Dendritic Biomimicry: Microenvironmental Hydrogen-Bonding Effects on Tryptophan Fluorescence

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Abstract: Two series of dendritically modified tryptophan derivatives have been synthesised and their emission spectra measured in a range of different solvents. This paper presents the syntheses of these novel dendritic structures and discusses their emission spectra in terms of both solvent and dendritic effects. In the first series of dendrimers, the NH group of the indole ring is available for hydrogen bonding, whilst in the second series, the indole NH group has been converted to NMe. Direct comparison of the emission wavelengths of analogous NH and NMe derivatives indicates the importance of the Kamlet–Taft solvent β parameter, which reflects the ability of the solvent to accept a hydrogen bond from the NH group, an effect not possible for the NMe series of dendrimers. For the NH dendrimers, the attachment of a dendritic shell to the tryptophan subunit leads to a red shift in emission wavelength. This dendritic effect only operates in non-hydrogen-bonding solvents. For the NMe dendrimers, however, the attachment of a dendritic shell has no effect on the emission spectra of the indole ring. This proves the importance of hydrogen bonding between the branched shell and the indole NH group in causing the dendritic effect. This is the first time a dendritic effect has been unambiguously assigned to individual hydrogen-bonding interactions and indicates that such intramolecular interactions are important in dendrimers, just as they are in proteins. Furthermore, this paper sheds light on the use of tryptophan residues as a probe of the microenvironment within proteins—in particular, it stresses the importance of hydrogen bonds formed by the indole NH group.

Keywords: dendrimers · fluorescence spectroscopy · hydrogen bonds · solvent effects · tryptophan

Introduction

Tryptophan is undoubtedly the most important source of emission in proteins and, as such, it is commonly used by biological chemists because it offers an intrinsic fluorescent probe of protein conformation and dynamics. Indeed, the wavelength of tryptophan emission is highly sensitive to microenvironmental conditions, and has consequently been extensively used as a probe of the local environment within a protein.[1] It is most commonly recognised that the polarity of this local environment plays the major role in governing the tryptophan emission wavelength.[2] Given the extensive biological interest in the optical properties of tryptophan, and the degree of debate surrounding its emission behaviour,[3] it was of great interest to us to create a new synthetic environment for tryptophan and investigate these microenvironmental effects on its optical properties.

It has recently been proposed that branched macromolecules (dendrimers)[4] possess a unique microenvironment within their structures which can mimic some aspects of the active site of enzymes.[5] For example, in 1993, Fréchet and co-workers published a key paper in which they illustrated that the polarity of aromatic-ether dendritic branching could modulate the absorption wavelength of a covalently attached solvatochromic probe (a *p*-nitroaniline derivative) through the generation of a dendritic microenvironment.[6] In particular, they demonstrated the dependence of this dendritic effect on the Kamlet–Taft solvent polarity parameter, π^*, which can be used to correlate the behaviour of *p*-nitroaniline derivatives in different solvents. Biologically important fragments have also been encapsulated within dendritic shells. For example, Diederich and co-workers reported that the redox potentials of zinc(II) or iron(III) porphyrins were modified by the presence of amide-ether dendritic branching,[7] whilst interestingly, Fréchet and co-workers reported that aromatic-ether branches had no dendritic effect on potential.[8] It therefore seems clear that the precise nature of the dendritic branching plays an important role in property modification—an observation which has been further verified by the dendritic encapsulation of ferrocene.[9] There have been a considerable number of other investigations of "dendritic effects" in which a functional core is encapsulated within the branching.[10–13] In such studies, it is of key importance to unambiguously prove the mechanism through which the

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dendritic effect operates—a goal which cannot always be achieved.

We therefore initiated a research program targeting the dendritic encapsulation of tryptophan. In this way we could shed new light both on the use of tryptophan as a probe of biological microenvironments and on the ability of a dendritic shell to generate a unique microenvironment within its superstructure. We recently communicated the effect of dendritic encapsulation on tryptophan.[14] It was observed that only in non-hydrogen-bonding solvents did the amide-ether dendritic shell alter the emission wavelength of the indole ring. It was proposed that a hydrogen bonding interaction between the dendritic branch and the indole NH group was responsible for this dendritic effect. Such hydrogen bonds to indoles have been previously reported to modulate emission spectra.[15]

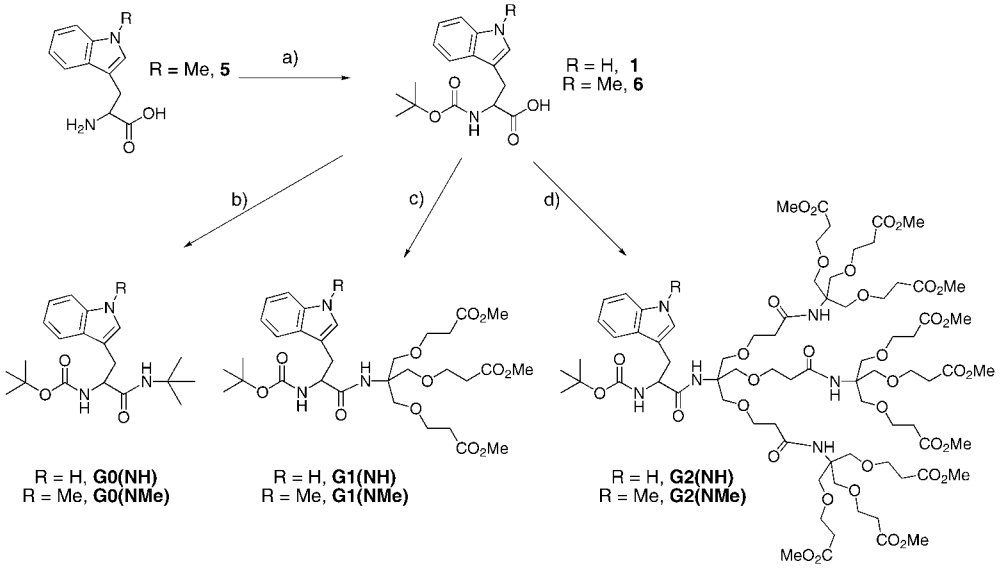
In this full paper we significantly expand the scope of these dendritic biological model systems through an investigation of encapsulated tryptophan derivatives in which the indole NH group has been converted to NMe. This new set of results has allowed us to unambiguously determine the role of hydrogen bonding in the dendritic effect and sheds additional light on the importance of hydrogen bonds in tuning tryptophan emission in the biological environment.

