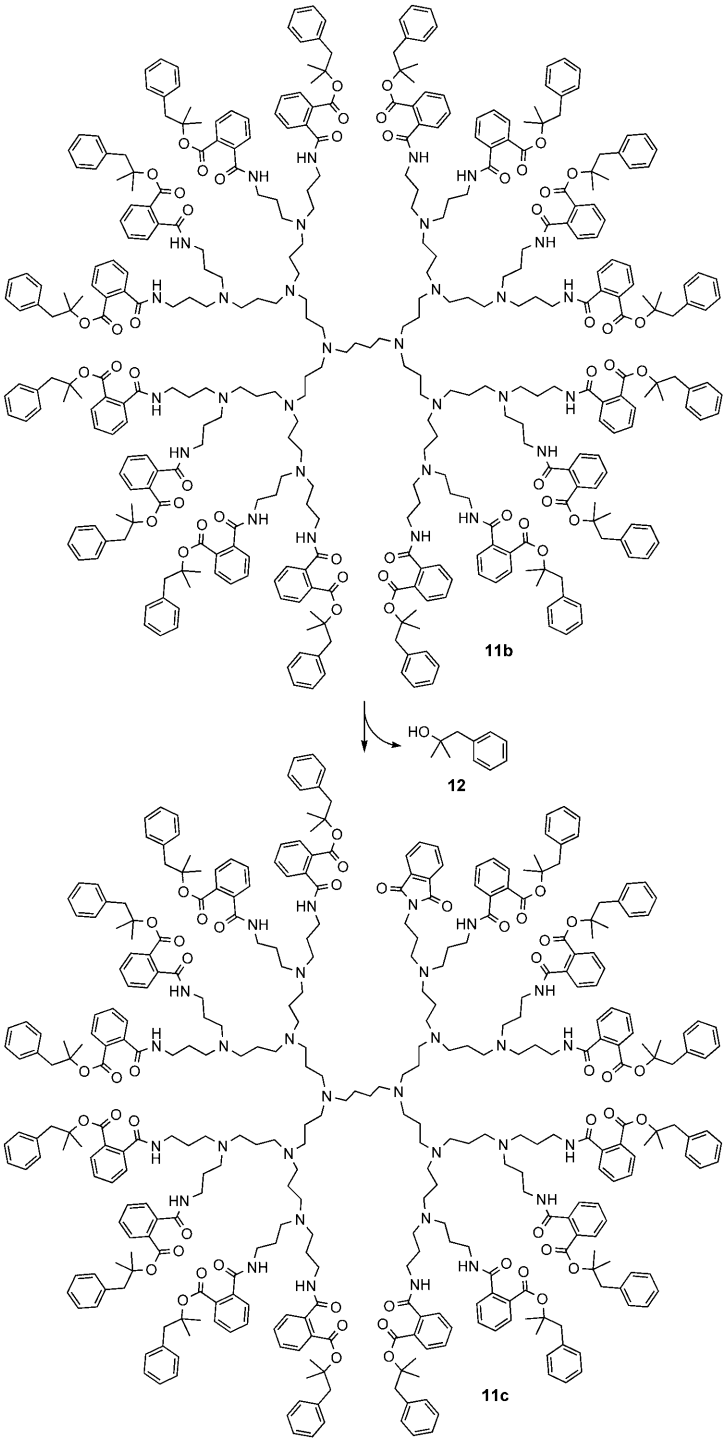
Scheme 3. Grafting of the 2-carbamoylbenzoate moiety onto primary amines **1a–11a** (TEA = triethylamine).

for the larger structures.[18] 2-Carbamoylbenzoates **2b–7b** and **9b–11b** were finally obtained from amines **2a–7a** and **9a–11a**, respectively, by reaction with acid fluoride **40** according to the method described by Carpino et al.[41] (Scheme 3).

Grafting of the 2-carbamoylbenzoate moiety onto multiamines **1a–11a** indicated that there must be some significant structural differences concerning the shape of the compounds. Whereas "spherical" dendrimers **9a–11a** reacted without particular problems with **40** to form even-numbered 2-carbamoylbenzoates **9b–11b**, respectively, the corresponding odd-numbered "linear" stylomers **4b–7b** were much more difficult to obtain. The preparation and purification of tridecamer **7b** was complicated (no pure product was obtained) and the synthesis of the corresponding pentadecamer failed.

The functionalisation was followed by analytical HPLC, and the products were purified by using reversed phase (RP) flash chromatography or medium-pressure liquid chromatography (MPLC). To avoid cyclisation of the products in the presence of ambient humidity during storage, the product fractions obtained from the chromatography were concentrated at low temperature in the presence of small amounts of $KHSO_4$.

Purification of dendrimer **11b** by MPLC afforded two different product fractions, which were identified by LC–MS analysis as being the entirely functionalised product **11b** and its monocyclised derivative **11c** (Scheme 4).[18] Co-injection of the two product fractions onto an analytical RP C2 phase and elution with a gradient of water/acetonitrile (containing 0.1% of TFA) allowed the baseline separation of the two compounds. RP chromatography was thus found to be an extremely powerful tool for the separation of the pure functionalised precursors **2b–11b** from their corresponding monocyclised intermediates **2c–11c**, respectively. This result allowed us to measure the kinetic rate constants for the first and second consecutive cyclisation steps.



Scheme 4. First step of the release of tertiary alcohol **12** from dendrimer **11b** to form monocyclised intermediate **11c**.

Kinetic measurements: By monitoring the appearance and disappearance of the different reaction intermediates rather than the formation of the tertiary alcohol, individual rate constants for the consecutive cyclisation steps could be measured by using RP-HPLC. In view of the targeted application as a delivery system to control the release of volatile fragrances, the measurements were carried out at 20°C in

aqueous solution at neutral pH (phosphate buffer).[30,31,42] For solubility reasons acetonitrile was added and, because almost all practical applications of functional perfumery comprise significant amounts of surfactants, the release of **12** as a typical fragrance alcohol was investigated in the presence of a non-ionic surfactant and was compared with the corresponding solutions without surfactant.

Nevertheless, only the smaller structures (**1b**, **2b**, **8b** and **9b**) could be entirely dissolved in the reaction mixtures without surfactant. Whereas tetrakis(2-carbamoylbenzoate) **9b** was still soluble at a concentration of 2.4×10^{-4} mol L^{-1}, its structural analogue **38b** formed an emulsion at the same concentration, which resulted in a slight non-linearity when plotting the logarithm of the peak area ratios versus time. As a consequence of the limited solubility of the larger structures in the reaction mixture, the rate constants for the release of **12** from all precursors could only be compared in solutions containing 1% of Triton X100, in which all compounds were found to be sufficiently soluble.

In a typical measurement, precursors **1b–11b** and **38b** were dissolved in acetonitrile and added to a phosphate buffer stock solution in water/acetonitrile 4:1 (with or without surfactant) to give a final mixture of water/acetonitrile 2:1 at pH 7.62. The reaction solution was immediately injected onto a RP C2 HPLC column ($t=0$) and eluted at 1 mL min^{-1} with a gradient of water/acetonitrile (both containing 0.1% of TFA). The reaction solution was then re-injected at constant time intervals. The TFA present in the eluent quenches the neighbouring-assisted cyclisation reaction and thus allows analysis of the reaction progress at different time intervals. All measurements were carried out at least twice, and the data were found to be reproducible with errors being generally below 10%. Rate constants were measured at equimolar concentrations of the precursors ($c_{mol}=4.3\times10^{-4}$ mol L^{-1}) and at equimolar "end-group" concentrations, which means that the same molar amount of tertiary alcohol **12** ($c_{eg}=8.6\times10^{-4}$ mol L^{-1}) is released after complete hydrolysis of the precursors. In the case of bis(2-carbamoylbenzoate) **8b** the two concentrations are identical, and the same solution was used for both measurements.

Figure 1 shows a typical HPLC trace obtained after approximately 20 min of hydrolysis for the stepwise cyclisation of pentakis(2-carbamoylbenzoate) **3b**. For the identification of the different reaction intermediates, five peaks were manually collected and the corresponding products were analysed by using electrospray ionisation mass spectrometry (ESI-MS). Besides two unknown impurities (from the surfactant), the peaks were attributed to the twofold cyclised species **3d** ($[M]^{2+}=759$ Da), monocyclised intermediate **3c** ($[M]^{2+}=834$ Da) and the corresponding precursor **3b** ($[M]^{2+}=909$ Da).

Whereas precursors **1b**, **2b** and **8b** and their larger, dendritic analogues **9b–11b** and **38b** (with an even number of 2-carbamoylbenzoate moieties) only form one single isomer after the first cyclisation step, this is not the case for their oligomeric counterparts. Due to their lower symmetry, stylomers **3b–7b** form isomeric mixtures upon cyclisation,

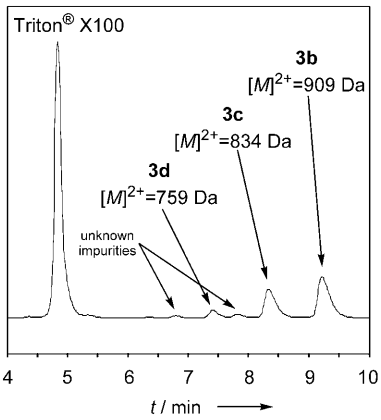


Figure 1. HPLC trace for the stepwise controlled release of tertiary fragrance alcohol **12** from pentakis(2-carbamoylbenzoate) **3b** (elution on a RP C2 column with a water/acetonitrile gradient in the presence of 0.1% of TFA and detection at $\lambda=254$ nm).

and the number of monocyclised isomers increases with the size of the molecules. Nevertheless, the possibility of isomer formation did not complicate the measurement of the kinetic rate constants. Despite the fact that intermediates with a different degree of cyclisation were all easily separated by using HPLC (and MPLC), the different isomers of each species (in the case of **3c** there are two possible isomers and in the case of **3d** there are three) were usually found to coelute as a mixture.

