Synthesis and special structure of a novel low-generation amide dendrimer with pseudo-symmetric branch distribution

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A novel low-generation amide dendrimer bearing four ester groups as terminal branches was conveniently synthesised by three-step reactions including acylation, hydrolysis and condensation from benzoyl chloride. Crystal X-ray diffraction and NMR analysis confirmed that one ester group of the four branches with pseudosymmetry was shielded by a benzene ring while the others were much further away. This was a difference from conventional dendrimers with symmetric branch distribution.

Keywords: amide dendrimer, synthesis, crystal structure, branch distribution, pseudosymmetry

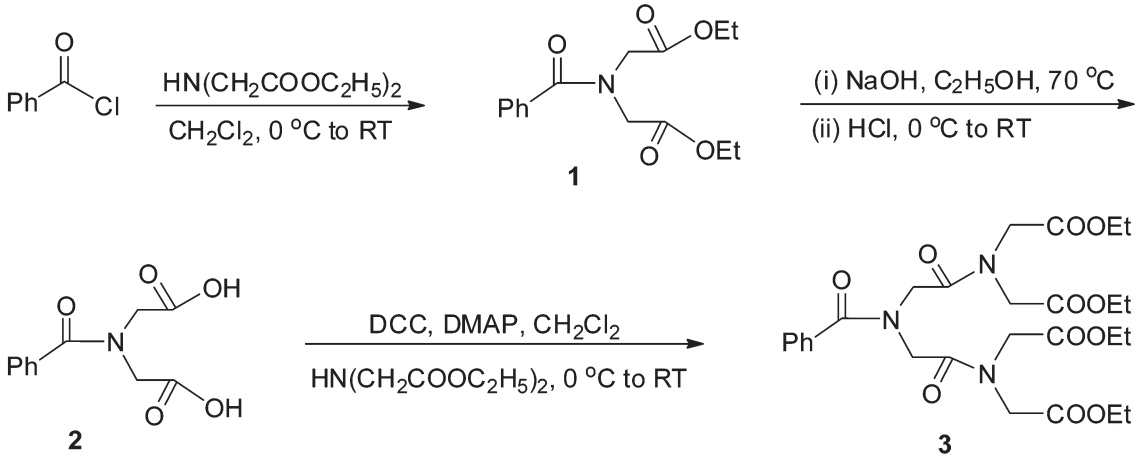
Recently, much attention had been paid to dendrimers because of their exciting structure and their commercial applications in medical diagnostics.[1] Moreover, several prospective dendrimers have been used as drug delivery systems and light harvesting antennae, *etc*.[2–5] Also as various types of biosensors involving dendrimers had been proposed.[6,7] In general, the synthesis of dendrimers can be performed in two main ways: divergent and convergent growth.[8,9] Divergent growth is based on the stepwise addition of low molecular mass building blocks starting from a multifunctional core molecule and results in a radial growth of the dendrimer. Convergent dendrimer synthesis, on the other hand, involved the coupling of preformed dendrons onto a central core molecule.[10] Most of these dendritic compounds involve a symmetric branch distribution, which can be shown by their NMR spectra.[11,12] We report here the convenient synthesis and special structure of a novel amide dendrimer with a pseudo-symmetric branch distribution.

The low-generation amide dendrimer **3** bearing four ester groups as terminal branches was synthesised by a series of three reactions (Scheme 1). First, acylation of diethyl iminodiacetate with benzoyl chloride was carried out smoothly in dichloromethane at 0 °C to smoothly give *N*,*N*-bis(ethylacetate) benzamide **1**.[13,14] Then, *N*,*N*-bis(acetic acid) benzamide **2** was obtained by the hydrolysis of **1** at 70 °C. Finally, in the presence of DCC (Dicyclohexylcarbodiimide) and DMAP (4-dimethylaminopyridine), condensation between **2** and diethyl iminodiacetate was performed in dichloromethane to give the target compound **3**.[15] All the resulting products in each step were characterised by ^{1}H and ^{13}C NMR spectra.

In general, dendritic compounds bearing a symmetric branch distribution display similar chemical shifts and splitting patterns in their NMR spectra for their branches.[11,12] However, the low-generation amide dendrimer **3** exhibited seven carbonyl signals in its ^{13}C NMR spectra, which indicates that all the branches are located in different chemical environments. Furthermore, obvious downfield shifts of the NCOCH_2CON and COOCH_2CH_3 protons on one branch were observed in the ^{1}H NMR spectrum in Fig. 1. This may be attributed to the obstructive rotation of amide N–CO bonds and the shielding effect of the benzene ring.

