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Linear and Pre-organized Carboxylic Acid Picket Porphyrins as Bismuth Chelators

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New picket porphyrins delivering at least one carboxylic group around the coordination site of the macrocycle were synthesized for bismuth coordination. The influence of the number, the length, and the pre-organization of the carboxylic acid pickets on the stability of the bismuth complexes was explored. Their stabilities in acidic medium were compared with those of their precursors bearing ester pickets. The molecular structure of one of the bismuth complexes, which is the only monomeric bismuth porphyrin reported up to now, is discussed. At the opposite of what we initially reported, and in agreement with the theoretical calculations, the distortion of the macrocycle in this structure is mainly due to the number of water molecules in the first sphere of coordination of the bismuth.

Introduction

Whereas the medical application of bismuth salts has been known for a long time, the coordination chemistry of this element remains poorly investigated. For instance, although both Bi(III) and Bi(V) are the two common oxidation states of bismuth, the chemistry of Bi(III) has been largely more developed and has led to the synthesis of numerous complexes with coordination numbers varying from 3 to 10.[1] The affinity of bismuth with nitrogen and oxygen atoms makes this element a good candidate for complexation with chelators and macrocycles, such as [(2-{[2-(bis-carboxymethyl-amino)-ethyl]-carboxymethyl-amino}-ethyl)-carboxymethyl-amino]-acetic acid (DTPA) and (4,7,10-tris-carboxymethyl-1,4,7,10-tetraaza-cyclododec-1-yl)-acetic acid (DOTA).[2] In the latter macrocycle carboxylate pickets, Bi(III) is found to be eight-coordinated in a distorted square antiprismatic geometry[3] with an identifiable influence of the stereochemically active pair[4] on the coordination chemistry, as also observed for bismuth complexes of scorpionate ligands.[5] In the former acyclic chelate, Bi(III) displays a coordination number of 10, resulting in a bicapped square-antiprismatic geometry. However, while the bismuth chelates of DOTA are inert, the kinetics of complex formation are too slow to be applied *in vivo* for radioimmunotherapy.[6] As a result, for this specific application with short half-life radiobismuth, the kinetics of metal insertion, which is usually insignificant, becomes of paramount importance.

Until the early eighties, few reports relative to the complexation of bismuth into porphyrins were published, presumably because of their instability.[7] However, during

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the past decade, various studies led to a better understanding of the coordination of bismuth in porphyrins, either in organic or aqueous medium.[8−11] We ourselves have investigated the potential of picket porphyrins as bismuth chelators, targeting both a better knowledge of the coordination of bismuth and also the preparation of bifunctional linkers ready to be connected to biological proteins, such as monoclonal antibodies.[12] Indeed, two alpha-emitter bismuth isotopes, ^{212}Bi and ^{213}Bi, are of particular interest in cancer therapy.[13] But for such an application, the resulting complex must be stable *in vivo* (kinetic inertness)[14] and be rapidly synthesized as the half-lives of the alpha-emitter isotopes of bismuth do not exceed 60 min. In two previous papers,[15,16] we reported the structure of a four-ester picket bismuth porphyrin and the influence of the number of ester pickets on the kinetics of bismuth insertion. In a third publication,[17] we discovered that a single carboxylic acid picket bismuth porphyrin led to the first mononuclear X-ray structure of a porphyrinic bismuth complex. In this structure, the aromatic macrocycle was significantly distorted and we attributed this distortion to the shortness of the arm bent over the porphyrin. Additionally, we reasonably proposed that the analogous complex bearing a longer arm, by releasing this distortion, should be more stable. Therefore, we report herein our investigations about the kinetics of metalation and the relative stability in acidic medium of various bismuth complexes of porphyrins bearing at least one carboxylic acid picket. In comparison with ester picket porphyrins, this relative stability is shown to be more important for most of the acid picket complexes. We also describe that neither a longer picket nor too much pre-organization leads to more stable complexes and that the computational studies show that the previously reported distortion is not related to the length of the arm delivering the counteranion to the bismuth inside the porphyrin.