For precursors bearing more than one 2-carbamoylbenzoate unit, a stepwise consecutive reaction according to Equation (1) is expected. With the hydroxide concentration being kept constant by the buffer solution, the general second-order rate expression, $r=k_2[OH^-][precursor]$, can be simplified to the pseudo-first-order relation, $r=k_0[precursor]$.[30,43] This was confirmed by plotting the logarithm of the (decreasing) peak area quotients (A_t/A_0) of the precursors **1b–11b** and **38b** against time, which resulted in straight lines with good correlation coefficients in all cases ($r^2>0.99$). The slopes of the correlations gave the rate constants k_a for the first cyclisation step.

$$\underset{(=\mathbf{1b}-\mathbf{11b},\,\mathbf{38b})}{\mathrm{A}} \xrightarrow{k_a} \underset{(=\mathbf{1c}-\mathbf{11c},\,\mathbf{38c})}{\mathrm{B}} \xrightarrow{k_b} \underset{(=\mathbf{2d}-\mathbf{11d},\,\mathbf{38d})}{\mathrm{C}} \rightarrow\rightarrow \cdots \quad (1)$$

The rate constants k_b for the second cyclisation step were then obtained by correlating the measured peak areas of monocyclised species **2c–11c** and **38c** with those calculated for consecutive first-order reactions by iteration of k_b in Equation (2) (in which A_0 and B_0 represent the peak areas measured for the first injection).[31,44]

$$B=\frac{k_aA_0}{k_b-k_a}e^{-k_a\Delta t}+\frac{k_bB_0-k_a(A_0+B_0)}{k_b-k_a}e^{-k_b\Delta t} \quad (2)$$

The rate constants measured for the first and second cyclisation step of precursors **1b–11b** and **38b**, together with the corresponding half-life times (obtained by dividing the value

of ln2 by the corresponding rate constants) are listed in Tables 1 and 2.

Influence of the surfactant: According to first-order kinetics, rate constants are expected to be independent of the precursor concentration. In the absence of the surfactant, and within a certain experimental error, the rate constants for a given precursor were all found to be of the same order of magnitude (Table 2), thus confirming first-order kinetics. However, this was not generally the case for the reactions carried out in the presence of Triton X100 as non-ionic surfactant (Table 1), which has therefore an influence on the rate constants. This is not surprising, as the surfactant facilitates the solubilisation of the precursors in the aqueous medium by inclusion into the micelle structure. Figure 2 shows a comparison of the half-life times obtained at equimolar concentrations (empty squares and circles) with those recorded at equimolar end-group concentrations (full squares and circles) in the presence of 1% of surfactant. Significant concentration-dependent differences were measured for the monocyclisation of stylomers **2b**–**6b**, as well as for dendrimers **9b** and **10b**. In the case of the smaller structures (**2b**, **3b** and **9b**) cyclisation is faster at lower (equimolar end-group) concentrations, whereas larger structures (**4b**–**6b** and **10b**) cyclise faster at higher (equimolar) concentrations. Nevertheless, with the ratio of the surfactant and precursor concentrations being constant, pseudo-first-order rate conditions were found for the individual measurements. For the following discussion only the measurements carried out in the presence of the surfactant will be considered.

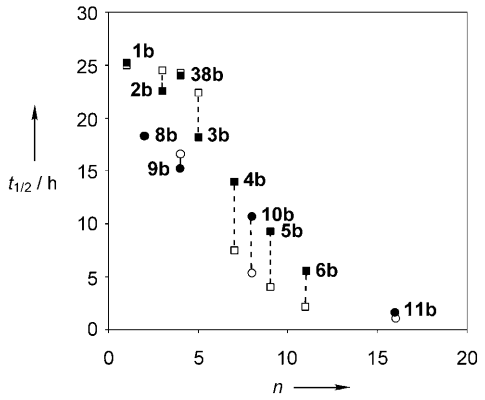


Figure 2. Comparison of the half-life times determined for the first cyclisation step of odd-numbered stylomers (squares) and even-numbered dendrimers (circles) with respect to the number of alcohols n to be released per molecule in the presence of Triton X100 at equimolar concentration (○ and □) and at equimolar end-group concentration (● and ■).

Table 1. Measured kinetic rate constants k_a and k_b and half-life times ($t_{1/2}$) for the first and second cyclisation steps of 2-carbamoylbenzoate derivatives **1b**–**11b** and **38b** in a buffered solution of water/acetonitrile 2:1 (pH 7.62) at 20°C and in the presence of 1 wt% of a non-ionic surfactant (Triton X100). All data are average values of at least two measurements.

First cyclisation step	No. of end groups	Equimolar concentration $c_{mol}=4.3\times10^{-4}$ mol L^{-1}		Equimolar end-group concentration $c_{eg}=8.6\times10^{-4}$ mol L^{-1}		Second cyclisation step	Equimolar concentration $c_{mol}=4.3\times10^{-4}$ mol L^{-1}		Equimolar end-group concentration $c_{eg}=8.6\times10^{-4}$ mol L^{-1}	
		k_a [s^{-1}]	$t_{1/2}$ [h]	k_a [s^{-1}]	$t_{1/2}$ [h]		k_b [s^{-1}]	$t_{1/2}$ [h]	k_b [s^{-1}]	$t_{1/2}$ [h]
1b→1c	1	7.71×10^{-6}	25.0	7.64×10^{-6}	25.2	–	–	–	–	–
8b→8c	2	1.05×10^{-5}	18.3	1.05×10^{-5}	18.3	**8c→8d**	1.36×10^{-5}	14.2	1.36×10^{-5}	14.2
2b→2c	3	7.88×10^{-6}	24.5	8.56×10^{-6}	22.5	**2c→2d**	1.04×10^{-5}	18.6	9.61×10^{-6}	20.1
9b→9c	4	1.16×10^{-5}[a]	16.6	1.27×10^{-5}	15.2	**9c→9d**	1.22×10^{-5}[a]	15.9	1.27×10^{-5}	15.2
3b→3c	5	8.60×10^{-6}	22.4	1.06×10^{-5}	18.2	**3c→3d**	1.10×10^{-5}	17.5	1.29×10^{-5}	15.3
4b→4c	7	2.56×10^{-5}[b]	7.5	1.38×10^{-5}	14.0	**4c→4d**	2.12×10^{-5}	9.1	1.74×10^{-5}	11.1
10b→10c	8	3.59×10^{-5}[a]	5.4	1.80×10^{-5}[a]	10.7	**10c→10d**	2.72×10^{-5}	7.2	1.69×10^{-5}	11.4
5b→5c	9	4.79×10^{-5}[c]	4.0	2.06×10^{-5}	9.3	**5c→5d**	8.63×10^{-5}[c]	2.2	2.33×10^{-5}	8.3
6b→6c	11	8.86×10^{-5}	2.2	3.47×10^{-5}	5.6	**6c→6d**	1.08×10^{-4}	1.8	3.81×10^{-5}	5.1
11b→11c	16	1.72×10^{-4}[d]	1.1	1.23×10^{-4}	1.6	**11c→11d**	2.25×10^{-4}[d]	0.9	1.09×10^{-4}	1.8
38b→38c	4	7.93×10^{-6}	24.3	8.02×10^{-6}	24.0	**38c→38d**	1.10×10^{-5}	17.5	1.08×10^{-5}	17.8

[a] Differences with respect to ref. [18] are due to additional measurements. [b] $r^2>0.98$. [c] $r^2>0.96$. [d] $c_{mol}=3.55\times10^{-4}$ mol L^{-1}.

Table 2. Measured kinetic rate constants k_a and k_b and half-life times ($t_{1/2}$) for the first and second cyclisation steps of 2-carbamoylbenzoate derivatives **1b**, **2b**, **8b** and **9b** in a surfactant-free buffered solution of water/acetonitrile 2:1 (pH 7.62) at 20°C. All data are average values of at least two measurements.

First cyclisation step	No. of end groups	Equimolar concentration $c_{mol}=4.3\times10^{-4}$ mol L^{-1}		Equimolar end-group concentration $c_{eg}=8.6\times10^{-4}$ mol L^{-1}		Second cyclisation step	Equimolar concentration $c_{mol}=4.3\times10^{-4}$ mol L^{-1}		Equimolar end-group concentration $c_{eg}=8.6\times10^{-4}$ mol L^{-1}	
		k_a [s^{-1}]	$t_{1/2}$ [h]	k_a [s^{-1}]	$t_{1/2}$ [h]		k_b [s^{-1}]	$t_{1/2}$ [h]	k_b [s^{-1}]	$t_{1/2}$ [h]
1b→1c	1	8.94×10^{-6}	21.5	7.97×10^{-6}[a]	24.2	–	–	–	–	–
8b→8c	2	1.46×10^{-5}	13.2	1.46×10^{-5}	13.2	**8c→8d**	1.60×10^{-5}	12.0	1.60×10^{-5}	12.0
2b→2c	3	1.30×10^{-5}	14.8	1.39×10^{-5}	13.9	**2c→2d**	1.26×10^{-5}	15.3	1.31×10^{-5}	14.7
9b→9c	4	n.d.[b]	n.d.[b]	1.80×10^{-5}	10.7	**9c→9d**	n.d.[b]	n.d.[b]	1.72×10^{-5}	11.2

[a] First point taken after 54 min. [b] n.d. = not determined.

Influence of polarity changes: The half-life times determined for the first and second step of the intramolecular cyclisation with respect to the total number of 2-carbamoylbenzoate units are illustrated in Figure 3. In most of the

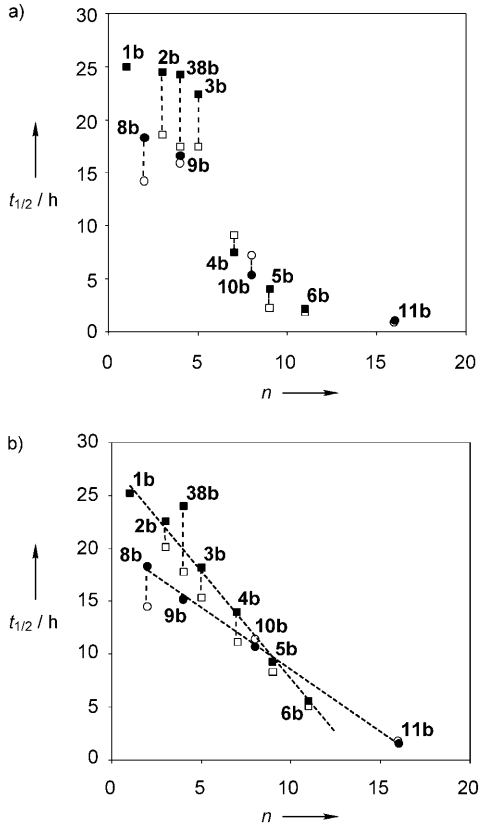
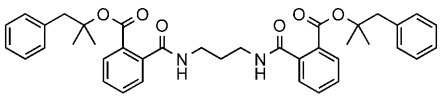


Figure 3. Comparison of the half-life times determined for the intramolecular cyclisation of precursors **1b**–**11b** and **38b** (● and ■) and **2c**–**11c** and **38c** (○ and □) with respect to the number of alcohols *n* to be released per molecule in the presence of Triton X100. a) Measurements at equimolar concentration and b) measurements at equimolar end-group concentration.

