Rapid synthesis of calix[4]resorcinarene-based dendrimers containing salicylideneimine terminal groups

Yun Ge and Chaoguo Yan*

College of Chemistry and Chemical Engineering, Yangzhou University, Yangzhou 225002, China

Second–generation calix[4]resorcinarene-based dendrimers containing 16 or 24 terminal salicylideneimines were synthesised by divergent method in five steps from the corresponding calix[4]resorcinarenes.

Keywords: calix[4]resorcinarenes, dendrimers, Schiff base, Salen

Dendrimers are receiving much interests as new polymeric materials in recent years, and are well defined, highly branched, three-dimensional compounds with a large number of reactive end groups.[1] Owing to their unique physical and chemical properties, dendrimers have found uses in many areas such as catalysis, supramolecular chemistry and nanoparticles.[2] A vast variety of dendrimer molecules with different functional groups have been synthesised by both divergent and convergent methodologies starting from the respective monomers. Because each type of dendrimers possesses its own structural and molecular properties, identification of new monomers for dendrimer synthesis continues to be attractive. In our goal to synthesise new types of denrimers, we were interested in using calixarenes as a polyfunctional core because of their ease of synthesis, their persistent shape and size which makes them less affected by steric constaints, as well as much more reactive sites, from which high molecular weight of dendrimers can be prepared rapidly. Indeed several examples of dendrimer synthesis based on *p-tert*-butylcalix[4]arenes or calix[4] resorcinarenes have been described in the literature.[3-7] In this article, we report a successful rapid synthesis of a new kind of calix[4]resorcinarene-core dendrimer with terminal salicylideneimine groups by a divergent method.

Results and discussion

Scheme 1 illustrates the synthesis of the second-generation dendrimers by the divergent method using tetraphenyl- and tetra(*p*-hydroxyphenyl)calix[4]resorcinarenes (**1a–b**) as core matrices.

The calix[4]resorcinarenes (**1a–b**) were prepared by reactions of resorcinol with benzaldehyde or 4-hydroxybenzaldehyde, respectively, according to the published literature.[8] They were fully alkylated firstly with the ethyl bromoacetate in K_2CO_3/acetone system to afford active ester derivatives (**2a–b**).[9] It must be noted that the hydroxyl groups in *p*-hydroxyphenyl substituents of (**2b**) were also alkylated in this step. So there are eight active ester groups in (**2a**) and 12 ester groups in (**2b**). The ester groups in (**2a–b**) could be easily converted to amide groups by amidanation reaction with organic amines.[10,11] Thus refluxing (**2a–b**) with a large excess of ethylenediamine or 1,4-diaminobutane in a mixture of ethanol and toluene (v/v, 1:1) gave the corresponding first-generation amide dendrimers (**3a–4b**) with free terminal amino groups in excellent yield (92–99%). Use of a large excess molar ratio of diamine in the reaction greatly diminish other kinds of diamidation products. It should be pointed out that (**3a–b**) have very poor solubility in most organic solvents and **4a–b** are more soluble in alcohol. In the IR spectrum of amides (**3–4**), the absorption band of C=O appears at 1675cm^{-1}, while the band of the C=O in the ester derivatives (**2a–b**) appears at 1750cm^{-1}, which indicates that all ethyl ester groups are transformed into amide groups. The absorption of NH_2 or NH was observed as a broad peak at about 3400cm^{-1}.