Experimental Procedures

General Considerations. ^{1}H (500.13 MHz) and ^{13}C (125.30 MHz) NMR spectra were recorded on Bruker Avance spectrometers and referenced to the residual protonated solvent. Mass spectrometry was performed on a MS/MS ZABSpec TOF spectrometer at the University of Rennes I (C.R.M.P.O.). UV−visible spectra were recorded on an Uvikon XL spectrometer. Infrared spectra were recorded on Bruker IFS 66 and 28 spectrometers. All solvents (ACS for analysis) were purchased from Carlo Erba. Tetrahydrofuran (THF) was distilled over potassium metal, whereas methanol was distilled over magnesium turnings. CH_2Cl_2 was used as received. Triethylamine was distilled over CaH_2. The starting materials were generally used as received (Acros, Aldrich) without any further purification. All reactions were performed under an argon atmosphere and monitored by thin-layer chromatography (TLC, silica, CH_2Cl_2/MeOH). Column flash chromatography was performed on silica gel (Merck TLC-Kieselgel 60H, 15 μm). Elemental analyses were obtained on an EA 1108 Fisons instrument.

Bismuth Decomplexation Experiments. A bismuth porphyrin solution (100 mL, 10 μmol L $^{-1}$) in dichloromethane was introduced into a 120 mL tonometer, and the first measurement (t_0) was then recorded. Then 2500 equiv of trifluoroacetyl (TFA, 240 μmol, 3.2 μL) was added, and the mixture was stirred vigorously. The second measurement was recorded at $t_1 = 2$ min, and one measurement was recorded every 20 min. In all the cases, equilibrium was reached after 1 h (Figure 3).

Typical Saponification Procedure. For instance, in the transformation of **8** to **4**, compound **8** (0.1 g, 0.08 mmol) was dissolved in THF (20 mL). KOH (0.5 g, 8.9 mmol) in ethyl alcohol (5 mL) was added, and the mixture was heated to 50 °C. After 4 h, the reaction mixture was cooled to room temperature, and ether was added until precipitation. The obtained precipitate was filtered and washed with dichloromethane. The resulting solid was dissolved in water. Then HCl (6 M) was added dropwise until porphyrin precipitation. The resulting precipitate was filtered and washed with water. The product was obtained in quantitative yields.

***N*-{2-[α-10,15,20-Tris-(2-acetylamino-phenyl)-porphyrin-α-5-yl]-phenyl}-succinamic Acid (1).** ESI-HRMS: calcd m/*z* = 939.3020 $[M + K]^+$ for $C_{54}H_{44}KN_8O_6Na$, found 939.3017. FTIR (KBr, cm^{-1}): 1710 $(C{=}O)_{acid}$, 1670 $(C{=}O)_{amide}$. UV−vis (MeOH/pyridine, 6%) λ_{max}/nm (log ϵ, dm^3 mol^{-1} cm^{-1}): 418 (362.3), 514 (16.7), 547 (4.7), 588 (4.4), 643 (1.5). ^{1}H NMR ($CDCl_3$, 298 K, 300 MHz): δ_H 11.85 (1H, s, COOH), 8.81 (2H, br s, NHCO), 8.78 (2H, br s, NHCO), 8.70 (8H, s, βpyr), 8.14 (4H, d, $J = 7.5$ Hz, aro), 8.10 (2H, d, $J = 7.5$ Hz, aro), 7.94 (4H, d, $J = 7.0$ Hz, aro), 7.83 (4H, t, $J = 8.0$ Hz, aro), 7.57 (4H, t, $J = 6.5$ Hz, aro), 1.99 (2H, t, $J = 5.0$ Hz, CH_2CH_2), 1.64 (2H, br s, CH_2CH_2), 1.24 (3H, s, CH_3), 1.22 (6H, s, CH_3), −2.72 (2H, s, NHpyr). ^{13}C NMR ($CDCl_3$, 298 K, 75 MHz): δ_C 136.4, 136.1, 129.4, 125.5, 124.7, 124.2, 40.0, 31.3, 29.7, 23.2. Microanalysis ($C_{54}H_{44}N_8O_6{\cdot}CH_3OH{\cdot}H_2O$): found (calc), C, 69.58 (69.46); H, 4.87 (5.30); N, 11.42 (11.78).