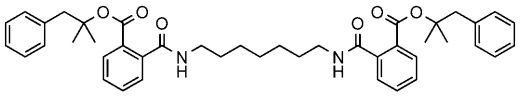
cases the first step of the reaction was found to be faster than the second step for both measurements carried out either at equimolar concentration (Figure 3a) or at equimolar end-group concentration (Figure 3b). Large differences in cyclisation rates were observed in particular for the smaller structures with two to four 2-carbamoylbenzoate moieties (precursors **2b**, **3b**, **8b** and **38b**), whereas with increasing size of the molecules the difference between the two rate constants was found to be smaller (compound **1b** can only cyclise once). This is consistent with the hypothesis that structurally induced changes resulting from the stepwise cyclisation (such as change in polarity) are more pronounced in the smaller molecules than in the larger structures in which the individual 2-carbamoylbenzoate units have a more similar environment. Stepwise cyclisation increased the polarity of the molecules (as shown by decreasing retention times on the RP column) and thus improves their solubility in an aqueous medium. Considering only the first step of cyclisation, this effect is much more pronounced for the smaller structures than for the larger ones.

Plotting the half-life times of the first cyclisation step against the number of alcohols to be released (at equimolar end-group concentration) resulted in a linear relationship for stylomers with an odd number of end-groups and dendrimers with an even number of end-groups, respectively (Figure 3b). Precursor **38b** is the only example that does not fit on either one of the two lines. The remarkable difference of the rate constants measured for precursors **9b** and **38b**, which differ only by one CH_2 group in the centre of the molecule, is in fact particularly remarkable, and it seems that the solubility of the precursor in the reaction medium, and thus the polarity of the environment in close proximity to the release unit, is an important factor influencing the release kinetics. This might be explained by the fact that the tertiary amine functions are partially protonated at neutral pH,[45] and that the degree of protonation depends on the distance between the tertiary amine functions, with the more distant amines having a slightly higher degree of protonation (and thus a better solubility).[40] A different degree of protonation is expected to change the polarity of the molecule by modifying the solubility of the two precursors in the reaction medium at a given pH and thus to influence the rate constants of the hydrolysis.

Influence of structural modifications: To further investigate the influence of structural changes on the release rates of alcohol **12**, we prepared bis(2-carbamoylbenzoates) **41b** and **42b**, both of which are lacking the tertiary amino group in



41b



42b

the linker between the alcohol-releasing moieties. The rates for the release of the tertiary alcohol from the two precursors were too slow to be determined accurately under the above-described conditions (without surfactant). At alkaline pH, rate constants $k_a = 7.99 \times 10^{-4}\ s^{-1}$ ($t_{1/2} = 0.24$ h at pH 10.28) and $3.44 \times 10^{-4}\ s^{-1}$ ($t_{1/2} = 0.56$ h at pH 10.47) were determined for the first cyclisation step of **41b** and **42b**, respectively. In agreement with our previous observations discussed above, the hydrolysis of the more hydrophilic (and thus more soluble) precursor **41b** was found to be about twice as fast as that of its slightly less hydrophilic analogue **42b**.

To further understand the catalytic effect of the tertiary amine group, we tested whether addition of one molar

equivalent of triethylamine to a solution of **41b** ($c = 4.39 \times 10^{-4}$ mol L^{-1}) in the phosphate buffer at pH 7.62 (without surfactant) increases the rate of hydrolysis of the precursor. For the first step of cyclisation an average rate constant of $k_a = 2.19 \times 10^{-6}$ s^{-1} was measured, which represents a slight increase in the rate of hydrolysis with respect to the measurement without triethylamine. However, intramolecular catalysis with the tertiary amine function in close proximity to the 2-carbamoylbenzaote moiety was found to be almost one order of magnitude more efficient, as illustrated by the rate constant of $k_a = 1.46 \times 10^{-5}$ s^{-1}, measured for compound **8b** (Table 2).

The presence of tertiary amine functions within the precursor structure thus accelerates the rate of hydrolysis by several orders of magnitude. Depending on the size of the precursors, different ratios for the number of tertiary amino functions ($n-2$) and the number of amide groups (number of alcohol-releasing groups, n) can be obtained, and for infinitely large structures this ratio approaches a value of 1. Plotting the half-life times of the first cyclisation step at equimolar end-group concentration against the ratio of the number of tertiary amino functions and the number of alcohol-releasing groups per molecule resulted in a roughly linear decrease of the half-life times for precursors **2b–11b** and **38b** with increasing ratio of the amine and amide functions (Figure 4). With the exception of mono(2-carbamoylbenzoate) **1b**, which seems to be a special case, an increasing amount of tertiary amino functions with respect to the number of alcohol-releasing groups in the molecule results in increasing rates of hydrolysis. The largest deviations from this roughly linear relationship were observed for the smaller structures, which are the most soluble precursors in the reaction mixture.

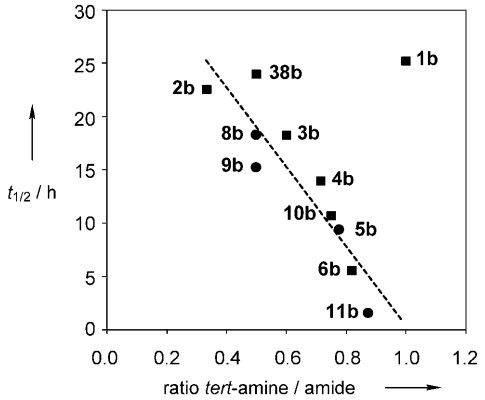


Figure 4. Relationship between the half-life times for the first cyclisation step and the ratio of the number of tertiary amino functions and the number of alcohol-releasing groups for dendrimers and stylomers at equimolar end-group concentration.

Influence of the precursor size: As, for practical applications, it is more interesting to compare samples releasing equivalent amounts of the active compound rather than equimolar precursor concentrations, we will now focus on the measurements carried out at equimolar end-group concentration and investigate structural features of the precursors in more detail.

To release the same amount of **12** from each sample, the precursor concentration in solution has to increase with a decreasing number of end groups as schematically shown in Figure 5 for the series of dendrimers **8b–11b** with two, four, eight and sixteen 2-carbamoylbenzoate units per molecule, respectively. The data in Tables 1 and 2 and in Figures 2 and 3 give the impression that the rates for the release of the tertiary alcohol **12** decrease with increasing size of the precursor. However, as the kinetic measurements described above follow the disappearance of the precursors and not the formation of alcohol **12**, this implies that the measured rate constants for the monocyclisation of a molecule with n alcohol-releasing units (end groups) should be n times higher than that of the reference compound with only one alcohol to be released ($n = 1$), if it is assumed that the alcohol release rates are independent of the precursor structure (Figure 5). To see whether the release rates depend on the size of the precursor, it is therefore convenient to plot the

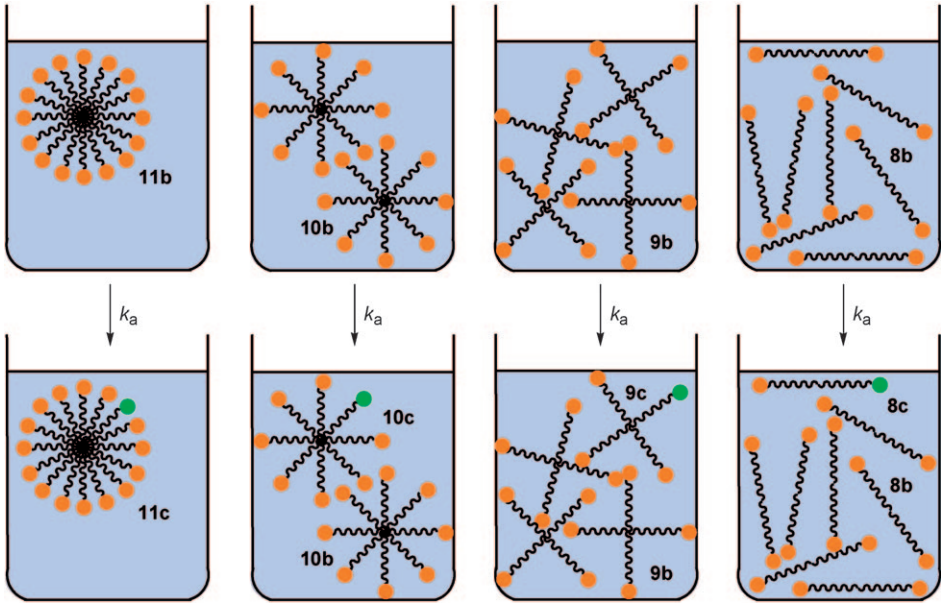


Figure 5. Schematic representation of the first cyclisation step of one 2-carbamoylbenzoate unit (orange→green) in dendrimers **8b–11b** at equimolar end-group concentration. As the disappearance of the precursors is monitored in the kinetic measurements and not the alcohol formation, the observed rate constants must be correlated with the total number of alcohol molecules to be released from each molecule.

rate constants or the corresponding half-life times against $1/n$. If there is no size dependence on the release rates, the rate constants measured for the cyclisation of the different precursors should be linearly related to each other.

Figure 6 shows the half-life times determined for the stepwise cyclisation of compounds **1b**–**11b** and **38b** (first cyclisation step; filled symbols) and of compounds **2c**–**11c** and **38c**

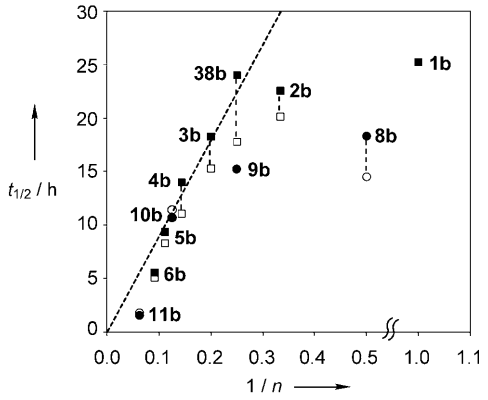


Figure 6. Half-life times measured for the cyclisation of **1b**–**11b** and **38b** (● and ■) and **2c**–**11c** and **38c** (○ and □) as a function of the inverse number of 2-carbamoylbenzoate units (in the starting molecule). For the compounds related by the dotted line the alcohol release is independent of the size of the precursor.