Results and Discussion

Synthesis and characterisation: Target molecules **G0(NH)**, **G1(NH)** and **G2(NH)** were synthesised by a convergent coupling strategy as shown in Scheme 1, in which commercially available *N-tert*-butoxycarbonyl-protected L-tryptophan (**1**) was coupled with *t*BuNH$_2$ (**2**) or preformed dendritic branches of first (**3**) or second (**4**) generation respectively. The dendritic branches were synthesised according to the methodology previously reported by Newkome and co-workers and subsequently modified by Diederich et al.[16] Coupling of the branching to the tryptophan subunit was achieved by using 1,3-dicyclohexylcarbodiimide/1-hydroxybenzotriazole (DCC/HOBt) in CH_2Cl_2 with Et_3N as base. For the synthesis, an excess of Boc-protected tryptophan was employed in order to ensure complete reaction of the dendritic branches, enabling easy purification of the desired products by gel permeation chromatography (GPC) (Biobeads SX-1, CH_2Cl_2).

For the synthesis of **G0(NMe)**, **G1(NMe)** and **G2(NMe)** it was first necessary to protect commercially available 1-methyl-L-tryptophan (**5**) with Boc. This was achieved by using a modification of the published methodology of Levy et al.: by protecting with Boc_2O in DMF and purifying the product (**6**) by precipitation from EtOAc/hexane (58% yield) (Scheme 1).[17] As before, the coupling of compound **6** with dendritic branches was achieved by using DCC/HOBt with Et_3N as base, although with dry THF as solvent (Scheme 1). These reactions provided products in moderate yield (30–50%) after purification by SiO_2 column chromatography (**G0(NMe)**, **G1(NMe)**) or GPC (**G2(NMe)**). It was necessary to add several portions of the coupling reagents during the reaction in order to maximise the yield.

All products were fully characterised by ^{1}H and ^{13}C NMR, IR and mass spectrometry (electrospray, high resolution FAB/CI), TLC and/or analytical GPC. Interestingly, compound **6** exhibited broadened splitting in the NMR spectrum at ambient temperature. It is well known that Boc carbamates can exist in two different conformations—*syn* and *anti*, with the *anti* conformer being more stable by about 1 kcal mol^{-1}.[18] It has, however, been reported that the presence of carboxylic acid groups (as in compound **6**) can favour the normally unobserved *syn* conformer as a consequence of hydrogen bond interactions with the C=O and NH groups of the



Scheme 1. Synthesis of two series of dendritically modified tryptophan derivatives: **G*n*(NH)** and **G*n*(NMe)**. a) Boc_2O, Et_3N, DMF, 58%; b) (R = H) *t*BuNH$_2$, DCC, HOBt, Et_3N, CH_2Cl_2, 80%; (R = Me) *t*BuNH$_2$, DCC, HOBt, Et_3N, THF, 33%; c) (R = H) First generation dendritic branch **3**, DCC, HOBt, Et_3N, CH_2Cl_2, 54%; (R = Me) First generation dendritic branch **3**, DCC, HOBt, Et_3N, THF, 46%; d) (R = H) Second generation dendritic branch **4**, DCC, HOBt, Et_3N, CH_2Cl_2, 53%; (R = Me) Second generation dendritic branch **4**, DCC, HOBt, Et_3N, THF, 32%.

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carbamate.[19] This stabilisation of the *syn* conformer and conformational freezing was shown to be operating for compound **6** through temperature dependent ^{1}H NMR spectrometry in $CDCl_3$. At 253 K, sharp split peaks were observed: for example two CH_3 peaks at $\delta = 1.09$ and 1.57 (respective relative intensities 40:60 *syn*/*anti*). At 300 K these peaks were broadened and shifted towards one another, whilst at 323 K, a single time-averaged peak at $\delta = 1.40$ was observed.

The NMR spectra of **G2(NH)** and **G2(NMe**) were also unclear in $CDCl_3$ solution, possibly as a consequence of conformational effects due to the steric hindrance provided by the branching, or extensive hydrogen bonding. **G2(NH)** gave a sharp spectrum in deuterated acetone, while the spectrum of **G2(NMe)** was improved in deuterated methanol (although still showed some broadening).

Emission Spectroscopy

General introduction: The emission of the novel dendritic tryptophan derivatives was measured after excitation at 290 nm, in a range of different solvents (Tables 1 and 2).

Table 1. Emissive wavelengths for **G0(NH)**, **G1(NH)** and **G2(NH)** measured in a range of solvents. All wavelengths are ± 0.5 nm. [Tryptophan derivative] $= 1 \times 10^{-4}$ M unless stated otherwise.

Solvents	**G0(NH)** λ_{max} [nm]	**G1(NH)** λ_{max} [nm]	**G2(NH)** λ_{max} [nm]	Dendritic effect [nm][a]
non-hydrogen bonding				
cyclohexane	321.5	326.5[b]	332[c]	10.5
benzene	330	331	333.5	3.5
dichloromethane	332.5	333.5	335.5	3.0
hydrogen-bond acceptors				
ethyl acetate	332	332.5	333.5	1.5
tetrahydrofuran	332.5	333	333	0.5
acetonitrile	337.5	337	338	0.5
hydrogen-bond donors and acceptors				
iso-propanol	340.5	340	339	−1.5
methanol	343.5	343	342.25	−1.25

[a] λ_{max}(**G2(NH)**) − λ_{max}(**G0(NH)**). [b] [Tryptophan derivative] $= 5 \times 10^{-5}$ M. [c] [Tryptophan derivative] $= 2 \times 10^{-5}$ M

Table 2. Emissive wavelengths for **G0(NMe)**, **G1(NMe)** and **G2(NMe)** measured in a range of solvents. All wavelengths are ± 0.5 nm. [Tryptophan derivative] $= 5 \times 10^{-6}$ M unless stated otherwise.

Solvents	**G0(NMe)** λ_{max} [nm]	**G1(NMe)** λ_{max} [nm]	**G2(NMe)** λ_{max} [nm]	Dendritic effect [nm][a]
non-hydrogen bonding				
cyclohexane	326	327	324[b]	−2.0
benzene	336.5	335	335.5	−1.0
dichloromethane	339	339	338	−1.0
dichloromethane[c]	340	340	339	−1.0
hydrogen-bond acceptors				
ethyl acetate	336.5	335.75	337.5	1.0
tetrahydrofuran	335.25	335	336	0.75
acetonitrile	343.25	342.5	343	−0.25
hydrogen-bond donors and acceptors				
iso-propanol	340.75	340	339.25	−1.5
methanol	344.5	343.75	343.5	−1.0

[a] λ_{max}(**G2(NMe)**) − λ_{max}(**G0(NMe)**). [b] [Tryptophan derivative] $= 2 \times 10^{-6}$ M. [c] [Tryptophan derivative] $= 1 \times 10^{-4}$ M.