In order to confirm further the structure of compound **3** and explain the special ^{1}H NMR spectrum in Fig. 1, the crystal structure of **3** was investigated. As depicted in Fig. 2, it is obvious that only the O(9) branch is located near the benzene ring while other three branches are much further away. This pseudo-symmetric branch distribution can be stabilised by the weak interactions including CO···H and CH···π present in compound **3** (Table 1). The actual reason for the special NMR spectrum of compound **3** discussed above is that amide N–CO bonds cannot rotate freely and that the protons of H18A(B) and COOCH_2CH_3 on O(9) chain are shielded by the benzene ring.

In conclusion, we have prepared a novel low-generation amide dendrimer **3** and studied its special branch distribution with pseudosymmetry by NMR and crystal X-ray diffraction experiments. The crystal structure of **3** disclosed that one ester group of four branches was shielded by the benzene ring while the others were some way away from the benzene ring because of the obstructive rotation of the amide N–CO bonds stabilised by the weak interactions of CO···H and CH···π. This confirms the pseudo-symmetric branch distribution and the abnormal chemical shifts of protons and carbons in the NMR spectra.



Scheme 1

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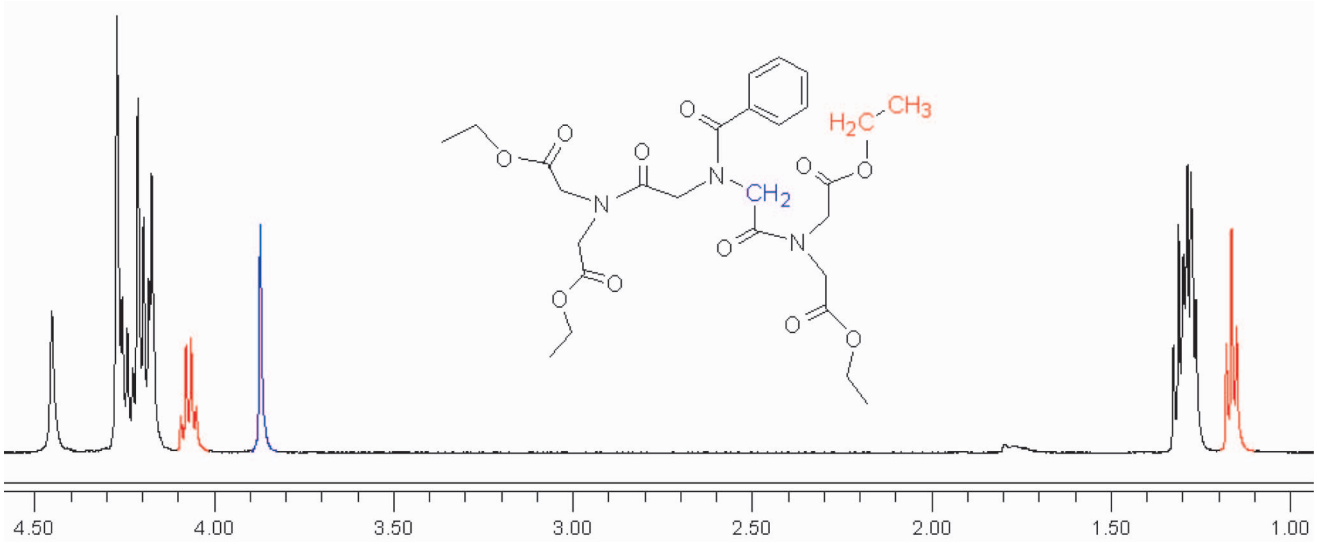

Fig. 1 The partial ^{1}H NMR spectrum of compound **3**.