4-{2-[α-10,15,20-Tris-(2-acetylamino-phenyl)-porphyrin-α-5-yl]-phenylcarbamoyl}-butyric Acid (5). FAB-HRMS: calcd *m*/*z* = 937.4438 $[M + Na]^+$ for $C_{55}H_{46}N_8O_6Na$, found 937.3437. FTIR (KBr, cm^{-1}): 1709 $(C{=}O)_{acid}$, 1669 $(C{=}O)_{amide}$. UV−vis (CH_2Cl_2) λ_{max}/nm (log ϵ, dm^3 mol^{-1} cm^{-1}): 418 (134.9), 512 (7.1), 546 (1.6), 586 (2.2), 643 (0.5). ^{1}H NMR (DMSO-d_6, 298 K, 500 MHz): δ_H 11.43 (1H, br s, CO_2H), 8.83 (1H, br s, NHCO), 8.78 (1H, br s, NHCO), 8.74 (2H, br s, NHCO), 8.69 (8H, br s, βpyr), 8.12 (4H, d, $J = 7.2$ Hz, aro), 7.94 (4H, d, $J = 6.9$ Hz, aro), 7.82 (4H, t, $J = 7.2$ Hz, aro), 7.57 (4H, br s, aro), 1.42 (4H, br s, CH_2), 1.22 (9H, br s, CH_3), 1.09 (2H, br s, CH_2), −2.72 (2H, s, NHpyr). ^{13}C NMR (DMSO-d_6, 298 K, 125 MHz): δ_C 168.7, 138.6, 136.6, 129.4, 125.3, 124.2, 34.9, 32.4, 20.3.

2-*trans*-{2-[α-10,15,20-Tris-(2-acetylamino-phenyl)-porphyrin-α-5-yl]-phenylcarbamoyl}-cyclohexanecarboxylic Acid (6). In a 50 mL flask, 40 mg (0.05 mmol) of TriAcTAPP was dissolved in 5 mL of acetic acid. Then 9.2 mg (0.06 mmol) of *trans*-1,2-

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cyclohexanedicarboxylic anhydride was added. The reaction was stirred at room temperature. After 3 h, diethylic ether was added until precipitation. The obtained precipitate was filtered and washed with ether. The resulting solid was dissolved in a minimum volume of $CHCl_3$ to be poured on a silica gel chromatography column. The product was eluted with a acetic acid/CH_3OH/CH_3Cl (0.5/0.7/98.8) mixture and obtained in 74% yield (36 mg, 0.037 mmol). ESI-HRMS: calcd m/z = 977.3751 $[M + Na]^+$ for $C_{58}H_{44}N_8O_6Na$, found 977.3766. FTIR (KBr, cm^{-1}): 1702 $(C{=}O)_{acid}$, 1667 $(C{=}O)_{amide}$. UV−vis (CH_2Cl_2) λ_{max}/nm (log ϵ, $dm^3\ mol^{-1}\ cm^{-1}$): 419 (204.7), 513 (7.9), 546 (2.1), 586 (2.6), 644 (1.2). ^1H NMR (DMSO-d_6, 323 K, 500 MHz): δ_H 11.94 (1H, br s, CO_2H), 8.83 (3H, s, NHCO), 8.78 (1H, s, NHCO), 8.76−8.62 (8H, m, βpyr), 8.12 (4H, br s, aro), 7.93 (3H, d, J = 7.0 Hz, aro), 7.88 (1H, d, J = 7.5 Hz, aro), 7.82 (4H, m, aro), 7.57 (3H, t, J = 7.5 Hz, aro), 7.51 (1H, t, J = 7.5 Hz, aro), 2.17 (1H, br s, cyclohexyl), 1.72 (1H, br s, cyclohexyl), 1.62 (1H, br s, cyclohexyl), 1.33−1.12 (9H, m, CH_3), 0.94 (1H, br s, cyclohexyl), 0.89−0.75 (2H, m, cyclohexyl), 0.64 (3H, br s, cyclohexyl), 0.30 (1H, br s, cyclohexyl), −2.73 (2H, s, NHpyr). ^{13}C NMR (DMSO-d_6, 300 K, 126 MHz): δ_C 172.5, 171.5, 168.8, 136.6, 129.4, 125.4, 124.3, 74.0, 40.3, 29.5, 21.4, 23.2, 21.5.