The emission spectra of the **G*n*(NH)** series of dendrimers were measured at a concentration of 1×10^{-4} M, while those of the **G*n*(NMe)** series of dendrimers had to be measured at a lower concentration (5×10^{-6} M) as a consequence of their generally higher emission intensities (see comment about quenching below). Control experiments were performed to ensure that changing the concentration in this way between the two series did not significantly alter the fluorescence data (see below).

Comparison of G0(NH) and G0(NMe): Before considering the dendritic tryptophan derivatives, the data for **G0(NH)** and **G0(NMe)** was fully analysed in order to obtain as much information as possible about the emission of simple non-dendritic tryptophan in a variety of solvent environments. Whereas Fréchet and co-workers correlated the emission of their solvatochromic probe with π^*,[6] we found no simple relationship between λ_{max} and π^* alone, neither for **G0(NH)** nor **G0(NMe)**. Indeed, for **G0(NH)**, instead of a straight line correlation (Figure 1), three groups of points were clearly

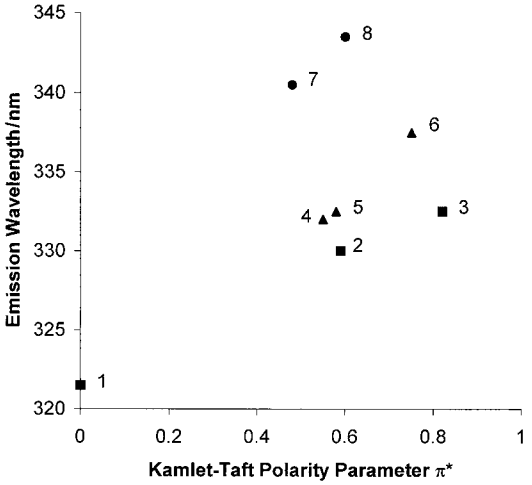

Figure 1. Attempted correlation of the emission wavelengths of **G0(NH)** with the Kamlet–Taft polarity parameter, π^*. Points: 1: cyclohexane, 2: benzene, 3: CH_2Cl_2, 4: EtOAc, 5: THF, 6: CH_3CN, 7: *i*PrOH, 8: MeOH.

visible: the one corresponding to primarily non-hydrogen bonding solvents (cyclohexane, benzene, CH_2Cl_2: points 1, 2 and 3) is the least red shifted, that corresponding to hydrogen bond acceptors (EtOAc, THF, MeCN: points 4, 5 and 6) is more red shifted and finally, that corresponding to hydrogen bond donor and acceptor solvents (*i*PrOH, MeOH: points 7 and 8) is most strongly red-shifted. This result indicates that, in addition to π^*, the α and β parameters of the solvent also play an important role in controlling the emission wavelength.[20] These parameters correspond to the ability of the solvent to donate and accept hydrogen bonds, respectively (Table 3). This behaviour, with emission dependent on π^*, α and β, would be theoretically expected for an indole ring as explained below:[21]

a) It is well known that the excited and ground states of indoles have different dipole moments[22]—hence there is some dependence of the energy gap between them (i.e., emission wavelength) on π^*.

Table 3. Kamlet–Taft parameters for the solvents used.[20] π^* is the solvent polarity parameter, β the ability of the solvent to accept a hydrogen bond, α the ability of the solvent to donate a hydrogen bond. The data in brackets are relatively less certain.

solvents	π^*	β	α
cyclohexane	0	0	0
benzene	0.59	0.10	0
dichloromethane	0.82	0	(0.30)
ethyl acetate	0.55	0.45	0
tetrahydrofuran	0.58	0.55	0
acetonitrile	0.75	0.31	0.19
iso-propanol	0.48	(0.95)	0.76
methanol	0.60	(0.62)	0.93

b) If the solvent is a proton acceptor, it can bind to the NH group of the indole ring through the formation of a hydrogen bond.[23, 24] This interaction is dependent on the β value of the solvent.
c) If the solvent is a proton donor, it can interact with the π-cloud of the aromatic ring. This interaction has been found to be surprisingly strong[21] and is dependent on the α value of the solvent.[25]

For the emission of methylated **G0(NMe)**, however (Figure 2), it can be observed that the hydrogen bond acceptor solvents (EtOAc, THF—points 4 and 5, respectively) appear

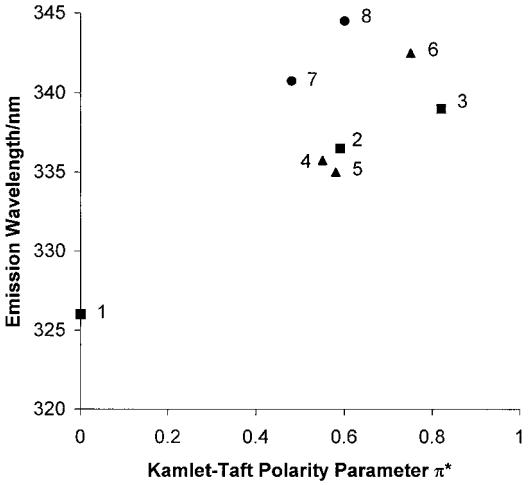

Figure 2. Attempted correlation of the emission wavelengths of **G0(NMe)** with the Kamlet–Taft polarity parameter π^*. Points: 1: cyclohexane, 2: benzene, 3: CH_2Cl_2, 4: EtOAc, 5: THF, 6: CH_3CN, 7 *i*PrOH, 8: MeOH.

to come into correlation with the non-hydrogen bonding solvents (points 1, 2 and 3). This is interesting because it indicates that the variation in β value is no longer important. This can be rationalised thus: the NH group has been blocked by NMe and is therefore not available for forming hydrogen bond interactions with the solvent. This is a significant result because it illustrates that blocking the 1-position of tryptophan does indeed have a significant effect on the emissive behaviour of the molecule—an observation contradictory to some previous reports,[3a, b] but in good agreement with others.[15] From the red shift of *i*PrOH and MeOH we can deduce that the effect of the α value is still important. It is noted that the point for CH_3CN (point 6) appears somewhat anomalous, but this solvent has a nonzero α value. In addition, it has been postulated that CH_3CN can become involved in an electron transfer reaction with the excited state of indoles.[26]