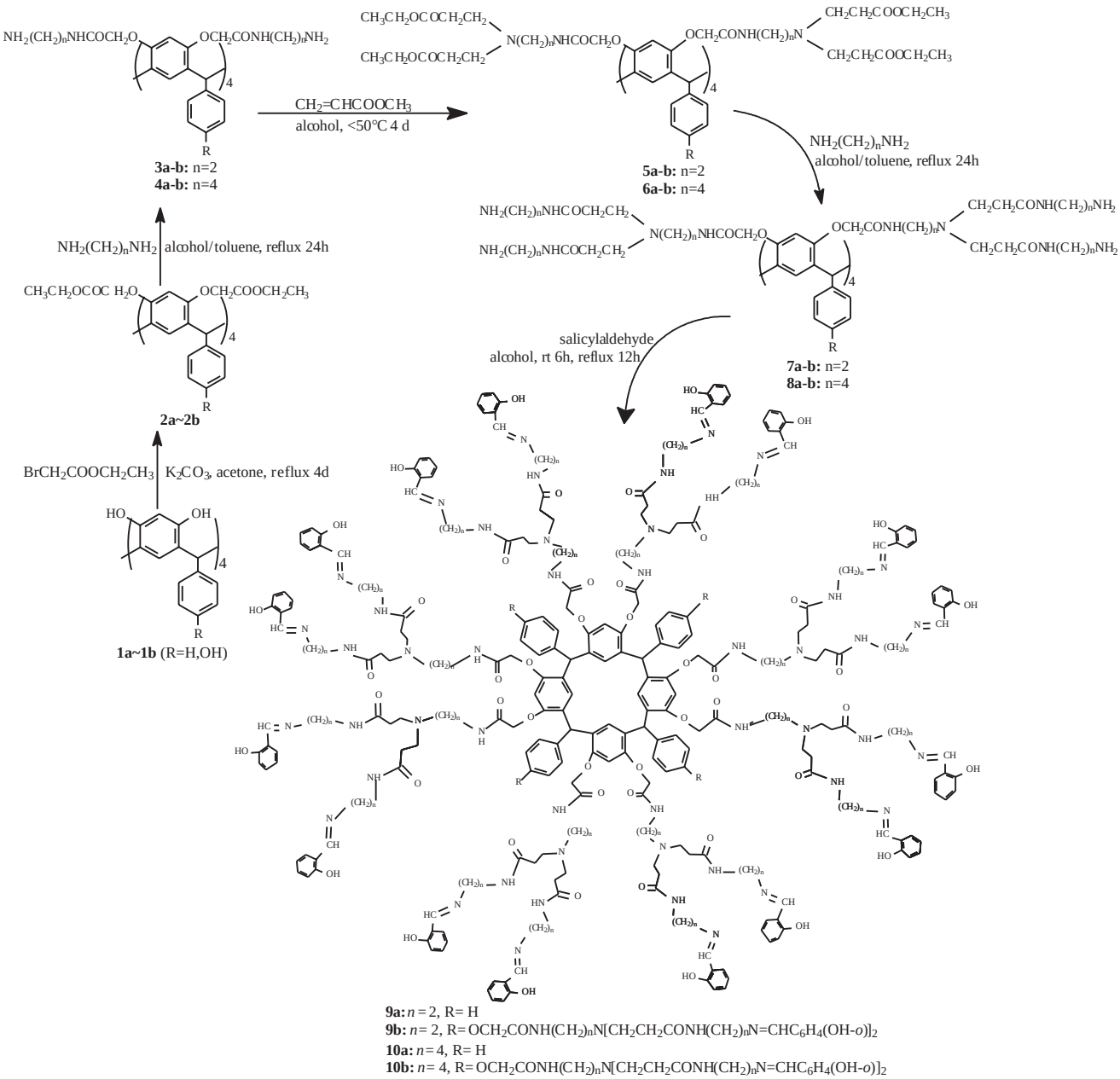
According to Tomalia's synthetic method for PAMAM,[12,13] the second round was constructed by treating these amides (**3a–4b**) with methyl acrylate in alcohol at 45–50°C for at least 4 days to ensure a complete addition reaction. In this step the amino groups in (**3–4**) smoothly added methyl acrylate to yield the corresponding branched methyl esters (**5a–6b**) (79–84%), which were consequently treated with the diamine, as mentioned above to transform them into the second-generation amide dendrimers with free terminal amino groups (**7a–8b**). Similarly, the absorption of C=O at 1689cm^{-1} and those of NH_2 or NH at about 3400cm^{-1} can be observed in their IR spectrum. The second-generation amide dendrimers (**7a–8b**) reacted smoothly with salicylaldehyde in hot ethanol to give the expected Schiff base derivatives (**9–10**) in moderate yields (49–64%). All the products (**9–10**) are solids with a sharp melting point range and are very soluble in common organic solvents. In their UV-vis spectrum, the new C=N group has λ_{max} in $CHCl_3$ at about 317–320nm. In the IR spectrum the C=O group amide shows a very strong absorption at 1675cm^{-1}, while the C=N group of imines shows a strong peak at 1633cm^{-1}. In their ^{1}H NMR the expected ratios of hydrogen atoms for each characteristic unit were observed by comparison of the integral intensity of their signals, [*e.g.* in (**10b**) the ratio of $\delta_{Ar\text{-}OH}(13.6ppm):\delta_{CH=N}(8.3ppm):\delta_{NH}(7.2ppm):\delta_{Ar\text{-}CH\text{-}Ar}(5.6ppm):\delta_{OCH2}(4.3–4.4ppm)$. = 6:6:9:1:6], which confirms the symmetry, the completeness of conversions, and the appropriate formation of dendrimers with low statistical defects. The molecular weight of second-generation dendrimers reached 6040 for (**9b**) and 7960 for (**10b**) respectively. Unfortunately attempts to get suitable single crystals for X-ray analysis have failed until now. Other kinds of dendrimers such as polyimine dendrimers with chiroptical properties[14] and polyamine dendrimers complexing three cobalt centres,[15] were reported before. In conclusion, calix[4]resorcinarenes especially with additional active sites in outer side groups such as (**1b**) are suitable as core molecules for rapid synthesis of highly functional dendrimers with larger molecular weights.