(second cyclisation step; empty symbols) as a function of the inverse of the number of 2-carbamoylbenzoate units at equimolar end-group concentrations. As no linear correlation between the half-life times of cyclisation and the inverse of the number of 2-carbamoylbenzoate groups was obtained, the alcohol release must depend on the size of the precursor. Nevertheless, a partial linear relationship can be obtained by correlating the data for the first step of cyclisation of the larger structures **3b**–**6b**, **10b** and **11b**. For these compounds, the alcohol release is almost independent of the precursor size. An independence of the release rates of the size of the precursor was also observed for the redox-triggered intramolecular cyclisation of quinone-terminated dendrimers of similar type.[12] The fact that the release rates of covalently attached biomolecules is independent of the size of the molecule is in line with the expected behaviour of polymers, in which (at a certain size) the individual monomers are all chemically equivalent. If this is the case, pentakis(2-carbamoylbenzoate) **3b** would, in our case, mark the borderline between monomeric and polymeric behaviour.

Our findings suggest that, in agreement with previous reports,[32,46] the nature of the local environment in close proximity to the release unit plays an important role for the release rate of hydrolytically cleavable substances. The polarity of the local environment, indirectly expressed by the solubility or dispersibility of the macromolecule in the reaction medium, and the presence of catalytic functionalities in close proximity to the reaction centre are more important than the topology of the macromolecule or polymer, especially for larger structures. The rates for the intramolecular cyclisation of 2-carbamoylbenzoates from increasingly larger structures seem to converge steadily towards typical macromolecular or polymeric properties, and the difference in shape between globular dendrimers and linear oligomers seems to be less important. Both the dendrimers and stylomers reported in this work are therefore expected to be reasonable model compounds for the investigation of polymer properties.

Conclusion

Neighbouring-group-assisted hydrolysis is an efficient tool to control the release of primary, secondary and even tertiary alcohols at neutral pH, and is therefore of particular interest for the delivery of bioactive compounds. To extrapolate the findings obtained for small precursor structures to polymeric systems, the influence of several structural parameters such as the topology or size of macromolecular conjugates on the release rates of a volatile tertiary alcohol were investigated by using the example of a series of 2-carbamoylbenzoate-modified linear stylomers and spherical dendrimers. In addition to the nature of the attacking nucleophile and the structure of the released alcohols as reported previously,[30] it was found that the rate of hydrolysis strongly depends on the presence of suitable catalysing groups and the solubility or dispersibility of the molecule in the reaction medium. The latter might be influenced by polarity changes, either as a consequence of the stepwise cyclisation or as a result of different degrees in protonation, as well as by the presence or absence of surfactants. In our systematic study we were able to now demonstrate that the total size or shape of the precursor structure has only a limited impact on covalent-bond cleavage reactions, as, for example, the neighbouring-group-assisted hydrolysis of 2-carbamoylbenzoates, and is therefore not a useful criterion to estimate the release properties of bioactive compounds from macromolecular conjugates.

We were also able to show that an understanding of the physico-chemical parameters determining the local environment of the release unit is the most important factor when aiming to transfer the characteristics of small molecules to larger structures such as oligomers and polymers. Due to the importance of bioconjugates in various life-science areas, we expect our findings to be of general interest for the development of future delivery technologies for the pharmaceutical, agrochemical or flavour and fragrance industry.

Experimental Section

General: Dendrimers **9b**–**11b** and **38b** were named according to the nomenclature proposed by Baker and Young.[47] Bis(1,1-dimethyl-2-phenylethyl) 2,2′-(6-methyl-1,11-dioxo-2,6,10-triazaundecane-1,11-diyl)dibenzoate (**8b**)[31] and (1,1-dimethyl-2-phenylethyl) hydrogen benzene-1,2-dicarboxylate (**39**)[30] were prepared as described previously.

Caution! Acrylonitrile is a toxic, highly volatile compound and should be handled with care and adequate personal protection.

General procedure for the synthesis of stylomers 3a–7a:[34] Under vigorous stirring, the multinitrile (**33**–**37**; prepared as described in the Supporting Information) was dissolved in ethanol (with ca. 5% of water) and, if necessary, heated to 50–60°C prior to the addition of sodium hydroxide. If no precipitation occurred while it was being cooled to room temperature, the mixture was placed in a stainless-steel autoclave, treated with Raney nickel (Actimet) and put under hydrogen pressure (50 bar). After stirring at room temperature for 1–4 d, the hydrogen was replaced with argon and the mixture was carefully filtered through a syringe filter (0.45 μm, for small quantities) or Celite (for larger quantities). The filtrate was diluted with water (5–10 mL) and concentrated (50°C, 15 mbar) to a small volume (5–10 mL). After several hours, a viscous oil spread out on top of the aqueous phase. The oil was removed by using a pipette and was extracted with CH_2Cl_2, dried (Na_2SO_4), filtered and concentrated. The residue was dried under high vacuum (0.2 mbar, 1–3 h) to give the target compound as a viscous oil. For additional details see the Supporting Information.

4,8,12-Tris(3-aminopropyl)-4,8,12-triaza-1,15-pentadecanediamine (3a):[34] Compound **3a** was prepared as described above with **33** (1.00 g, 2.5 mmol), ethanol (20 mL), sodium hydroxide (1.12 g, 28.0 mmol) and Raney nickel (2.00 g) to give a colourless viscous oil (0.35 g, 34%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=2.72$ (t, $J=6.9$ Hz, 10H), 2.49–2.36 (m, 18H), 1.63–1.51 (m, 14H), 1.32 ppm (s, 10H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta=52.30$ (t), 51.88 (t), 40.71 (t), 30.96 (t), 24.60 ppm (t); IR (neat): $\tilde{\nu}=3355$ (m), 3276 (m), 3183 (w), 2927 (s), 2855 (m), 2793 (s), 1598 (m), 1461 (m), 1365 (m), 1299 (m), 1257 (m), 1185 (m), 1128 (w), 1071 (m), 1013 (w), 884 (m), 816 (s), 749 cm^{-1} (w); MS (APCI): m/z (%): 419 (3), 418 (27), 417 (100) $[M+H]^+$, 284 (3), 132 (3); HRMS: m/z calcd for $C_{21}H_{53}N_8$ $[M+H]^+$: 417.4382; found: 417.4307.

4,8,12,16,20-Pentakis(3-aminopropyl)-4,8,12,16,20-pentaazatricosane-1,23-diamine (4a): Compound **4a** was prepared as described above with **34** (2.14 g, 3.47 mmol), ethanol (40 mL), sodium hydroxide (1.60 g, 40.00 mmol) and Raney nickel (4.00 g) to give a viscous yellow oil (1.77 g, 79%). ^{1}H NMR (400 MHz, D_2O/DCl): $\delta=2.61$ (t, $J=6.9$ Hz, 14H), 2.54–2.42 (m, 30H), 1.70–1.56 ppm (m, 22H); ^{13}C NMR (100.6 MHz, D_2O/DCl): $\delta=53.98$ (br t), 53.50 (br t), 41.87 (t), 31.21 (t), 31.14 (t), 24.64 (t), 24.58 ppm (t); IR (neat): $\tilde{\nu}=3357$ (w), 3282 (w), 3177 (w), 2933 (s), 2859 (m), 2797 (m), 1690 (m), 1595 (m), 1463 (m), 1370 (m), 1301 (m), 1249 (w), 1199 (m), 1169 (m), 1124 (s), 1074 (m), 892 (w), 822 (s), 799 (s), 748 (m), 718 cm^{-1} (m); MS (MM): m/z (%): 646 (38), 645 (100) $[M+H]^+$, 589 (12), 588 (36), 531 (15), 215 (11); HRMS: m/z calcd for $C_{33}H_{81}N_{12}$ $[M+H]^+$: 645.6690; found: 645.6704.

4,8,12,16,20,24,28-Heptakis(3-aminopropyl)-4,8,12,16,20,24,28-heptaazahentriacontane-1,31-diamine (5a): Compound **5a** was prepared as described above with **35** (1.0 g, 1.19 mmol), ethanol (45 mL), sodium hydroxide (2.80 g, 70.0 mmol) and Raney nickel (2.0 g) to give a white solid (0.93 g, 89%) containing small amounts of unknown impurities. ^{1}H NMR (400 MHz, D_2O): $\delta=2.72$ (t, $J=7.2$ Hz, 18H), 2.56–2.40 (m, 42H), 1.71–1.55 ppm (m, 30H); ^{13}C NMR (100.6 MHz, D_2O): $\delta=54.02$ (t), 54.00 (t), 53.49 (t), 53.43 (t), 41.85 (t), 31.09 (t), 31.01 (t), 24.65 (t), 24.57 ppm (t); IR (neat): $\tilde{\nu}=3350$ (w), 3276 (w), 2960 (m), 2929 (w), 2857 (w), 2796 (w), 2733 (w), 1583 (m), 1462 (m), 1414 (w), 1376 (w), 1300 (w), 1259 (s), 1082 (s), 1015 (s), 863 (m), 795 (s), 702 (w), 686 (w), 662 (w), 647 (w), 624 (w), 608 cm^{-1} (w); MS (MM): m/z (%): 875 (13), 874 (52), 873 (100) $[M+H]^+$, 816 (15); HRMS: m/z calcd for $C_{45}H_{109}N_{16}$ $[M+H]^+$: 873.8998; found: 873.8895.

4,8,12,16,20,24,28,32,36-Nonakis(3-aminopropyl)-4,8,12,16,20,24,28,32,36-nonaazanonatricontane-1,39-diamine (6a): Compound **6a** was prepared as described above with **36** (1.00 g, 0.95 mmol), ethanol (100 mL), sodium hydroxide (5.60 g, 140 mmol) and Raney nickel (1.00 g) to give a viscous yellow oil (1.02 g, 98%). ^{1}H NMR (400 MHz, D_2O/DCl): $\delta=3.47$–3.30 (m, 54H), 3.20–3.09 (m, 22H), 2.38–2.25 (m, 16H), 2.25–2.10 ppm (m, 22H); ^{13}C NMR (100.6 MHz, D_2O/DCl): $\delta=53.01$ (t), 39.51 (t), 39.44 (t), 24.71 (t), 24.63 (t), 22.10 (t), 22.01 ppm (t); IR (neat): $\tilde{\nu}=3326$ (s), 2949 (s), 2782 (s), 2644 (m), 2602 (m), 2537 (m), 2461 (s), 2192 (s), 2616 (s), 2138 (s), 1966 (w), 1671 (w), 1626 (m), 1597 (m), 1484 (s), 1470 (s), 1446 (s), 1409 (s), 1341 (s), 1297 (w), 1261 (w), 1248 (w), 1172 (s), 1140 (m), 1060 (s), 982 (w), 939 (m), 904 (w), 839 (w), 798 (w), 753 (s), 722 (w), 671 (w), 623 cm^{-1} (w); MS (MM): m/z (%): 1104 (15), 1103 (43), 1102 (69) $[M+H]^+$, 1045 (17), 559 (13), 557 (9), 552 (49), 551 (71), 523 (18), 368 (50), 280 (20), 276 (100), 262 (20), 221 (15); HRMS: m/z calcd for $C_{57}H_{137}N_{20}$ $[M+H]^+$: 1102.1306; found: 1102.1195.