In a recent study of the fluorescent behaviour of β-naphthol, Solntsev et al. compared the emissive properties of the title compound and its methylated analogue in order to determine the importance of specific hydrogen bonding effects.[27] They observed that the difference between the emissive wavelengths of −OMe and −OH compounds was dependent only on the solvent β parameter, as π^* and α effects were equivalent for both molecules. We therefore attempted to correlate the difference between the emissive wavelengths of **G0(NH)** and **G0(NMe)** with β (Figure 3). Although a perfect correlation was not obtained, the general

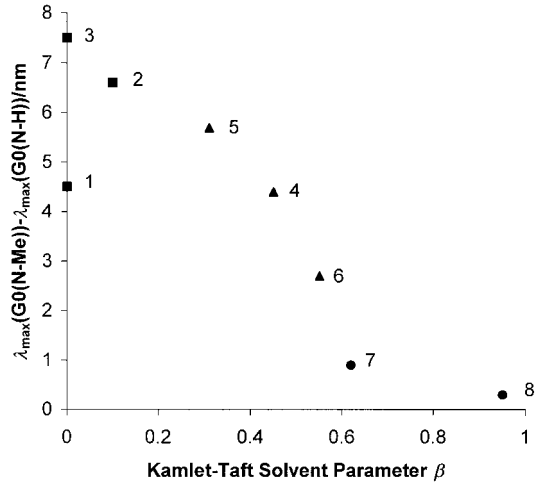

Figure 3. Attempted correlation plot between λ_{max}(**G0(NMe)**) – λ_{max}(**G0(NH)**) and the Kamlet–Taft solvent parameter β, which reflects the ability of the solvent to accept a hydrogen bond. Points: 1: cyclohexane, 2: benzene, 3: CH_2Cl_2, 4: EtOAc, 5: THF, 6: CH_3CN, 7: *i*PrOH, 8: MeOH.

trend indicated that the difference in behaviour between the two tryptophan derivatives does primarily depend on β (and presumably also to a lesser extent on α and π^*—hence nonlinearity). As a consequence, this result further proves that the hydrogen bond between the indole NH group and the hydrogen bond acceptor solvent has a very significant influence on the emissive behaviour of tryptophan.

Fluorescence of the branched tryptophans—The dendritic effect: With the knowledge gained above, it was possible to analyse the emission wavelength data for the branched tryptophan derivatives and come to meaningful conclusions about the origin of any dendritic effects.

Considering first the **G*n*(NH)** series of dendrimers: in certain solvents, λ_{max} was shifted strongly to the red on going from **G0(NH)** to **G2(NH)** (Table 1). This is a clear *dendritic effect*. It is noteworthy that the shift in wavelength is most marked in non-hydrogen bonding solvents, which have low β values (cyclohexane, benzene, CH_2Cl_2). Furthermore, if the π^* parameter is also low, this dendritic effect is larger (cyclohexane). In solvents capable of accepting hydrogen bonds,

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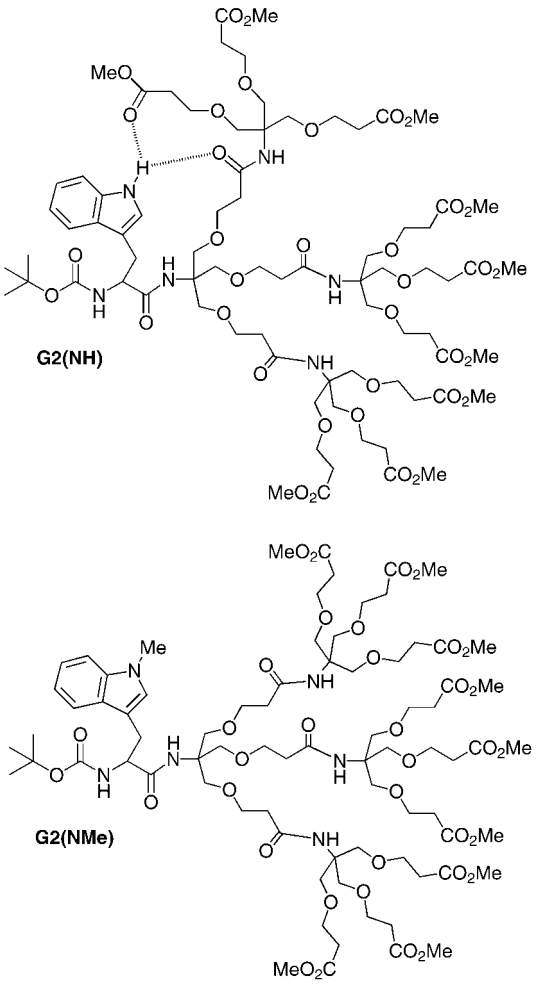
however, there is only a small red-shift dendritic effect, whilst for hydrogen-bond-acceptor and -donor solvents a small blue-shift dendritic effect was observed. The strong dendritic effect in solvents with low β values can be explained as a consequence of the ability of the NH group of the indole ring to become involved in hydrogen-bond interactions with H-bond acceptor groups in the dendritic shell, such as C=O (Scheme 2). As long as the β value of the solvent is low,



Scheme 2. Schematic representation of the intramolecular hydrogen bonding microenvironment provided by the dendritic shell for **G2(NH)** but not for **G2(NMe)**.

competition from the solvent is negligible and the branches bind to the tryptophan core through hydrogen bonding. Further evidence for the importance of this dendritic hydrogen-bonding microenvironment[28] was provided by ^{1}H NMR spectroscopy. A shift of the resonance for the NH proton of the indole ring was observed in $CDCl_3$: from $\delta = 8.10$ for **G0(NH)** to $\delta = 8.60$ for **G1(NH)** to $\delta = 9.45$ for **G2(NH)**.

The emission spectra obtained for the **G*n*(NMe)** series of dendrimers confirm the assignment of the dendritic effect to microenvironmental hydrogen bonding provided by the dendritic branches. For this methylated series of dendrimers, the branches have *no dendritic effect* on λ_{max} (Table 2). In no solvent was a marked dendritic effect observed, not even for solvents with low β and π^* values. In other words, the NMe tryptophan showed the same behaviour irrespective of whether it was encapsulated within a dendritic shell or not. This is due to the methyl group which prevents hydrogen bonding from occurring between the branched shell and the indole ring (Scheme 2). This effectively proves that the dendritic effect observed for the **G*n*(NH)** dendrimers is mediated through hydrogen bonding between the branching and the NH group on the tryptophan core. It is interesting to note that for dendrimers, as for proteins, individual hydrogen bond interactions can therefore play crucial roles in determining behaviour and function.