Experimental

Melting points were taken on a hot-plate microscope apparatus and are not corrected. IR spectra were obtained on a Nicolet FT-IR 740 spectrometer (KBr disc). ^{1}H NMR spectra were recorded with a Bruker AV-600 spectrophotometer at 500 MHz with $CDCl_3$, as solvent and TMS as internal Standard. Ethyl bromoacetate, ethylenediamine, 1,4-diaminobutane are commercial chemical reagents and used as received. Solvents (acetone, alcohol and ether) were purified by standard techniques. Calix[4]resorcinarenes (**1a–b**) were prepared from the reaction of resorcinol with benzaldehyde or *p*-hydrobenzadehyde according to the published method.[6] TLC monitored the reaction process.

General procedure for the synthesis of ester derivatives (**2a–b**): A suspension of (**1a**) (2.376g, 3mmol) or (**1b**) (2.568g, 3mmol) and anhydrous potassium carbonate(8.28g, 60mmol) in dry acetone (60ml) was heated to reflux under dinitrogen for at least 0.5 h. Then the mixture was cooled to room temperature and ethyl

* Correspondence. E-mail: cgyan@yzu.edu.cn



9a: *n* = 2, R= H
9b: *n*= 2, R= $OCH_2CONH(CH_2)_nN[CH_2CH_2CONH(CH_2)_nN{=}CHC_6H_4(OH\text{-}o)]_2$
10a: *n* = 4, R= H
10b: *n*= 4, R= $OCH_2CONH(CH_2)_nN[CH_2CH_2CONH(CH_2)_nN{=}CHC_6H_4(OH\text{-}o)]_2$

Scheme 1

bromoacetate (5.3ml, 50mmol for (**1a**) or 8.48ml, 80mmol for (**1b**) was added. The reaction mixture was refluxed for 4 days. After removal of acetone, the residue was dissolved in water and acidified with hydrochloric acid, then extracted with $CHCl_3$. The yellow organic layers were separated and dried with $MgSO_4$. Evaporation of the solvent yielded a red oil which was crystallised from alcohol to give yellow crude products which were recrystallised from alcohol to obtain pure product as white crystals.

(**2a**) (R=H)**:** white crystals. Yield: 58.1% (2.58g). m.p: 143–144°C (alcohol). IR (KBr) [cm^{-1}]: μ= 2985, 2936, 1760, 1732, 1612, 1584, 1548, 1499, 1450, 1408, 1379, 1295, 1203, 1154, 1119, 1084, 1069, 929, 858, 809, 703. ^{1}HNMR($CDCl_3$,ppm): 6.2–6.9 (m, 28H, ArH); 5.9 (s, 4H, CH); 4.3 (m, 16H, OCH_2); 4.1–4.2 (m, 16H, CH_2); 1.2–1.3 (m, 24H, CH_3).

(**2b**) (R=$OCH_2CO_2CH_2CH_3$)**:** white crystals. Yield: 56.5% (3.21g). m.p: 151–153°C (alcohol). IR (KBr) [cm^{-1}]: μ= 2985, 2936, 1760, 1732, 1612, 1584, 1548, 1513, 1443, 1408, 1379, 1309, 1203, 1161, 1112, 1076, 1027, 929, 858, 823, 731. ^{1}H NMR($CDCl_3$,ppm): 6.2–6.6 (m, 24H, ArH); 5.9 (s, 4H, CH); 4.3–4.4, 4.5 (m, 24H, OCH_2); 4.1–4.3, 4.6 (m, 24H, CH_2); 1.2–1.3 (m, 36H, CH_3).