4,8,12,16,20,24,28,32,36,40,44-Undecakis(3-aminopropyl)-4,8,12,16,20,24,28,32,36,40,44-undecaazaheptatetracontane-1,47-diamine (7a): Compound **7a** was prepared as described above with **37** (0.50 g, 0.39 mmol), ethanol (100 mL), sodium hydroxide (5.60 g, 140 mmol) and Raney nickel (1.00 g) to give a slightly yellow paste (1.02 g, quant). ^{1}H NMR (400 MHz, D_2O/DCl): $\delta=3.08$–2.99 (m, 26H), 2.85–2.53 (m, 66H), 1.99–1.84 (m, 26H), 1.84–1.67 ppm (m, 20H); ^{13}C NMR (100.6 MHz, D_2O/DCl): $\delta=53.81$ (t), 53.68 (t), 53.45 (t), 52.80 (t), 52.70 (t), 40.80 (t), 40.66 (t), 26.28 (t), 26.10 (t), 24.33 (t), 24.16 ppm (t); IR (neat): $\tilde{\nu}=3379$ (s, br), 2955 (s, br), 2754 (m), 2640 (s, br), 2054 (w), 1614 (m, br), 1468 (s), 1405 (w), 1395 (m), 1201 (w), 1174 (m), 1135 (w), 1061 (m), 998 (w), 950 (m), 835 (w), 797 (w), 755 (s), 720 (m), 672 cm^{-1} (m); HRMS: m/z calcd for $C_{69}H_{165}N_{24}$ $[M+H]^+$: 1330.3614; found: 1330.3417.

1,1-Dimethyl-2-phenylethyl 2-{[3-(dimethylamino)propylamino]carbonyl}benzoate (1b):[31] A solution of (1,1-dimethyl-2-phenylethyl) hydrogen benzene-1,2-dicarboxylate (**39**;[30] 0.50 g, 1.7 mmol) and triethylamine (0.34 g, 3.4 mmol) in CH_2Cl_2 (3 mL) was cooled to 0°C prior to the dropwise addition of ethyl chloroformate (0.20 g, 1.9 mmol) in CH_2Cl_2 (3 mL). The formation of the mixed anhydride was verified by using HPLC on a Macherey–Nagel Nucleosil 100-5 C18 column (250×4 mm i.d.), eluted at 1 mL min^{-1} with a gradient of water/acetonitrile (from 70:30 to 20:80, over 20 min) containing 0.1% of TFA. The reaction mixture was stirred at 0°C for 10 min and then left to warm up to room temperature before *N,N*-dimethylpropylenediamine (**1a**; 0.17 g, 1.7 mmol) in CH_2Cl_2 (2 mL) was added. The mixture was kept stirring for 30 min and was concentrated to give the crude compound (0.86 g). Column chromatography (RP-C4 (Vydac 214TP C4), water/acetonitrile 1:1, containing 0.1% of TFA) of 0.30 g gave, after drying under high vacuum, a colourless oil (0.14 g, 62%). ^{1}H NMR (360 MHz, $CDCl_3$): $\delta=7.73$ (d, $J=7.5$ Hz, 1H), 7.54–7.16 (m, 9H), 3.60–3.47 (m, 2H), 3.45–3.30 (m, 2H), 3.14 (s, 2H), 2.89 (s, 6H), 2.19–2.04 (m, 2H), 1.54 ppm (s, 6H); ^{13}C NMR (90.6 MHz, $CDCl_3$): $\delta=172.37$ (s), 165.79 (s), 136.81 (s), 136.73 (s), 132.00 (d), 130.61 (d), 130.49 (s), 130.25 (d), 130.05 (d), 128.13 (d), 127.67 (d), 126.74 (d), 84.06 (s), 55.56 (t), 46.65 (t), 43.20 (q), 36.41 (t), 25.90 (q), 24.87 ppm (t); IR (neat): $\tilde{\nu}=3283$ (w, br), 3062 (w), 3030 (w), 2978 (w), 2923 (w), 2850 (w), 2727 (w), 2527 (w), 1774 (m), 1708 (m), 1646 (m), 1597 (w), 1544 (m), 1456 (m), 1448 (m), 1388 (w), 1372 (w), 1300 (m), 1290 (m), 1196 (m), 1160 (m), 1137 (s), 1115 (m), 1085 (m), 1004 (w), 972 (w), 935 (w), 894 (w), 844 (w), 795 (m), 778 (m), 726 (w), 701 cm^{-1} (s); UV/Vis (water/acetonitrile 2:1): λ (ε) = 273 (550), 268 (sh) (540), 264 nm (sh) (560 L mol^{-1} cm^{-1}); MS (ESI): m/z (%): 384 (24), 383 (100) $[M+H]^+$, 252 (5), 251 (31), 206 (5); HRMS: m/z calcd for $C_{23}H_{31}N_2O_3$ $[M+H]^+$: 383.2327; found: 383.3298.

1,1-Dimethyl-2-phenylethyl 2-(fluorocarbonyl)benzoate (40):[41] A solution of **39** (11.00 g, 36.9 mmol) and pyridine (2.90 g, 36.9 mmol) in CH_2Cl_2 (80 mL) was cooled to −20°C before cyanuric fluoride (6.00 g, 44.3 mmol) in CH_2Cl_2 (20 mL) was added dropwise over 10 min. A precipitate formed. The reaction mixture was left stirring at −20°C for 30 min and for 2 h at room temperature, and was then filtered and rinsed with CH_2Cl_2 (30 mL). The filtrate was washed with water (100 mL) and the aqueous phase was extracted with CH_2Cl_2 (50 mL, 2×). The organic phases were dried (Na_2SO_4) and concentrated. Column chromatography (silica gel, heptane/diethyl ether 4:1) and drying (0.2 mbar, 30 min) yielded a slightly yellow oil (8.88 g, 80%). The anhydrous compound was found to be stable when stored at −20°C. ^{1}H NMR (360 MHz, $CDCl_3$): $\delta=7.80$–7.75 (m, 1H), 7.75–7.69 (m, 1H), 7.67–7.54 (m, 2H), 7.31–7.17 (m, 5H), 3.21 (s, 2H), 1.60 ppm (s, 6H); ^{13}C NMR (90.6 MHz, $CDCl_3$): $\delta=165.61$ (s), 157.60 (d, $J_{C,F}=349.3$ Hz; C-F), 136.85 (s), 134.56 (s), 133.10 (d), 131.09 (d), 130.62 (d), 130.07 (d), 129.39 (d), 128.06 (d), 126.61 (s), 125.88 (s), 85.31 (s), 46.38 (t), 25.62 ppm (q); IR (neat): $\tilde{\nu}=$ 3061 (w), 3028 (w), 2978 (w), 2928 (w), 1816 (s), 1712 (s), 1598 (m), 1578 (m), 1493 (m), 1468 (w), 1452 (m), 1385 (m), 1369 (m), 1289 (s), 1269 (s), 1215 (s), 1232 (s), 1177 (m), 1138 (m), 1108 (s), 1090 (s), 1043 (m), 1029 (w), 1005 (s), 914 (w), 890 (w), 863 (w), 845 (m), 826 (w), 777 (m), 759

(m), 772 (s), 699 (s), 673 cm^{-1} (m); MS (CI): *m/z* (%): 319 (13), 318 (68) $[M+NH_4]^+$, 185 (3), 184 (10), 183 (100), 169 (3), 168 (31), 167 (6), 166 (54), 93 (5).

General procedure for the synthesis of 2-carbamoylbenzoates 2b–6b, 9b–11b, 38b and 41b: A solution of **40** and triethylamine in CH_2Cl_2 was added dropwise to a cold solution (−78 or 0°C) of the multiamine (**2a**–**6a**, **9a**–**11a**, **38a** or propane-1,3-diamine) in CH_2Cl_2 while keeping the temperature below 5°C. The formation of the product can be monitored by using HPLC on a Macherey–Nagel Nucleosil 100-7 C2 column (250× 4 mm i.d.) eluted at 1 mL min^{-1} with a gradient of water/acetonitrile from 50:50 to 5:95, over 20 min (containing 0.1% of TFA). After stirring at room temperature for 1–3 h, the reaction mixture was treated with an aqueous solution of $KHSO_4$ (5%, 40–100 mL). The aqueous phase was extracted with CH_2Cl_2 (30–40 mL) and the organic phases were dried (Na_2SO_4) and filtered. After addition of some crystals of $KHSO_4$, the solvent was evaporated under reduced pressure and the product was dried under high vacuum (0.5 mbar). MPLC of the crude compound (RP-C4, water/acetonitrile 7:3, both containing 0.1% of TFA) and addition of some crystals of $KHSO_4$ to the product fraction, concentration and drying under high vacuum (0.2 mbar, 2 h) gave the target compound.