In order to ensure that the lack of dendritic effect for the methylated dendrimers was not simply a consequence of performing the fluorescence spectroscopy at a lower concentration, the emission of the **G*n*(NMe)** dendrimers in CH_2Cl_2 was also monitored at 1×10^{-4} M (the same concentration as the **G*n*(NH)** dendrimers). This increase in concentration caused a small (1 nm) but consistent red shift in the emission wavelength for all three molecules (Table 2). Notably, the overall dendritic effect for the **G*n*(NMe)** dendrimers remained around 1 nm (compared with 3 nm for the **G*n*(NH)** dendrimers).

Quenching: During the investigations, some interesting quenching effects were observed. Firstly, as mentioned above, the **G*n*(NH)** dendrimers emit with much lower intensity than the **G*n*(NMe)** dendrimers. Consequently the NH group may play an important role in the quenching mechanism—indeed for hydrogen-bonding solvents this can be easily understood by considering that these solvents can interact with the indole ring through the NH group. Such a quenching effect mediated by hydrogen-bond interactions has been previously reported for indoles.[29] Secondly, for all tryptophan derivatives in CH_2Cl_2, we observed a low intensity of emission which decreased on repeated scanning. It is probable that an excited-state reaction between indole and solvent occurs.

Conclusion

This paper proves unambiguously that, for NH tryptophan derivatives, hydrogen bonds involving the indole NH group play a key role in controlling its emission properties. The importance of the Kamlet–Taft solvent parameters, π^*, α and β in governing tryptophan emission have been clearly illustrated. It has been shown that a dendritic shell attached to a tryptophan derivative modulates its emission wavelength (dendritic effect) through the formation of a hydrogen-bonding microenvironment at the indole NH group. On blocking this NH group, the possibility of hydrogen-bond formation is removed and the dendritic effect is switched off. It is interesting to speculate that by using this approach in the future, specific supramolecular interactions will be manipulated with increasing control inside the dendritic superstructure, and that the possibilities for the application of dendrimers as protein or enzyme mimics will increase dramatically.

Experimental Section

THF was dried over Na, CH_2Cl_2 was dried over CaH_2, and both were freshly distilled before use. Other solvents and reagents were used as supplied. Compounds **1**, **2** and **5** were obtained from standard commercial sources. Compounds **3** and **4** were synthesised by using literature methods.[16] All reactions in an inert atmosphere were performed under dried nitrogen gas. Silica column chromatography was carried out by using silica gel provided by Fluorochem Ltd. (35–70 μm). Thin layer chromatography was performed on commercially available Merck aluminium backed silica plates. Preparative gel permeation chromatography was carried out with a 2 m glass column packed with Biobeads SX-1 supplied by Biorad. Proton and carbon NMR spectra were recorded on a Bruker AMX-500 (^{1}H 500 MHz, ^{13}C 125 MHz). Samples were recorded as solutions in deuterated chloroform, acetone or methanol, and chemical shifts (δ) are quoted in parts per million, referenced to residual solvent. Coupling constant values (J) are given in Hz. DEPT experiments were used to assist in the assignment of ^{13}C NMR spectra. Melting points were measured on an Electrothermal IA 9100 digital melting point apparatus and are uncorrected. Mass spectra were recorded on a Fisons Instruments VG Analytical Autospec as electrospray spectra. Chemical ionisation and high resolution spectra were measured on a Micromass Autospec spectrometer. Infra-red spectra were recorded with an ATI Mattson Genesis Series FTIR spectrometer. Emission spectroscopy was performed by using a Shimadzu RF-1501 Spectrofluorophotometer following excitation at 290 nm.

***N*-α-(*tert*-Butoxycarbonyl)-1-methyl-L-tryptophan-*tert*-butylamide (G0(NH))**: A solution of HOBt (0.210 g, 5.0 mmol) and DCC (0.316 g, 15.3 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a solution of *N*-α-(*tert*-butoxycarbonyl)-L-tryptophan (0.700 g, 23.0 mmol), *tert*-butylamine (0.110 g, 15.3 mmol) and Et_3N (0.256 g, 25.3 mmol) in CH_2Cl_2 (5 mL) at 0 °C under an inert atmosphere. The mixture was stirred for 72 hours at RT. The solution was filtered, washed with $NaHCO_3$ (satd. aq., 15 mL) and water (15 mL) and dried ($MgSO_4$). The solution was then concentrated with a rotary evaporator to afford the crude product (0.570 g) as a yellowish oil. Purification by column chromatography (SiO_2, CH_2Cl_2/EtOAc 90:10) gave a white solid. Yield: 0.442 g, 12.3 mmol, 80% with respect to *tert*-butylamine); m.p. 79.5–81.0 °C; $R_f = 0.47$ (CH_2Cl_2/EtOAc 90:10); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.10$ (br s, 1H; indole NH), 7.63 (d, $^3J(H,H) = 7.8$ Hz, 1H; ArH), 7.30 (d, $^3J(H,H) = 8.1$ Hz, 1H; ArH), 7.13 (dt, $^3J(H,H) = 1.0$, 7.6 Hz, 1H; ArH), 7.07 (dt, $^3J(H,H) = 1.0$, 7.5 Hz, 1H; ArH) 6.98 (d, $^3J(H,H) = 2.0$ Hz, 1H; ArH), 5.25 (br s, 1H; NH), 5.15 (br s, 1H; NH), 4.26 (br app s, 1H; C*H*NH), 3.22 (m, 1H; CH_2CHNH), 3.01 (m, 1H; CH_2CHNH), 1.37 (s, 9H; $(CH_3)_3CO$), 1.05 (s, 9H; $(CH_3)_3CN$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 170.5$ (C=O), 155.6 (C=O), 136.3, 127.5, 123.2, 122.4, 119.9, 119.1, 111.2 (all Ar), 79.91 ($(CH_3)_3CO$), 55.49 (*C*HCO) 51.09 ($(CH_3)_3CN$) 28.86 (CH_2CHCO) 28.51 (CH_3) 28.41 (CH_3); IR ($CHCl_3$) $\tilde{\nu} = 3480$m, 3424m, 3026m, 3018s, 2981m, 2934w, 1704s, 1676s, 1490s, 1457m, 1394w, 1368s, 1229s, 1167s, 1092w, 1056w, 1013w, 864w cm^{-1}; MS (electrospray): m/z: 383 (22) $[M+Na+H]^+$, 382 (100) $[M+Na]^+$; HRMS (CI) ($C_{20}H_{29}N_3O_3 + H$) $[M+H]^+$: calculated 360.2287, found 360.2281.