General procedure for the synthesis of second-generation amide derivatives (7a–b) and (8a–b)

A mixture of ester-containing derivatives (**2a–b**) (1.0mmol) and diamine (ethylenediamine or 1,4-diaminobutane) (25.0ml) in ethanol (15ml) and toluene (15ml) was refluxed for 24 h under an atmosphere of dinitrogen, during in which time a precipitate was formed for the reaction of (**2a–b**) with ethylenediamine. For the reaction of (**2a–b**) with 1,4-diaminobutane, a yellow solution was retained throughout. After the esters (**2a–b**) disappeared (TLC analysis), the organic solvent and excess of diamine were removed *in vacuo*. The residue was thoroughly washed with alcohol for (**3a–b**) or crystallised from alcohol/ether for (**4a–b**) to give the amide products. Then the suspension of derivatives (**3–4**) (0.5mmol) and methyl acrylate (15ml) in alcohol (15ml) was stirred at no more than 50°C for at least 4 days under an atmosphere of dinitrogen. The organic solvent and excess of methyl acrylate were removed *in vacuo*. The residue was crystallised from alcohol/ether twice to give the ester products(**5–6**). A mixture of second-generation ester derivatives (**5–6**) (0.5mmol) and diamine (ethylenediamine or 1,4-diaminobutane) (25.0ml) in ethanol (15ml) and toluene (15ml) was refluxed for 24 h under an atmosphere of dinitrogen. After the esters (**5–6**) disappeared (TLC analysis), the organic solvent and excess of diamine were removed *in*

vacuo. The residue was crystallised from alcohol/ether twice to give the amide products.

(**7a**) (*n*=2, R=H)**:** white solid. Yield: 80.8% (1.38g). m.p: 250°C (decomp.). IR (KBr) [cm^{-1}]: μ= 3387, 3063, 2929, 2865, 1675, 1572, 1527, 1492, 1436, 1238, 1097, 1048, 929, 760.

(**7b**) (*n*=2, R=$OCH_2CONH(CH_2)_2N[CH_2CH_2CONH(CH_2)_2NH_2]_2$)**:** white solid. Yield: 88.5% (2.12g). m.p: 232°C (decomp.). IR (KBr) [cm^{-1}]: μ= 3394, 3060, 2929, 2865, 1661, 1584, 1548, 1499, 1443, 1238, 1196, 1105, 1055, 929, 759.

(**8a**) (*n*=4, R=H)**:** white solid. Yield: 74.5% (1.44g). m.p: 220°C (decomp.) (alcohol-ether). IR (KBr) [cm^{-1}]: μ= 3394, 3056, 2929, 2859, 1675, 1584, 1534, 1499, 1302, 1105,929, 710.

(**8b**) (*n*=4, R=$OCH_2CONH(CH_2)_2N[CH_2CH_2CONH(CH_2)_2NH_2]_2$)**:** white solid. Yield: 92.6% (2.53g). m.p: 202°C (decomp.) (alcohol-ether). IR (KBr) [cm^{-1}]: μ= 3394, 3063, 2929, 2856, 1675, 1534, 1499, 1302, 1105, 929, 731.

General procedure for the synthesis of schiff base derivatives (9a–b) and (10a–b)

The suspension of (**7a–b**)**,** (**8a–b**) (0.2mmol) in 30ml of alcohol was added salicylaldehyde (0.21mole for each NH_2 group)) at room temperature. This reaction mixture was allowed to stir at room temperature for 6 h, and then heated to reflux for about 12h under a dinitrogen atmosphere. A brown-yellow suspension was observed. After removal of alcohol under a reduced pressure, the residue was washed with ether. Crystallised by alcohol gave pure materials (**9a-b**) and alcohol-ether gave pure materials (**10a–b**).

(**9a**) (*n*=2, R=H)**:** yellow solid. Yield: 50.6% (0.43g). m.p: 190–192°C. UV-vis ($\lambda_{max}(CHCl_3)$): 320.4, 283.6, 257.2 nm. IR (KBr) [cm^{-1}]: μ=3400, 1689, 1633, 1572, 1534, 1499, 1281, 1196, 1105, 1055, 929, 759. ^{1}HNMR ($CDCl_3$) [ppm]: δ=13.2 (s, 16H, OH); 8.3 (s, 16H, CH=N); 7.25 (m, 24H, NH); 6.0–7.0 (m, 92H, ArH); 5.7 (s, 4H, CH); 4.3 (br, s, 16H, OCH_2); 3.8 (m, 32H, $C=NCH_2$); 2.8–2.9 (m, 128H, NCH_2).

(**9b**) (*n*=2, R=$OCH_2CONH(CH_2)_2N[CH_2CH_2CONH(CH_2)_2N=CHC_6H_4$(*o*-OH)$]_2$)**:** yellow solid. Yield: 49.7% (0.60g). m.p: 165–168°C. UV-vis ($\lambda_{max}(CHCl_3)$): 318.2, 290.2, 258.6 nm. IR (KBr) [cm^{-1}]: μ= 3403, 1675, 1633, 1584, 1499, 1281, 1196, 1105, 1055, 929, 759. ^{1}HNMR ($CDCl_3$) [ppm]: δ=13.2 (s, 24H, OH); 8.3 (s, 24H, CH=N); 7.25 (m, 36H, NH); 6.0–7.0 (m, 120H, ArH); 5.7 (s, 4H, CH); 4.3 (br, s, 24H, OCH_2); 3.8 (m, 48H, $C=NCH_2$); 2.8–2.9 (m, 192H, NCH_2).