Tris(1,1-dimethyl-2-phenylethyl)-2,2′,2″-[nitrilotris(3,1-propanediyliminocarbonyl)]tribenzoate (2b): Compound **2b** was prepared as described above with **2a** (0.50 g, 2.66 mmol) in CH_2Cl_2 (10 mL) and **40** (2.88 g, 9.59 mmol) and triethylamine (1.94 g, 19.16 mmol) in CH_2Cl_2 (50 mL) at 0°C to give a white solid (2.29 g, 84%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63–7.58 (m, 3H), 7.38–7.29 (m, 9H), 7.27–7.12 (m, 15H), 3.49–3.32 (br m, 12H), 3.09 (s, 6H), 2.14–2.04 (br s, 6H), 1.48 ppm (s, 18H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 170.84 (s), 166.19 (s), 137.11 (s), 136.89 (s), 131.49 (d), 131.17 (s), 130.63 (d), 129.74 (d), 129.67 (d), 128.06 (d), 127.50 (d), 126.62 (d), 83.84 (s), 50.45 (t), 46.53 (t), 36.75 (t), 25.84 (q), 25.57 (q), 23.75 ppm (t); IR (neat): $\tilde{\nu}$ = 3299 (w, br), 3059 (w), 3027 (w), 2977 (w), 2939 (w), 2863 (w), 2650 (w), 2377 (w), 2366 (w), 2346 (w), 2277 (w), 2162 (w), 2051 (w), 1980 (w), 1708 (s), 1660 (m, br), 1527 (w), 1580 (w), 1535 (m, br), 1496 (w), 1480 (w), 1469 (w), 1454 (w), 1385 (w), 1369 (w), 1289 (s), 1258 (w), 1200 (m), 1175 (m), 1115 (s), 1085 (m), 1031 (w), 972 (w), 917 (w), 891 (w), 847 (m), 827 (w), 797 (w), 772 (w), 730 (s), 701 (s), 649 (w), 611 cm^{-1} (w); MS (ESI): *m/z* (%): 1054 (7), 1053 (26), 1052 (72), 1051 (100) $[M+Na]^+$, 1031 (8), 1030 (24), 1029 (33) $[M+H]^+$, 920 (5), 919 (9); HRMS: *m/z* calcd for $C_{63}H_{73}N_4O_9$ $[M+H]^+$: 1029.5359; found: 1029.5243.

1,1-Dimethyl-2-phenylethyl 2-{6,10,14-tris[3-({2-[(1,1-dimethyl-2-phenylethoxy)carbonyl]benzoyl}amino)propyl]-19-{2-[(1,1-dimethyl-2-phenylethoxy)carbonyl]phenyl}-19-oxo-2,6,10,14,18-pentaazanonadec-1-anoyl}benzoate (3b): Compound **3b** was prepared as described above with **40** (2.16 g, 7.2 mmol) and triethylamine (1.45 g, 14.4 mmol) in CH_2Cl_2 (10 mL) and **3a** (0.50 g, 1.20 mmol) in CH_2Cl_2 (40 mL) at room temperature to give a transparent paste (0.26 g, 12%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64–7.58 (m, 5H), 7.43–7.35 (m, 10H), 7.35–7.29 (m, 5H), 7.28–7.19 (m, 15H), 7.19–7.12 (m, 10H), 3.41–3.32 (m, 10H), 3.32–3.23 (m, 10H), 3.20–3.11 (m, 8H), 3.08 (s, 10H), 2.40–2.22 (m, 4H), 2.05–1.92 (m, 8H), 1.88–1.79 (m, 2H), 1.48 ppm (s, 30H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 171.25 (s), 166.33 (s), 136.86 (s), 136.84 (s), 131.61 (d), 131.10 (s), 130.63 (d), 129.85 (d), 129.74 (d), 128.08 (d), 127.53 (d), 126.66 (d), 83.13 (s), 50.85 (t), 49.45 (t), 49.24 (t), 46.54 (t), 36.66 (t), 25.77 (q), 23.71 (q), 23.49 (t), 18.50 ppm (t); IR (neat): $\tilde{\nu}$ = 3311 (w, br), 3063 (w), 3027 (w), 2983 (w), 2936 (w), 2863 (w), 2650 (w), 2345 (w), 2295 (w), 2254 (w), 2163 (w), 2050 (w), 1980 (w), 1778 (s), 1706 (m), 1647 (m, br), 1597 (w), 1580 (w), 1547 (m, br), 1496 (w), 1480 (w), 1469 (w), 1454 (w), 1442 (w), 1386 (w), 1371 (w), 1303 (m), 1288 (m), 1258 (w), 1201 (m), 1158 (s), 1141 (s), 1117 (s), 1086 (m), 1031 (w), 972 (w), 918 (w), 890 (w), 846 (m), 798 (w), 780 (w), 730 (m), 702 (s), 649 (w), 609 cm^{-1} (w); MS (ESI): *m/z* (%): 1818 (7) $[M+H]^+$, 1017 (3), 929 (4), 920 (9), 919 (85), 910 (38), 909 (100), 908 (21), 843 (7), 777 (9), 711 (5), 645 (8), 579 (6), 386 (19), 133 (6); HRMS: *m/z* calcd for $C_{111}H_{133}N_8O_{15}$ $[M+H]^+$: 1817.9857; found: 1817.9747.

1,1-Dimethyl-2-phenylethyl 2-{6,10,14,18,22-pentakis[3-({2-[(1,1-dimethyl-2-phenylethoxy)carbonyl]benzoyl}amino)propyl]-27-{2-[(1,1-dimethyl-2-phenylethoxy)carbonyl]phenyl}-27-oxo-2,6,10,14,18,22,26-heptaazaheptacos-1-anoyl}benzoate (4b): Compound **4b** was prepared as described above with **40** (3.10 g, 10.41 mmol) and triethylamine (2.10 g, 20.80 mmol) in CH_2Cl_2 (80 mL) and **4a** (0.80 g, 1.24 mmol) in CH_2Cl_2 (20 mL) at −78°C followed by MPLC of 1.00 g of the crude compound to give a translucent paste (0.51 g, 56%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67–7.59 (m, 7H), 7.44–7.33 (m, 14H), 7.33–7.27 (m, 7H), 7.27–7.19 (m, 21H), 7.18–7.13 (m, 14H), 3.46–3.26 (br m, 20H), 3.26–3.13 (br m, 18H), 3.13–3.04 (m, 20H), 2.39–2.21 (br m, 8H), 2.06–1.93 (m, 8H), 1.93–1.78 (m, 6H), 1.47 ppm (s, 42H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 170.67 (s), 171.50 (s), 166.24 (s), 166.17 (s), 136.83 (s), 136.68 (s), 131.67 (d), 130.99 (s), 130.62 (d), 129.93 (d), 129.84 (d), 128.09 (d), 127.56 (d), 126.69 (d), 84.16 (s), 50.92 (t), 49.55 (t), 46.60 (t), 36.63 (t), 25.78 (q), 23.85 (t), 18.42 (t), 18.26 ppm (t); IR (neat): $\tilde{\nu}$ = 3284 (w, br), 3064 (w), 3030 (w), 2983 (w), 2938 (w), 1775 (w), 1705 (s), 1663 (s), 1597 (w), 1579 (w), 1540 (m, br), 1491 (w), 1470 (w), 1454 (w), 1444 (w), 1385 (w), 1369 (w), 1290 (s), 1258 (w), 1197 (s), 1164 (s), 1134 (s), 1115 (s), 1085 (m), 1044 (w), 1031 (w), 974 (w), 917 (w), 891 (w), 846 (m), 832 (w), 797 (m), 777 (m), 730 (m), 719 (m), 701 (s), 649 (w), 611 cm^{-1} (w); MS (MM): *m/z* (%): 2630 (20), 2629 (24), 2610 (19), 2609 (43), 2608 (77), 2607 (86) $[M+H]^+$, 2606 (40), 1315 (18), 1305 (57), 1304 (100), 1303 (53), 870 (31), 869 (36), 826 (19), 825 (22); HRMS: *m/z* calcd for $C_{159}H_{193}N_{12}O_{21}$ $[M+H]^+$: 2606.4355; found: 2606.4499.

1,1-Dimethyl-2-phenylethyl 2-{6,10,14,18,22,26,30-heptakis[3-({2-[(1,1-dimethyl-2-phenylethoxy)carbonyl]benzoyl}amino)propyl]-35-{2-[(1,1-dimethyl-2-phenylethoxy)carbonyl]phenyl}-35-oxo-2,6,10,14,18,22,26,30,34-nonaazapentatriacont-1-anoyl}benzoate (5b): Compound **5b** was prepared as described above with **40** (1.86 g, 6.18 mmol) and triethylamine (1.25 g, 12.36 mmol) in CH_2Cl_2 (10 mL) and **5a** (0.50 g, 0.57 mmol) in CH_2Cl_2 (50 mL) at room temperature followed by MPLC of 1.00 g of the crude compound (water/acetonitrile 1:1, both containing 0.1% of TFA) to give a translucent paste (0.10 g, 11%) containing small amounts of impurities. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58–7.52 (m, 9H), 7.37–7.27 (m, 27H), 7.25–7.16 (m, 27H), 7.16–7.10 (m, 18H), 3.39–3.09 (m, 60H), 3.05 (s, 18H), 2.36–2.18 (br m, 12H), 2.02–1.80 (br m, 18H), 1.44 ppm (s, 54H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 170.71 (s), 170.67 (s), 170.65 (s), 166.65 (s), 166.62 (s), 166.52 (s), 136.98 (s), 136.93 (s), 136.90 (s), 131.43 (s), 131.37 (d), 131.34 (d), 130.64 (d), 129.70 (d), 129.52 (d), 128.05 (d), 128.02 (d), 127.55 (d), 126.61 (d), 84.61 (s), 84.09 (s), 84.04 (s), 84.00 (s), 51.27 (t), 50.93 (t), 50.77 (t), 49.67 (t), 49.41 (t), 46.57 (t), 46.52 (t), 36.64 (t), 25.72 (q), 25.70 (q), 25.68 (q), 25.61 (q), 23.63 (t), 18.60 (t), 18.48 ppm (t); IR (neat): $\tilde{\nu}$ = 3287 (w, br), 3063 (w), 3029 (w), 2982 (w), 2938 (w), 2624 (w), 1979 (w), 1773 (w), 1706 (s), 1663 (s), 1597 (w), 1579 (w), 1535 (m, br), 1470 (w), 1454 (w), 1444 (w), 1385 (w), 1369 (w), 1290 (s), 1258 (w), 1196 (s), 1175 (s), 1115 (s), 1085 (m), 1045 (w), 1031 (w), 974 (w), 915 (w), 891 (w), 846 (m), 830 (m), 797 (w), 773 (w), 731 (m), 719 (m), 701 (s), 648 (w), 612 cm^{-1} (w); MS (ESI): *m/z* (%): 1747 (15), 1698 (18) $[M+2H]^{2+}$, 1672 (3), 1670 (3), 1623 (3), 1198 (7), 1172 (3), 1165 (46), 1146 (5), 1140 (4), 1132 (48), 1121 (4), 1115 (8), 1113 (11), 1088 (6), 1082 (7), 1071 (4), 1039 (3), 874 (16), 849 (100), 841 (7), 835 (15), 816 (31), 812 (15), 808 (3), 804 (3), 802 (5), 783 (13), 779 (8), 774 (3), 750 (5), 746 (3), 321 (3), 282 (3), 155 (3), 133 (7); HRMS: *m/z* calcd for $C_{207}H_{254}N_{16}O_{27}$ $[M+2H]^{2+}$: 1697.9466; found: 1698.4383.