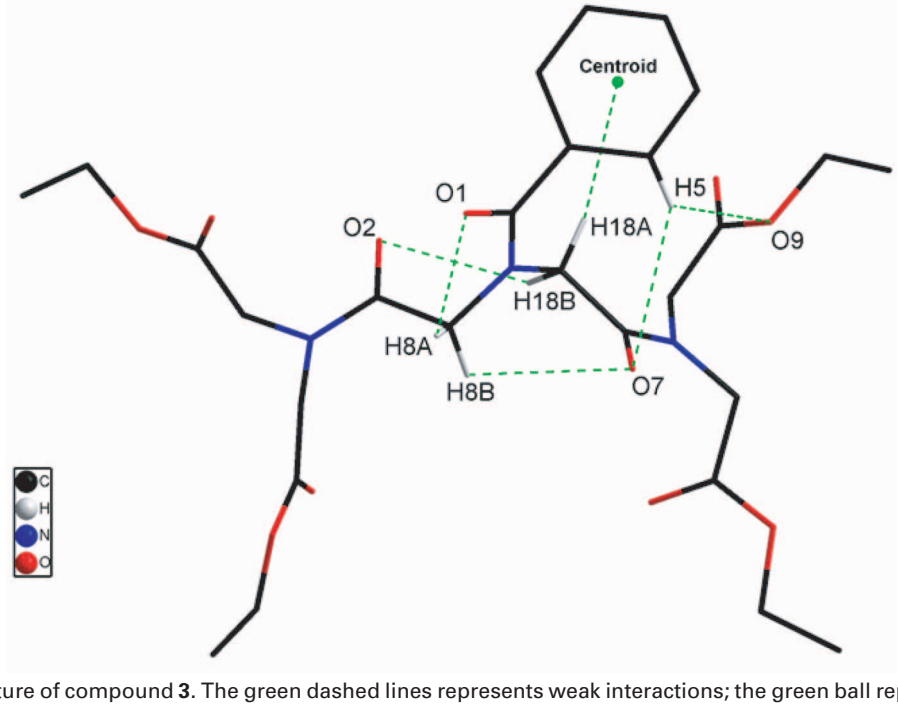

Fig. 2 Crystal structure of compound **3**. The green dashed lines represents weak interactions; the green ball represents the centroid of the benzene ring.

Table 1 Distances and angles of possible weak interactions for compound **3**

Atoms involved	Distance /Å		Angle /°
	D···A	H···A	D–H···A
C(5)–H5···O(7)	3.749(3)	2.96	142.6
C(5)–H5···O(9)	3.948(2)	3.52	110.4
C(8)–H8A···O(1)	2.655(1)	2.32	99.2
C(8)–H8B···O(7)	3.223(2)	2.85	103.8
C(18)–H18B···O(2)	3.160(2)	2.73	107.4
C(18)–H18A···centroid	3.980(2)	3.31	127.9

This study provides significant evidence for the future identification of similar structures as dendrimers with a pseudo-symmetric branch distribution.

Experimental

Crystal data was obtained on a Bruker APEX-II diffractometer with CCD detector. NMR spectra were recorded on a Varian Mercury 500 spectrometer with TMS as an internal standard. IR spectroscopy was recorded using KBr pellets in the range of 4000–400 cm^{-1} on a Bio-Rad FTS-135 spectrophotometer. Melting points (uncorrected) were determined on a WRS-2 Computer MP apparatus.

Synthesis of N,N-bis(ethyl acetate)benzamide **1**

Benzoyl chloride (4.2 g, 30 mmol) was added dropwise to a solution of diethyl iminodiacetate (11.3 g, 60 mmol) in CH_2Cl_2 (20 mL) at 0 °C. The reaction was stirred for 5 h at room temperature. Diluted with CH_2Cl_2 (20 mL), the organic layer was washed with HCl (1 M, 20 mL), saturated $NaHCO_3$ solution (10 mL), brine (20 mL) and dried over $MgSO_4$. Concentration of the CH_2Cl_2 solution gave compound **1** as a yellow oil (8.2 g, 94% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.26 (t, J = 7.1 Hz, 3H, CH_3), 1.31 (t, J = 7.1 Hz, 3H, CH_3), 4.11 (s, 2H,

NCH_2CO), 4.18–4.25 (m, 4H, OCH_2), 4.32 (s, 2H, NCH_2CO), 7.38–7.45 (m, 5H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.3 (ArCON), 169.2 (COO), 169.0 (COO), 134.9 (ArC), 130.3 (ArC), 128.6 (ArC), 126.9 (ArC), 61.6 (OCH_2), 61.3 (OCH_2), 51.8 (NCH_2), 47.6 (NCH_2), 14.2 (CH_3), 14.1 (CH_3). Anal. Calcd for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.53; N, 4.78; found C, 61.56; H, 6.65; N, 4.66%.