Compound G1(NH): The method was similar to that described for **G0(NH)**, only compound **3** was used rather than *tert*-butylamine. The product was purified by gel permeation chromatography to give a colourless viscous oil. Yield: 54% with respect to branch **3**; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.60$ (br s, 1H; indole NH) 7.67 (d, $^3J(H,H) = 7.5$ Hz, 1H; ArH), 7.32 (d, $^3J(H,H) = 8.0$ Hz, 1H; ArH), 7.13 (t, $^3J(H,H) = 7.5$ Hz, 1H; ArH), 7.09 (m, 2H; ArH), 5.90 (br s, 1H; NH), 5.29 (br s, 1H; NH), 4.37 (br app s, 1H; C*H*NH), 3.65 (s, 9H; CO_2CH_3), 3.60–3.40 (m, 12H; CH_2O), 3.23 (m, 1H; CH_2CHNH), 3.08 (m, 1H; CH_2CHNH), 2.42 (t, $^3J(H,H) = 6.0$ Hz, 6H; CH_2CO_2Me), 1.39 (s, 9H, $(CH_3)_3CO$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 172.0$ (*C*OOMe), 171.3 (C=O), 155.2 (C=O), 136.1, 127.6, 123.6, 121.8, 119.3, 119.0, 111.0, 110.6 (all Ar), 79.47 ($(CH_3)_3CO$), 68.92 (CH_2O), 66.61 (CH_2O), 59.55 (NH*C*$(CH_2)_3$), 55.46 (*C*HCO) 51.61 ($CO_2(CH_3)_3$) 34.68 (CH_2CO_2Me), 28.67 (CH_2CHCO) 28.24 (CH_3CO); IR (neat) $\tilde{\nu} = 3363$br s, 2954m, 2929s, 2880m, 1739s, 1682s, 1488m, 1458m, 1438s, 1368m, 1253m, 1199s, 1176s, 1112s, 1074m, 1024m, 850w, 743m, 702w cm^{-1}; MS (electrospray): m/z: 689 (34) $[M+Na+H]^+$, 688 (100, $[M+Na]^+$), 588 (25); HRMS (CI) ($C_{32}H_{47}N_3O_{12} + H$) $[M+H]^+$: calculated 666.3238, found 666.3237.

Compound G2(NH): The method was similar to that for **G0(NH)**, only using branch **4** rather than *tert*-butylamine. Purification by gel permeation chromatography generated a colourless viscous oil. Yield 53% with respect to branch **4**; ^{1}H NMR (500 MHz, $(CD_3)_2CO$): $\delta = 10.10$ (s, 1H; indole NH), 7.70 (d, $^3J(H,H) = 8.0$ Hz, 1H; ArH), 7.39 (d, $^3J(H,H) = 8.0$ Hz, 1H; ArH), 7.27 (d, $^3J(H,H) = 2.0$ Hz, 1H; ArH), 7.09 (dt, $^3J(H,H) = 1.0$, 7.5 Hz, 1H; ArH), 7.03 (dt, $^3J(H,H) = 1.0$, 7.25 Hz, 1H; ArH), 6.74 (s, 1H; NH), 6.61 (s, 3H; NH), 5.92 (d, 1H; NH), 4.45 (m, 1H; C*H*NH), 3.70–3.60 (m, 75H; CH_2O, CH_3O), 3.30–3.10 (m, 2H, CH_2CHNH), 2.54 (t, 18H, $J = 6.5$ Hz, CH_2CO_2Me), 2.37 (t, $^3J(H,H) = 6.25$ Hz, 6H; CH_2CONH), 1.40 (s, 9H; $(CH_3)_3CO$); ^{13}C NMR (125 MHz, $(CD_3)_2CO$): $\delta = 171.7$ (*C*O_2Me), 171.5 (1CONH), 170.9 (3CONH), 155.2 (C=O), 136.7, 128.1, 124.2, 121.2, 118.9, 118.6, 111.3, 110.6 (all Ar), 78.39 ($(CH_3)_3CO$), 68.94 (9CH_2O), 68.81 (3CH_2O), 67.53 (3CH_2O), 66.82 (9CH_2O), 59.99 (NH*C*$(CH_2)_3$), 55.38 (*C*HCO) 50.94 (CO_2CH_3) 36.90 (*C*H_2CONH), 34.52 (*C*H_2CO_2Me), 29.5–28.5 (*C*H_2CHCO under solvent peak), 27.84 (*C*H_3CO); IR (neat) $\tilde{\nu} = 3374$br s, 2950s, 2925s, 2880s, 1732s, 1668s, 1538m, 1436m, 1368m, 1250m, 1200s, 1177s, 1110s, 1075m, 1025m, 849w, 747w cm^{-1}; MS (electrospray): m/z: 1730 (100) $[M+Na]^+$, 1731 (87) $[M+Na+H]^+$, 1732 (33) $[M\{^{13}C_1\}+Na+H]^+$.