(**10a**) (*n*=4, R=H)**:** yellow solid. Yield: 64.2% (0.71g). m.p: 138–140°C (alcohol-ether). UV-vis ($\lambda_{max}(CHCl_3)$): 317.0, 285.0, 255.0 nm. IR (KBr) [cm^{-1}]: μ=3401, 3056, 2929, 2859, 1689, 1633, 1584, 1534, 1499, 1442, 1281, 1203, 1105, 1055, 935, 851, 759, 583. ^{1}HNMR ($CDCl_3$) [ppm]: δ=13.6 (s, 16H, OH); 8.3 (s, 16H, CH=N); 7.2 (m, 24H, NH); 6.6–7.5 (m, 92H, ArH); 5.6 (s, 4H, CH); 4.3–4.4 (br, s, 16H, OCH_2); 3.5–3.7 (m, 32H, $C=NCH_2$); 2.1 (m, 96H, NCH_2); 1.25–1.28 (m, 128H, CH_2).

(**10b**) (*n*=4,R=$OCH_2CONH(CH_2)_4N[CH_2CH_2CONH(CH_2)_4N=CHC_6H_4$(*o*-OH)$]_2$)**:** yellow solid. Yield: 62.2% (0.99g). m.p: 133–135°C (alcohol-ether). UV-vis ($\lambda_{max}(CHCl_3)$): 317.0, 284.5, 254.5 nm. IR (KBr) [cm^{-1}]: μ=3401, 3063, 2929, 2859, 1682, 1633, 1534, 1499, 1443, 1281, 1203, 1105, 1055, 935, 851, 759, 569. ^{1}HNMR ($CDCl_3$) [ppm]: δ= 13.6 (s, 24H, OH); 8.3 (s, 24H, CH=N); 7.2 (m, 36H, NH); 6.6–7.5 (m, 120H, ArH); 5.6 (s, 4H, CH); 4.3–4.4 (br, s, 24H, OCH_2); 3.5–3.7 (m, 48H, $C=NCH_2$); 2.1 (m, 144H, NCH_2); 1.25–1.28 (m, 192H, CH_2).

Received 30 December 2003; accepted 22 March 2004
Paper 03/2272

References

1 G.R. Newkome, Y.F. Hu and M.J. Saunders, *Tetrahedron. Lett.*, 1991, **32**, 1133.
2 C.B. Gorman and J.C. Smith, *Acc. Chem. Res.*, 2001, **34**, 60.
3 O. Haba, K. Haga and M. Ueda, *Chem. Mater.*, 1999, **11**, 427.
4 Y. Yamakawa, M. Ueda and R. Nagahata, *et al., J. Chem. Soc., Perkin Trans. 1*, 1998, 4135.
5 D. Eisler, W. Hong and M.C. Jennings, *et al., Organometallics*, 2002, **21**, 3955.
6 E.C. Wiener, M.W. Brechbiel and H. Brothers, *et al., Magn. Reson. Med.*, 1994, **31**, 1.
7 T. Nagasaki, S. Tamagaki and K. Ogino, *Chem. Lett.*, 1997, 717.
8 L.M. Tunstad, J.A. Tucker and E. Dalcanale, *et al., J. Org. Chem.*, 1989, **54**, 1305.
9 B.M. Vuano and O.I. Pieroni, *An. Asoc. Quim. Argent.* 1998, **86**(1-2): 69. (CA 129: 260214b)
10 R. Abidi, I. Oueslati and H. Amri, *et al., Tetrahedron Lett.*, 2001, **42**, 1685.
11 I. Oueslati, R. Abidi and P. Thuéry, *et al., Tetrahedron Lett.*, 2001, **41**, 8263.
12 D.A. Tomalia, H. Baker and J. Dewald, *et al., Polym. J.*, 1985, **17**, 117.
13 D.A. Tomalia, H. Baker and J. Dewald, *et al., Macromolecules*, 1986, **19**, 2466.
14 J. Issberner, M. Bohme and S. Grimme, *et al., Tetrahedron: Asymmetry*, 1996, **7**(8), 2223.
15 R. Moors and F. Vogtle, *Chem. Ber.*, 1993, **126**, 2133.