Synthesis of N,N-bis(acetic acid)benzamide **2**

A mixture of *N*,*N*-bis(ethyl acetate)benzamide **1** (7.2 g, 24.6 mmol) and NaOH (2.5 M, 50 mL) in ethanol (5 mL) was heated to 70 °C for 5 h and then cooled to 0 °C. HCl (6 M, 50mL) was added. The reaction mixture was stirred for 3 h at room temperature. After reaction, pure *N*,*N*-bis(ethyl acetate)benzamide **2** was obtained as a white solid (5.0 g, 86%) by filtration. m.p. 88–90 °C. ^1H NMR (500 MHz, DMSO-d_6) δ 3.99 (s, 2H, NCH_2CO), 4.14 (s, 2H, NCH_2CO), 7.30–7.50 (m, 5H, ArH), 12.86 (s, 2H, COOH); ^{13}C NMR (125 MHz, DMSO-d_6) δ 171.2 (ArCON), 170.7 (COOH), 170.2 (COOH), 135.3 (ArC), 129.9 (ArC), 128.6 (ArC), 126.3 (ArC), 51.5 (NCH_2), 47.8 (NCH_2). Anal. Calcd for $C_{11}H_{11}NO_5$: C, 55.70; H, 4.67; N, 5.90. Found: C, 55.83; H, 4.77; N, 5.74%.

Synthesis of N,N-bis{carbonyl methylene[N,N-bis(ethoxy carbonyl methylene)amino]}benzamide **3**

Diethyl iminodiacetate (2.4 g, 12.9 mmol) was added dropwise to a solution of *N*,*N*-bis(acetic acid)benzamide **2** (1.0 g, 4.3 mmol), DCC (2.2 g, 10.7 mmol) and DMAP (52.4 mg, 0.4 mmol) in dry dichloromethane (5 mL), at 0 °C. The reaction mixture was stirred under nitrogen at room temperature for 8 h. The resulting mixture was filtered and the filtrate was washed with HCl (1 M, 20 mL), saturated $NaHCO_3$ solution (10 mL), and brine (10 mL) and dried over $MgSO_4$. Concentration and chromatography on a silica gel column (petroleum ether/acetone 2:1) furnished **3** (1.5 g, 61% yield) as a white solid. m.p. 85–86 °C. IR (KBr): 2983, 2937, 1748, 1731, 1676, 1642, 1466, 1197 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.16 (t, *J* = 7.1 Hz, 3H, CH_3), 1.26–1.33 (m, 9H, CH_3), 3.87 (s, 2H, NCH_2), 4.05 (q, 2H, OCH_2), 4.17–4.27 (m, 14H, OCH_2 + NCH_2), 4.45 (s, 2H, NCH_2), 7.38–7.47 (m, 5H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2 (ArCON), 169.4 (COO), 169.3 (COO), 168.8 (COO), 168.6 (COO), 168.5 (NCO), 167.9 (NCO), 134.8 (ArC), 130.1 (ArC), 128.5 (ArC), 127.2 (ArC), 61.9 (OCH_2), 61.9 (OCH_2), 61.4 (OCH_2), 61.3 (OCH_2), 50.8 (NCH_2), 49.9 (NCH_2), 49.5 (NCH_2), 48.6 (NCH_2), 48.5 (NCH_2), 46.6 (NCH_2), 14.2 (CH_3), 14.1 (CH_3), 14.0 (CH_3). LC-MS (ESI): *m/z* 602.35 ([M + Na]$^+$, 100%). Anal. Calcd for $C_{27}H_{37}N_3O_{11}$: C, 55.95; H, 6.43; N, 7.25. Found: C, 56.08; H, 6.33; N, 7.14%.

Crystal data for amide dendrimer **3**

M = 579.60, $C_{27}H_{37}N_3O_{11}$, monoclinic, Space group *P*2(1)/c, *a* = 14.414 (4) Å, *b* = 9.066 (2) Å, *c* = 23.922 (6) Å, α = 90°, β = 93.022(5)°, γ = 90°, V = 3121.6 (14) Å^3, *Z* = 4, D_{Calcd} = 1.233 g cm^{-3}. A colourless crystal of dimension 0.21 × 0.21 × 0.16 mm was used for measurement at 295(2) K with the φ and ω scans mode on a Bruker APEX-II diffractometer with CCD detector using Mo *K*α radiation (λ = 0.71073 Å). The data were corrected for Lorentz and polarisation effects and absorption corrections based on the multi-scan method were performed using SADABS program. The structure was solved by direct methods and refined by full matrix least-squares methods on F^2 using the SHELXS-97[16] and SHELXL-97[17] programs.The positions of hydrogen atoms were calculated theoretically and included in the final cycles of refinement in a riding model along with attached carbons. The final cycle of full matrix least-squares refinement was based on 8026 independent reflections [I >2 σ (I)] and 383 variable parameters with R_1 = 0.0667, wR_2 = 0.2350. CCDC 752074 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request.cif

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