***N*-α-(*tert*-Butoxycarbonyl)-1-methyl-L-tryptophan (6)**: Adapted from reference.[17] 1-Methyl-L-tryptophan (3.00 g, 13.75 mmol) was dissolved in dry DMF (45 mL). Then Et_3N (5.8 mL, 41.25 mmol) and di-*tert*-butyldicarbonate (3.31 g, 15.18 mmol) were added. The white suspension turned clear orange in less than 1 h when stirred under N_2 at RT. The reaction was followed by TLC (CH_2Cl_2/MeOH 90:10). After 46 h the mixture was concentrated to dryness. The orange-brown residue was dissolved in EtOAc (100 mL) and extracted with sat. aq. $NaHCO_3$ (3 × 50 mL). The combined aqueous layers were acidified to pH 3 (pH paper) by dropwise addition of 6 M HCl (ca. 35 mL), then the product was immediately extracted with EtOAc (3 × 50 mL). The organic phase was dried ($MgSO_4$), filtered under gravity and evaporated (rotary evaporation and vacuum line) to recover the crude product as a yellow solid (3.54 g). Purification by precipitation from EtOAc/hexane gave the pure product as a white solid. Yield: 2.53g, 7.96 mmol, 58%; m.p. 145–147 °C; $R_f = 0.42$ (CH_2Cl_2/MeOH 90:10); ^{1}H NMR (500 MHz, $CDCl_3$, 300 K): $\delta = 7.75$ (d, $^3J(H,H) = 8.0$ Hz, 1H; ArH), 7.45 (d, $^3J(H,H) = 8.0$ Hz, 1H; ArH), 7.38 (t, $^3J(H,H) = 7.5$ Hz, 1H; ArH), 7.27 (t, $^3J(H,H) = 7.5$ Hz, 1H, ArH) 7.07 (s, 1H; ArH), 5.85 (br s, NH other conformer), 5.19 (d, $^3J(H,H) = 5$ Hz, 1H; NH), 4.81 (s, 1H; C*H*CO_2H), 4.60 (br s, C*H*CO_2H other conformer), 3.89 (m, 3H; NCH_3), 3.50 (m, 1H; CH_2CHNH), 3.26 (br s, CH_2CHNH other conformer), 1.59 (s, 7H; $(CH_3)_3CO$), 1.43 (m, 2H; $(CH_3)_3CO$ other conformer); ^{1}H NMR (500 MHz, $CDCl_3$, 323 K): $\delta = 7.57$ (d, $^3J(H,H) = 8.0$ Hz, 1H; ArH), 7.26 (d, $^3J(H,H) = 8.0$ Hz, 1H; ArH), 7.20 (t, $^3J(H,H) = 7.0$ Hz, 1H; ArH), 7.09 (t, $^3J(H,H) = 7.0$ Hz, 1H; ArH), 6.89 (s, 1H; ArH), 5.04 (s, 1H; NH), 4.60 (s, 1H; C*H*NH), 3.71 (s, 3H; NCH_3), 3.30 (dd, $^3J(H,H) = 15.0$, 5.5 Hz, 1H; CH_2CHNH), 3.20 (br dd, 1H; CH_2CHNH), 1.40 (s, 9H; $(CH_3)_3CO$); ^{1}H NMR (500 MHz, $CDCl_3$, 253 K): $\delta = 7.78$, 7.75 (2d, $^3J(H,H) = 7.5$ Hz, 1H; ArH), 7.47, 7.46 (2d, 1H, $^3J(H,H) = 7.5$ Hz, 1H; ArH), 7.40 (m, 1H; ArH), 7.28 (m, 1H; ArH) 7.08, 7.06 (2s, 1H; ArH), 5.60–5.30 (br s, 0.4H; NH first conformer), 5.20 (d, $^3J(H,H) = 7.5$ Hz, 0.6 H; NH second conformer), 4.85–4.64 (m, 1H; C*H*NH), 3.91, 3.89 (2s, 3H; NCH_3), 3.65–3.10 (m, 2H; CH_2CHNH), 1.57, 1.09 (2s, 9H; $(CH_3)_3CO$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 176.9$ (CO_2H), 155.4 (NH*C*O), 136.8, 128.5, 127.6, 121.7, 119.1, 118.8, 109.2, 108.3 (all Ar), 80.11 ($(CH_3)_3CO$), 54.34 (*C*HCO), 32.62 (NCH_3), 28.27 (C(*C*$H_3)_3$), 27.83 (*C*H_2CHCO); IR (KBr) $\tilde{\nu} = 3326$m (NH), 3050w, 2921m, 2544w, 1737s, 1658s, 1550w, 1479m, 1438w, 1403s, 1365m, 1324m, 1249m, 1224m, 1159m, 1134m, 1116w, 1049m, 1026w, 964w, 850w, 776w, 742s cm^{-1}; MS (CI): m/z: 319 (46) $[M+H]^+$, 263 (100) $[M - C(CH_3)_3]^+$, 219 (26) $[M - CO_2C(CH_3)_3]^+$, 144 (37) [indole *C*$H_2]^+$; HRMS (FAB) ($C_{17}H_{23}N_2O_4 + H$) $[M+H]^+$: calculated 319.1658, found 319.1663.

***N*-α-(*tert*-Butoxycarbonyl)-1-methyl-L-tryptophan-*tert*-butylamide (G0(NMe))**: This compound was prepared by using a similar method to **G0(NH)**, only with THF as solvent and compound **6** as carboxylic acid. Work-up: after 24 hours the mixture was filtered under gravity and the solvent was removed by rotary evaporation. The yellow oily residue was dissolved in CH_2Cl_2 (15 mL), washed with sat. aq. $NaHCO_3$ (2 × 15 mL) and H_2O (2 × 15 mL). The organic phase was dried ($MgSO_4$), filtered under gravity and evaporated to give the crude product as a yellow oil. Purification by column chromatography (SiO_2, CH_2Cl_2/EtOAc 90:10) gave the pure product as a white solid. Yield: 33%; m.p. 121–123 °C; $R_f = 0.48$

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(CH_2Cl_2/EtOAc 90:10); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.61$ (d, $^3J(H,H) = 8.0$ Hz, 1H; ArH), 7.22 (d, $^3J(H,H) = 8.0$ Hz, 1H; ArH), 7.16 (t, $^3J(H,H) = 7.5$ Hz, 1H; ArH), 7.05 (t, $^3J(H,H) = 7.5$ Hz, 1H; ArH), 6.83 (s, 1H; ArH), 5.31 (s, 1H; NH), 5.16 (s, 1H; NH), 4.23 (s, 1H; C*H*NH), 3.67 (s, 3H; NCH_3), 3.10 (m, 1H; CH_2CHNH), 1.37 (s, 9H; $(CH_3)_3CO$), 1.06 (s, 9H; $(CH_3)_3$CNH); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 170.6$ (C=O), 155.6 (C=O), 137.1, 128.0, 127.9, 121.9, 119.3, 119.2, 109.6, 109.3 (all Ar), 79.88 ($(CH_3)_3CO$), 55.53 (*C*HCO), 51.10 ($(CH_3)_3CN$), 32.67 (NCH_3), 28.66 (*C*H_2CHCO), 28.48 (C(*C*$H_3)_3$), 28.37 (C(*C*$H_3)_3$); IR (KBr) $\tilde{\nu} = 3341$m, 3055w, 2973m, 2930m, 1658s, 1543s, 1475m, 1454m, 1391m, 1365m, 1323w, 1303w, 1270m, 1250m, 1224w, 1175m, 1056w, 1013w, 863w, 738m cm^{-1}. MS (CI): *m*/*z*: 374 (100) $[M+H]^+$, 318 (65) $[M+H-C(CH_3)_3]^+$, 274 (100) $[M+H-CONHC(CH_3)_3]^+$, 171 (41), 144 (31) [indole CH_2]$^+$; HRMS (FAB) ($C_{21}H_{32}N_3O_3+H$) $[M+H]^+$: calculated 374.2444, found 374.2446.