***N*-{2-[α-10,15,20-Tris-(2-acetylamino-phenyl)-porphyrin-α-5-yl]-phenyl}-phthalamic Acid (7).** In a 50 mL flask, 50 mg (0.06 mmol) of TriAcTAPP and 6.7 mg (0.06 mmol) of aluminum oxide were dissolved in 10 mL of CH_2Cl_2. Then 9.8 mg (0.066 mmol) of phthalic anhydride was added. The reaction was stirred at room temperature. After 3 h, the solvent was evaporated to dryness and the residue dissolved in a minimum volume of $CHCl_3$ to be poured on a silica gel chromatography column. The product was eluted with a acetic acid/CH_3OH/CH_3Cl (0.5/0.7/98.8) mixture and obtained in 83% yield (49 mg, 0.052 mmol). ESI-HRMS: calcd m/z = 949.3462 $[M + H]^+$ for $C_{58}H_{45}N_8O_6$, found 949.3466. FTIR (KBr, cm^{-1}): 1702 $(C{=}O)_{acid}$, 1667 $(C{=}O)_{amide}$. UV−vis (CH_2Cl_2) λ_{max}/nm (log ϵ, $dm^3\ mol^{-1}\ cm^{-1}$): 419 (223.4), 512 (8.1), 544 (2.2), 585 (2.8), 644 (1.5). ^1H NMR (DMSO-d_6, 323 K, 500 MHz): δ_H 9.31 (1H, br s, CO_2H), 8.89 (2H, d, J = 4.5 Hz, βpyr), 8.82 (2H, d, J = 4.5 Hz, βpyr), 8.69 (4H, s, βpyr), 8.64 (1H, br s, NHCO), 8.60 (1H, br s, NHCO), 8.27 (1H, br s, aro), 8.17−8.12 (3H, m, aro), 7.95−7.91 (6H, m, 2HNCO + 4aro), 7.83 (3H, t, J = 7.5 Hz, aro), 7.84−7.53 (5H, m, aro), 7.18 (1H, d, J = 8.5 Hz, phthal), 6.98 (1H, t, J = 7.5 Hz, phthal), 6.72 (1H, br s, phthal), 6.17 (1H, br s, phthal), 1.27 (3H, s, CH_3), 1.21 (6H, s, CH_3), −2.73 (2H, s, NHpyr). ^{13}C NMR (DMSO-d_6, 323 K, 126 MHz): δ_C 172.3, 169.2, 168.5, 139.0, 136.3, 131.4, 130.8, 129.4, 126.2, 125.6, 125.3, 124.2, 23.3.

***N*-{2-Bismuth(III) Nitrate-[α-10,15,20-tris-(2-acetylamino-phenyl)-porphyrin-α-5-yl]-phenyl}-succinamic Acid (1Bi).** In a 50 mL flask, 11.1 mg (0,01 mmol) of **1** was dissolved in 5 mL of pyridine. Then 5.3 mg (0.01 mmol) of $Bi(NO_3)_3{\cdot}5H_2O$ was added. The reaction was stirred at room temperature. After 10 min, the solvent was evaporated, and the residue was dissolved in CH_2Cl_2 and then filtered. The solution was concentrated to dryness and dissolved in a minimum volume of CH_2Cl_2, to which pentane was added. This allowed the precipitation of the product that was filtered. The product was then washed with more pentane and finally dried under vacuum overnight. Product **1Bi** was obtained in 90% yield. ESI-HRMS: calcd m/z = 1129.2863 $[M - NO_3 - H + Na]^+$ for $C_{54}H_{41}BiN_8O_6Na$, found 1129.2850. FTIR (KBr, cm^{-1}): 1670 (CO), 990 (Bi−Np). UV−vis (CH_2Cl_2) λ_{max}/nm (log ϵ, $dm^3\ mol^{-1}\ cm^{-1}$): 350 (4.8), 472 (13.5), 598 (1.7), 646 (1.5). ^1H NMR (DMSO-d_6, 300 K, 500 MHz): δ_H 9.03 (2H, d, J = 4.5 Hz, βpyr), 9.03 (2H, d, J = 4.5 Hz, βpyr), 8.99 (6H, d, J = 8 Hz, pyr), 8.97 (2H, d, J = 5 Hz, βpyr), 8.89 (2H, d, J = 5 Hz, βpyr), 8.72 (4H, br s, aro), 8.55 (3H, t, J = 7 Hz, pyr), 8.33 (1H, br s, aro), 8.33−8.26 (2H, m, aro), 8.07 (1H, t, J = 6.6 Hz, aro), 7.99 (6H, t, J = 7.8 Hz, pyr), 7.90 (3H, m, aro), 7.73 (1H, br s, aro), 7.45 (4H, br s, NHCO), 7.36 (2H, t, J = 7 Hz, aro), 7.16 (2H, m, aro), 1.87 (2H, br s, CH_2CH_2), 1.63 (2H, br s, CH_2CH_2), 1.49 (9H, s, CH_3). ^{13}C NMR (DMSO-d_6, 300 K, 125 MHz): δ_C 172.5, 149.9, 135.9, 134.3, 132.7, 132.1, 131.9, 129.3, 123.9, 122.2, 121.8, 31.3, 29.7, 23.2.