1,1-Dimethyl-2-phenylethyl 2-{6,10,14,18,22,26,30,34,38-nonakis[3-({2-[(1,1-dimethyl-2-phenylethoxy)carbonyl]benzoyl}amino)propyl]-43-{2-[(1,1-dimethyl-2-phenylethoxy)carbonyl]phenyl}-43-oxo-2,6,10,14,18,22,26,30,34,38,42-undecaazatriteracont-1-anoyl}benzoate (6b): Compound **6b** was prepared as described above with **40** (1.44 g, 4.79 mmol) and triethylamine (1.16 g, 11.5 mmol) in CH_2Cl_2 (10 mL) and **6a** (0.50 g, 0.57 mmol) in CH_2Cl_2 (50 mL) at −20°C followed by MPLC of 0.90 g of the crude product to give a translucent paste (0.35 g, 23%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62–7.52 (m, 11H), 7.41–7.28 (m, 33H), 7.25–7.18 (m, 33H), 7.18–7.11 (m, 22H), 3.42–2.98 (m, 76H), 3.08 (s, 22H), 2.36–2.18 (br m, 16H), 2.01–1.77 (br m, 22H), 1.51 (s, 4H), 1.47 ppm (s, 62H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 170.48 (s), 170.38 (s), 170.65 (s), 166.68 (s), 166.55 (s), 137.26 (s), 137.19 (s), 136.94 (s), 131.53 (s), 131.41 (d), 130.65 (d), 129.67 (d), 129.47 (d), 128.09 (d), 127.55 (d), 126.65 (d), 83.99 (s), 83.96 (s), 50.63 (t), 49.33 (t), 46.56 (t), 46.49 (t), 36.51 (t), 25.78 (q), 23.63 (t), 18.23 ppm (t); IR (neat): $\tilde{\nu}$ = 3288 (w, br), 3063 (w), 3030 (w), 2984 (w), 2938 (w), 2652 (w, br), 1980 (w), 1774 (w),

1704 (m), 1665 (s), 1598 (m), 1579 (w), 1535 (m, br), 1471 (m), 1454 (m), 1445 (w), 1385 (w), 1370 (w), 1291 (s), 1261 (w), 1196 (s), 1175 (s), 1115 (s), 1085 (s), 1047 (w), 1032 (w), 975 (w), 918 (w), 892 (w), 847 (m), 831 (m), 797 (m), 774 (w), 731 (m), 719 (m), 702 (s), 650 (w), 613 cm^{-1} (w); MS (ESI): *m/z* (%): 2104 (13), 2103 (10), 2093 (100) $[M+2H]^{2+}$, 2064 (19), 2027 (14), 2026 (14), 1615 (13), 1614 (10), 1571 (11), 1570 (10), 1395 (11), 1358 (12), 1352 (10), 1351 (39), 1350 (12), 1307 (67), 1292 (11), 1291 (10), 1288 (11), 1263 (62), 1244 (13), 1220 (31), 1219 (43), 1218 (20), 1200 (13), 1175 (25), 1144 (11), 1131 (25), 1125 (10), 1087 (37), 1081 (16), 1043 (44), 1038 (18), 1037 (18), 999 (35), 998 (22), 980 (12), 955 (28), 949 (22), 915 (12), 914 (14), 911 (21), 905 (24), 900 (12), 881 (23), 861 (25), 856 (12), 848 (20), 815 (14), 812 (23), 782 (13), 763 (14), 762 (14), 133 (35), 130 (10), 91 (33), 60 (39); HRMS: *m/z* calcd for $C_{255}H_{314}N_{20}O_{33}$ $[M+2H]^{2+}$: 2093.1793; found: 2093.1881.

4-Cascade:1,4-diaminobutane[4-*N*,*N*,*N*′,*N*′]:*N*-{2-[(1,1-dimethyl-2-phenylethoxy)carbonyl]benzoyl}propylamine (9b): Compound **9b** was prepared as described above with **9a** (0.44 g, 1.4 mmol) in CH_2Cl_2 (10 mL) and **40** (2.00 g, 6.7 mmol) and triethylamine (1.35 g, 13.3 mmol) in CH_2Cl_2 (40 mL) at room temperature followed by MPLC (water/acetonitrile 7:3 then 1:1, both containing 0.1% of TFA) to give a colourless oil (0.85 g, 43%). ^{1}H NMR (360 MHz, $CDCl_3$): δ = 7.70–7.62 (m, 4H), 7.47–7.33 (m, 8H), 7.33–7.08 (m, 28H), 3.52–3.20 (m, 16H), 3.19–2.98 (m, 4H), 3.08 (s, 8H), 2.08–1.89 (m, 8H), 1.89–1.70 (m, 4H), 1.47 ppm (s, 24H); ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 172.37 (s), 165.86 (s), 136.76 (s), 136.39 (s), 131.87 (d), 130.58 (d), 130.45 (s), 130.04 (2d), 128.10 (d), 127.55 (d), 126.70 (d), 84.17 (s), 51.38 (t), 50.66 (t), 46.46 (t), 36.73 (t), 25.72 (q), 23.80 (t), 20.46 ppm (t); IR (neat): $\tilde{\nu}$ = 3306 (w, br), 3061 (w), 3027 (w), 2979 (w), 2936 (w), 2872 (w), 2693 (w, br), 2533 (w, br), 1772 (m), 1706 (s), 1658 (m), 1596 (m), 1579 (w), 1542 (m), 1468 (w), 1452 (m), 1440 (m), 1397 (w), 1385 (m), 1368 (m), 1301 (m), 1288 (m), 1257 (w), 1201 (s), 1140 (s), 1116 (s), 1085 (s), 1042 (w), 1030 (w), 972 (w), 907 (s), 845 (m), 797 (m), 776 (m), 721 (s), 700 cm^{-1} (s); MS (ESI): *m/z* (%): 1459 (16), 1440 (4), 1439 (60), 1438 (100), 1437 (44) $[M+H]^+$, 654 (4), 588 (3), 456 (4), 455 (8); HRMS: *m/z* calcd for $C_{88}H_{105}N_6O_{12}$ $[M+H]^+$: 1437.7764; found: 1437.7820.

8-Cascade:1,4-diaminobutane[4-*N*,*N*,*N*′,*N*′]:1-azobutylidene:*N*-{2-[(1,1-dimethyl-2-phenylethoxy)carbonyl]benzoyl}propylamine (10b): Compound **10b** was prepared as described above with **10a** (0.53 g, 0.7 mmol) in CH_2Cl_2 (10 mL) and **40** (2.00 g, 6.7 mmol) and triethylamine (1.35 g, 13.3 mmol) in CH_2Cl_2 (40 mL) at 0°C followed by MPLC of 1.50 g of the crude compound (water/acetonitrile 7:3 then 1:1, both containing 0.1% of TFA) to give a white solid (0.78 g, 65%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62–7.54 (m, 8H), 7.47–7.08 (m, 72H), 3.52–3.23 (m, 32H), 3.23–2.93 (m, 20H), 3.06 (s, 16H), 2.42–2.15 (m, 8H), 2.11–1.91 (m, 16H), 1.77–1.57 (m, 4H), 1.45 ppm (s, 48H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 171.48 (s), 166.16 (s), 136.83 (s), 136.57 (s), 131.58 (d), 131.08 (s), 130.61 (d), 129.88 (d), 129.72 (d), 128.06 (d), 127.54 (d), 126.64 (d), 84.08 (s), 52.06 (t), 50.86 (t), 49.73 (t), 49.09 (t), 46.50 (t), 36.70 (t), 25.68 (q), 23.62 (t), 20.33 (t), 18.43 ppm (t); IR (neat): $\tilde{\nu}$ = 3274 (w, br), 3062 (w), 3026 (w), 2977 (w), 2932 (w), 2871 (w), 2648 (w, br), 2518 (w, br), 1775 (m), 1706 (m), 1649 (m), 1596 (m), 1578 (w), 1536 (m), 1470 (w), 1453 (m), 1443 (m), 1384 (m), 1369 (m), 1300 (m), 1289 (m), 1258 (w), 1198 (s), 1161 (s), 1136 (s), 1114 (s), 1085 (s), 1044 (m), 1030 (w), 974 (w), 890 (w), 845 (m), 796 (m), 779 (w), 773 (w), 730 (m), 720 (m), 701 (s), 663 cm^{-1} (w); MS (ESI): *m/z* (%): 3056 (4), 3055 (7), 3054 (3), 3017 (4), 3016 (9), 3014 (4) $[M+H]^+$, 2771 (3), 2769 (3), 2204 (3), 2141 (3), 1562 (3), 1561 (3), 1560 (7), 1559 (10), 1558 (6), 1509 (12), 1508 (3) $[M+2H]^{2+}$, 1494 (3), 1072 (6), 1040 (5), 1039 (13), 1038 (100), 1007 (3), 1006 (7), 994 (5), 962 (3); HRMS: *m/z* calcd for $C_{184}H_{227}N_{14}O_{24}$ $[M+3H]^+$: 3016.6916; found: 3016.6869.

16-Cascade:1,4-diaminobutane[4-*N*,*N*,*N*′,*N*′]:(1-azobutylidene)^2:*N*-{2-[(1,1-dimethyl-2-phenylethoxy)carbonyl]benzoyl}propylamine (11b):[18] Compound **11b** was prepared as described above with **11a** (0.59 g, 0.35 mmol) in CH_2Cl_2 (10 mL) and **40** (2.00 g, 6.66 mmol) and triethylamine (1.35 g, 13.32 mmol) in CH_2Cl_2 (20 mL) at room temperature followed by MPLC of 1.5 g of the crude compound (water/acetonitrile 1:1, both containing 0.1% of TFA) to give a white solid (0.79 g, ≈76%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.60–7.51 (m, 16H), 7.46–7.34 (m, 16H), 7.36–7.26 (m, 48H), 7.25–7.08 (m, 80H), 3.45–3.31 (m, 32H), 3.31–3.18 (m, 32H), 3.16–2.88 (m, 52H), 3.06 (s, 32H), 2.36–2.14 (m, 24H), 2.06–1.88 (m, 32H), 1.75–1.63 (m, 4H), 1.45 ppm (s, 96H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 170.70 (s), 166.46 (s), 137.02 (s), 136.89 (s), 131.41 (d), 130.63 (d, s), 129.72 (d), 129.53 (d), 128.05 (d), 127.52 (d), 126.62 (d), 83.99 (s), 52.14 (brt), 50.65 (t), 49.23 (brt), 48.62 (brt), 46.50 (t), 36.50 (t), 25.71 (q), 23.63 (t), 20.32 (brt), 18.04 ppm (brt); IR (neat): $\tilde{\nu}$ = 3294 (m, br), 3061 (w), 2952 (m, br), 2869 (w), 2647 (w, br), 1777 (m), 1707 (s), 1665 (s), 1649 (s), 1596 (m), 1578 (m), 1540 (m), 1469 (m), 1453 (m), 1384 (m), 1369 (m), 1292 (s), 1259 (w), 1199 (s), 1173 (s), 1139 (s), 1118 (s), 1086 (s), 1044 (m), 980 (m), 920 (w), 889 (w), 847 (m), 817 (w), 798 (m), 778 (w), 772 (w), 761 (w), 730 (m), 720 (m), 702 (s), 676 cm^{-1} (w); MS (ESI): *m/z* (%): strong fragmentation with dominant peaks at 2058 $[M+3H]^{3+}$, 1543 $[M+4H]^{4+}$, and 1235 $[M+5H]^{5+}$.