Compound G1(NMe): Method as for **G1(NH)**, only with dry THF as solvent and **6** as carboxylic acid. Work-up: when reaction was complete (44 h), the mixture was filtered under gravity and the solvent was evaporated. CH_2Cl_2 (15 mL) was added to the yellow oil residue, which was then washed with sat. aq. $NaHCO_3$ (2×15 mL) and H_2O (2×15 mL). The organic layer was dried over $MgSO_4$, filtered under gravity and evaporated (rotary evaporation and vacuum line) to give the crude product as a viscous yellow oil. Purification by column chromatography (SiO_2, CH_2Cl_2/MeOH 90:10) gave the pure product as a viscous yellow oil. Yield: 46%; $R_f = 0.80$ (CH_2Cl_2/MeOH 90:10); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta =$ 7.62 (d, $^3J(H,H) = 7.5$ Hz, 1H; ArH), 7.19 (d, $^3J(H,H) = 8.0$ Hz, 1H; ArH), 7.12 (t, $^3J(H,H) = 7.8$ Hz, 1H; ArH), 7.03 (t, $^3J(H,H) = 7.8$ Hz, 2H; ArH), 6.90 (s, 1H; ArH), 5.95 (s, 1H; NH), 5.22 (s, 1H; NH), 4.31 (m, 1H; C*H*NH), 3.60–3.40 (m, 24H; CH_2O, CO_2CH_3, NCH_3), 3.10 (m, 2H; CH_2CHNH), 2.39 (t, $^3J(H,H) = 6.5$ Hz, 6H; CH_2CO_2Me), 1.30 (s, 9H; $(CH_3)_3CO$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 172.0$ (*C*O_2Me), 171.5 (C=O), 155.4 (C=O), 137.0, 128.3, 128.1, 121.7, 119.3, 119.1, 109.6, 109.1, (all Ar), 79.56 ($(CH_3)_3CO$), 69.10 (CH_2O), 66.72 (CH_2O), 59.66 (NH*C*$(CH_2)_3$), 55.53 (*C*HCO) 51.68 (CO_2CH_3) 34.70 (*C*H_2CO_2Me), 32.67 (N*C*H_3), 28.73 (*C*H_2CHCO) 28.34 (*C*H_3CO); IR (neat) $\tilde{\nu} = 3369$m, 2953m, 2880m, 1738s, 1679s, 1620m, 1515s, 1485s, 1439s, 1367s, 1328m, 1252s, 1198s, 1176s, 1113m, 1074m, 1024m, 892w, 849m, 782w, 743m cm^{-1}; MS (electrospray): *m*/*z*: 702 (100) $[M+Na]^+$, 703 (31); HRMS (FAB): ($C_{33}H_{49}N_3O_{12}+$ Na) $[M+Na]^+$: calculated 702.3214, found 702.3215.

Compound G2(NMe): The synthesis was as for **G2(NH)**, only with dry THF as solvent and **6** as carboxylic acid. The reaction was followed by GPC and pushed to completion by adding several portions of Boc-protected methyltryptophan and coupling agents (HOBt and DCC) dissolved in THF. After 4 days the precipitate contained in the mixture was removed by filtration under gravity. The solvent was rotary evaporated; the pale yellow residue was dissolved in CH_2Cl_2 (15 mL) and washed with sat. aq. $NaHCO_3$ (2×15 mL) and H_2O (2×15 mL). The organic phase was dried ($MgSO_4$), filtered under gravity and rotary evaporated to give the crude product as a viscous pale yellow oil. The product was purified by GPC to afford a viscous pale yellow oil. Yield: 32%; $R_f = 0.70$ (CH_2Cl_2/MeOH 90:10); ^{1}H NMR (500 MHz, CD_3OD) peaks in ^{1}H NMR spectrum were broadened—presumably due to conformational effects: $\delta = 7.50$ (br d, $^3J(H,H) = 8.0$ Hz, 1H; ArH), 7.18 (br d, $^3J(H,H) = 8.0$ Hz, 1H; ArH), 7.03 (m, 1H; ArH), 6.93–6.88 (m, 2H; ArH), 4.50–4.40 (br m, 1H; C*H*NH), 3.80–3.60 (m, 75H; CO_2CH_3, CH_2O, NCH_3), 3.25–3.10 (m, 2H; CH_2CHNH), 2.38 (t, $^3J(H,H) = 7.0$ Hz, 18H; CH_2CO_2Me), 2.36 (t, $^3J(H,H) = 7.0$ Hz, 6H; CH_2CONH), 1.42 (s, 9H; $(CH_3)_3CO$); ^{13}C NMR (125 MHz, CD_3OD): $\delta = 174.1$ (CONH $\times$ 1), 173.9 (*C*O_2Me), 173.6 (*C*ONH $\times$ 3), 157.3 (C=O), 138.5, 129.5, 129.2, 122.5, 120.0, 119.9, 110.8, 110.2 (all Ar), 80.54 ($(CH_3)_3CO$), 70.14 ($CH_2O\times3$), 69.98 ($CH_2O\times9$), 68.80 ($CH_2O\times3$), 67.98 ($CH_2O\times9$), 61.39 (NH*C*$(CH_2)_3$), 57.06 (*C*HCO), 52.20 (CO_2CH_3), 38.04 (*C*H_2CONH), 35.66 (*C*H_2COOMe), 32.89 (NCH_3), 28.76 (*C*H_3CO), 26.04 (*C*H_2CHCO); IR (neat) $\tilde{\nu} = 3327$br s, 2952s, 2928s, 2875s, 1737s, 1674s, 1625m, 1560m, 1438m, 1366m, 1270m, 1198s, 1176s, 1111s, 1074m, 1025w cm^{-1}; MS (electrospray): *m*/*z*: 1744 (100) $[M+Na]^+$, 1745 (87) $[M+Na+H]^+$, 1746 (33), $[M\{^{13}C_1\}+Na+H]^+$.

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