***N*-(2-Bismuth(III) Nitrate-{α-10,15,20-tris-[2-(3-carboxy-propionylamino)-phenyl]-porphyrin-α-5-yl}-phenyl)-succinamic Acid (4Bi).** The same experimental procedure used for compound **1Bi** was applied to porphyrin **4**. The product was obtained in 92% yield. FAB-MS: m/z = 1281.7 $[M - NO_3]^+$. FTIR (KBr, cm^{-1}): 1384 (NO_3), 990 (Bi−Np). UV−vis (CH_2Cl_2/pyridine, 1/1) λ_{max}/nm (%): 351 (31), 471 (100), 596 (8), 644 (7). ^1H NMR (pyridine-d_5, 300 K, 500 MHz): δ_H 8.98 (8H, s, βpyr), 8.81 (20H, d, J = 4.7 Hz, pyr), 8.67 (4H, d, J = 8.2 Hz, aro), 8.62 (4H, s, NHCO), 8.31 (10H, t, J = 7.8 Hz, pyr), 7.96 (4H, d, J = 6.5 Hz, aro), 7.83 (24H, t, J = 6.1 Hz, aro, pyr), 7.50 (4H, t, J = 7.0 Hz, aro), 2.05 (8H, br s, CH_2), 1.77 (8H, br s, CH_2). ^{13}C NMR (pyridine-d_5, 300 K, 125 MHz): δ_C 175.4, 171.5, 149.7, 146.1, 142.9, 141.2, 134.9, 133.0, 131.5, 130.2, 126.7, 123.1, 121.8, 118.9, 31.5.

4-{2-Bismuth(III) Nitrate-[α-10,15,20-tris-(2-acetylamino-phenyl)-porphyrin-α-5-yl]-phenylcarbamoyl}-butyric Acid (5Bi). The same experimental procedure used for compound **1Bi** was applied to porphyrin **5**. Product **5Bi** was obtained in 90% yield. FAB-HRMS: calcd m/z = 1143.3007 $[M - H - NO_3 + Na]^+$ for $C_{55}H_{43}BiN_8O_6Na$, found 1143.3005. FTIR (KBr, cm^{-1}): 1384 (NO_3), 895 ρ(Bi−Np). UV−vis (CH_2Cl_2) λ_{max}/nm (log ϵ, $dm^3\ mol^{-1}\ cm^{-1}$): 351 (253.3), 472 (72.3), 600 (5.0), 646 (4.2). ^1H NMR (DMSO-d_6, 298 K, 500 MHz): δ_H 8.95 (8H, br s, βpyr), 8.68 (4H, br s, aro), 8.43 (1H, bs s, NHCO), 8.40 (3H, bs s, NHCO), 7.92 (4H, d, J = 7.5 Hz, aro), 7.86 (4H, t, J = 7.5 Hz, aro), 7.52 (4H, t, J = 8.0 Hz, aro), 1.87 (2H, t, J = 7.0 Hz, CH_2), 1.70 (2H, br s, CH_2), 1.44 (11H, br s, $1CH_2 + 3CH_3$). ^{13}C NMR (DMSO-d_6, 298 K, 125 MHz): δ_C 175.4, 174.6, 165.3, 149.2, 146.2, 135.3, 130.1, 122.9, 121.8, 34.9, 33.0, 24.1, 20.3.