4-Cascade:1,3-diaminopropane[4-*N*,*N*,*N*′,*N*′]:*N*-{2-[(1,1-dimethyl-2-phenylethoxy)carbonyl]benzoyl}propylamine (38b): Compound **38b** was prepared as described above with **40** (0.953 g, 3.17 mmol) and triethylamine (0.64 g, 6.34 mmol) in CH_2Cl_2 (50 mL) and **38a** (0.20 g, 0.66 mmol) in CH_2Cl_2 (10 mL) at −78°C followed by MPLC (water/acetonitrile 1:1, both containing 0.1% TFA) to give a translucent paste (0.55 g, 58%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65–7.59 (m, 4H), 7.44–7.27 (m, 12H), 7.27–7.11 (m, 20H), 3.40–3.14 (brm, 20H), 3.08 (s, 8H), 2.42–2.27 (brm, 2H), 2.04–1.89 (m, 8H), 1.47 ppm (s, 24H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 171.55 (s), 166.23 (s), 136.81 (s), 136.73 (s), 131.67 (d), 130.95 (s), 130.62 (d), 129.90 (d), 129.79 (d), 128.09 (d), 126.68 (d), 84.13 (s), 50.71 (t), 49.11 (t), 46.56 (t), 36.62 (t), 25.75 (q), 23.69 (t), 18.39 ppm (t); IR (neat): $\tilde{\nu}$ = 3275 (w, br), 3063 (w), 3027 (w), 2980 (w), 2931 (w), 1775 (w), 1706 (s), 1661 (s), 1597 (w), 1578 (w), 1534 (m), 1480 (w), 1471 (w), 1453 (w), 1444 (w), 1385 (w), 1369 (w), 1290 (s), 1258 (w), 1198 (s), 1175 (s), 1114 (s), 1084 (m), 1047 (w), 1031 (w), 974 (w), 917 (w), 890 (w), 846 (w), 829 (w), 798 (m), 772 (w), 730 (m), 719 (m), 701 (s), 648 (w), 611 cm^{-1} (w); HRMS: *m/z* calcd for $C_{87}H_{103}N_6O_{12}$ $[M+H]^+$: 1423.7608; found: 1423.7603.

Bis(1,1-dimethyl-2-phenylethyl) 2,2′-[1,3-propanediylbis(iminocarbonyl)]-dibenzoate (41b): Compound **41b** was prepared as described above with **40** (0.70 g, 2.33 mmol) and triethylamine (0.47 g, 4.66 mmol) in CH_2Cl_2 (20 mL) and propane-1,3-diamine (0.072 g, 0.97 mmol) in CH_2Cl_2 (10 mL) at −75°C to give a translucent paste (0.31 g, 50%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48–7.44 (m, 2H), 7.34–7.11 (m, 16H), 7.10 (t, *J* = 5.6 Hz, 2H), 3.60 (q, *J* = 5.8 Hz, 4H), 3.12 (s, 4H), 1.96–1.89 (brm, 2H), 1.50 ppm (s, 12H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 169.74 (s), 166.54 (s), 138.23 (s), 137.08 (s), 131.14 (d, s), 130.72 (d), 129.51 (d), 129.06 (d), 128.00 (d), 127.31 (d), 126.53 (d), 84.96 (s), 46.52 (t), 37.73 (t), 28.25 (t), 25.88 ppm (q); IR (neat): $\tilde{\nu}$ = 3300 (w, br), 3063 (w), 3028 (w), 2978 (w), 2935 (w), 2872 (w), 2299 (w), 1711 (s), 1645 (s), 1597 (w), 1578 (w), 1528 (m), 1494 (w), 1481 (w), 1469 (w), 1453 (m), 1443 (m), 1384 (w), 1368 (w), 1288 (s), 1257 (m), 1215 (m), 1177 (w), 1162 (w), 1114 (s), 1086 (m), 1040 (w), 984 (w), 956 (w), 916 (w), 890 (w), 867 (w), 846 (m), 826 (w), 772 (m), 730 (s), 701 (s), 661 (w), 648 (w), 611 cm^{-1} (w); HRMS: *m/z* calcd for $C_{39}H_{43}N_2O_6$ $[M+H]^+$: 635.3110; found: 635.3196.

Bis(1,1-dimethyl-2-phenylethyl) 2,2′-(1,11-dioxo-2,10-diazaundecane-1,11-diyl)dibenzoate (42b): A solution of **39** (2.00 g, 6.7 mmol) and triethylamine (1.35 g, 13.4 mmol) in CH_2Cl_2 (20 mL) was cooled to 0°C prior to the dropwise addition of ethyl chloroformate (0.73 g, 6.7 mmol) in CH_2Cl_2 (10 mL). The formation of the mixed anhydride was verified by HPLC on a Macherey–Nagel Nucleosil 100-5 C18 column (250×4 mm i.d.), eluted at 1 mL min^{-1} with a gradient of water/acetonitrile (from 70:30 to 20:80, over 20 min) containing 0.1% of TFA. The reaction mixture was stirred at 0°C for 10 min and then left to warm up to room temperature before 1,7-diaminoheptane (0.39 g, 3.0 mmol) in CH_2Cl_2 (10 mL) was added. To quench the remaining **39** more ethyl chloroformate (0.11 g, 1.0 mmol) in CH_2Cl_2 (5 mL) was added after 10 min followed by *N*,*N*-dimethylethylenediamine (0.11 g, 1.2 mmol) in CH_2Cl_2 (5 mL) 30 min later. The mixture was kept stirring for 15 min, then poured into an aqueous solution of $KHSO_4$ (5%, 50 mL), stirred for 1 h and extracted with CH_2Cl_2 (30 mL). The organic phase was washed with $KHSO_4$ (5%, 20 mL, 6×), dried (Na_2SO_4), filtered, concentrated and dried under high vacuum. Plug filtration of the crude reaction product

(RP C4 (Vydac), 50 g, water/acetonitrile 1:1 then pure acetonitrile, containing 0.1% of TFA) gave, after drying under vacuum, a highly viscous yellow oil (1.36 g, 29%). ^{1}H NMR (360 MHz, $CDCl_3$): δ = 7.77–7.71 (m, 2H), 7.52–7.35 (m, 6H), 7.30–7.15 (m, 10H), 6.06 (t, J = 5.7 Hz, 2H), 3.34 (q, J = 6.6 Hz, 4H), 3.19 (s, 4H), 1.97 (s, 4H), 1.54 (s, 12H), 1.36 ppm (s, 6H); ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 170.07 (s), 166.00 (s), 137.53 (s), 137.14 (s), 131.51 (d), 130.79 (s), 130.65 (d), 129.96 (d), 129.59 (d), 128.02 (d), 127.77 (d), 126.55 (d), 84.14 (s), 46.15 (t), 40.13 (t), 29.19 (t), 28.79 (t), 26.74 (t), 25.88 ppm (q); IR (neat): $\tilde{\nu}$ = 3281 (m, br), 3063 (w), 3027 (w), 2930 (m), 2854 (w), 2251 (w), 1777 (w), 1711 (s), 1640 (s), 1596 (w), 1576 (w), 1537 (s), 1493 (w), 1482 (w), 1467 (w), 1452 (m), 1443 (m), 1383 (m), 1368 (m), 1289 (s), 1256 (m), 1208 (s), 1158 (s), 1113 (s), 1081 (m), 1039 (w), 1030 (w), 974 (w), 917 (w), 890 (w), 846 (m), 801 (w), 772 (m), 729 (s), 701 cm^{-1} (s); UV/Vis (water/acetonitrile 2:1): λ (ε) = 273 (6800), 264 (sh) (7300), 258 nm (sh) (9000 L mol^{-1} cm^{-1}); MS (ESI): m/z (%): 791 (5), 719 (5), 718 (8), 713 (6), 693 (11), 692 (41), 691 (100) $[M+H]^+$, 560 (6), 559 (16), 428 (5), 427 (18).

Preparation of the buffer solution: A phosphate buffer stock solution containing 1 wt% of a non-ionic surfactant was prepared by dissolving (upon sonication) two buffer tablets pH 7.0 (phosphate, Fluka) and Triton X100 (2.24 g) in a mixture of water (160 mL) and acetonitrile (31.3 g, 40 mL). To determine the exact pH value of the final reaction solutions, the buffer (10 mL) was diluted with acetonitrile (2 mL) to give the final mixture of water/acetonitrile 2:1, which was used for the kinetic measurements. The pH value of the final phosphate buffer solution was measured on a Mettler Toledo MP220 apparatus with an InLab 410 Ag/AgCl glass electrode to be 7.62 ± 0.02 at (19.9 ± 0.21) °C.

Measurement of the kinetic rate constants:[30,42] Solutions (maintained at 20 °C by using a thermostat) of compounds **1b**–**11b** and **38b** with given concentration in acetonitrile (0.2 mL) were added to the above-described phosphate buffer stock solution (1.0 mL, water/acetonitrile 4:1; maintained at 20 °C by using a thermostat). The mixture (20 μL) was immediately injected into a HPLC apparatus (t = 0), eluted at 1 mL min^{-1} on a Macherey–Nagel, Nucleosil 100–7 C2 column (250 × 4 mm i.d.) using a water/acetonitrile gradient (from 50:50 to 5:95, over 20 min) containing 0.1% of TFA and re-injected every 53 min (12–25 times). All chromatograms were recorded at λ = 254 and 280 nm and all experiments were carried out at least twice.

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