2-{2-Bismuth(III) Nitrate-[α-10,15,20-tris-(2-acetylamino-phenyl)-porphyrin-α-5-yl]-phenylcarbamoyl}-cyclohexanecarboxylic Acid (6Bi). The same experimental procedure used for compound **1Bi** was applied to porphyrin **6**. Product **6Bi** was obtained in 92% yield. ESI-HRMS: calcd m/z = 1183.3320 $[M - NO_3 - H + Na]^+$ for $C_{58}H_{47}BiN_8O_6Na$, found 1183.3320. FTIR (KBr, cm^{-1}): 1672 (CO), 988 (Bi−Np). UV−vis (CH_2Cl_2) λ_{max}/nm (log ϵ, $dm^3\ mol^{-1}\ cm^{-1}$): 350 (5.1), 471 (13.8), 598 (1.8), 646 (1.4). ^1H NMR (DMSO-d_6, 323 K, 500 MHz): δ_H 9.19 (2H, br s, βpyr), 9.06 (1H, br s, βpyr), 8.87 (1H, d, J = 4.0 Hz, βpyr), 8.82−8.69 (6H, m, 4H βpyr + 2H NHCO), 8.66 (1H, s, NHCO), 8.55 (1H, d, J = 8.0 Hz, aro), 8.45 (1H, d, J = 7.5 Hz, aro), 8.34 (1H, s, NHCO), 8.20 (1H, d, J = 7.0 Hz, aro), 8.03 (1H, d, J = 8.0 Hz, aro), 7.98 (1H, d, J = 7.0 Hz, aro), 7.89−7.79 (5H, m, aro), 7.62 (1H, t, J = 7.5 Hz, aro), 7.58 (1H, t, J = 7.5 Hz, aro), 7.54 (1H, t, J = 7.5 Hz, aro), 7.47 (1H, t, J = 7.0 Hz, aro), 1.55−1.32 (11H, m, 9H CH_3 + 2H cyclohexyl), 1.28−1.22 (2H, m, cyclohexyl), 1.08 (1H, br s, cyclohexyl), 0.97 (1H, t, J = 11.5 Hz, cyclohexyl), 0.80−0.54 (3H, m, cyclohexyl), −0.14 (1H, q, J = 11.5 Hz, cyclohexyl). ^{13}C NMR (DMSO-d_6, 300 K, 125 MHz): δ_C 175.3, 169.1, 149.6, 141.5, 140.8, 135.6, 134.1, 132.1, 131.1, 129.5, 47.8, 45.0, 40.5, 31.3, 27.4, 25.3, 24.2, 23.0.

***N*-{2-Bismuth(III) Nitrate-[α-10,15,20-tris-(2-acetylamino-phenyl)-porphyrin-α-5-yl]-phenyl}-phthalamic Acid (7Bi).** In a 50 mL flask, 50 mg (0.06 mmol) of **7** was dissolved in 10 mL of pyridine. Then 91 mg (0.19 mmol) of $Bi(NO_3)_3{\cdot}5H_2O$ was added.

The reaction was stirred at room temperature. After 10 min, the solvent was evaporated, and the residue was dissolved in CH_2Cl_2 and then filtered. The solution was concentrated to dryness. This allowed the precipitation of the product, which was filtered, washed with more pentane, and finally dried under vacuum overnight. The product was obtained in 94% yield. ESI-HRMS: calcd m/z = 1177.2851 $[M - HNO_3 + Na]^+$ for $C_{58}H_{41}BiN_8O_6Na$, found 1177.2846. FTIR (KBr, cm^{-1}): 1669 (CO), 990 (Bi−Np). UV−vis (CH_2Cl_2) λ_{max}/nm (log ϵ, $dm^3\ mol^{-1}\ cm^{-1}$): 350 (5.5), 472 (14.8), 597 (2.2), 645 (1.8). ^1H NMR (DMSO-d_6, 323 K, 500 MHz): δ_H 11.00 (1H, s, CO_2H), 9.09 (2H, d, J = 4.5 Hz, βpyr), 8.97 (2H, d, J = 4.5 Hz, βpyr), 8.90 (2H, d, J = 4.5 Hz, βpyr), 8.79 (2H, d, J = 4.5 Hz, βpyr), 8.66 (2H, br s, NHCO), 8.58 (1H, d, J = 8.1 Hz, aro), 8.49−8.40 (5H, m, 2NHCO + 3aro), 7.99−7.89 (4H, m, aro), 7.83−7.73 (6H, m, 5aro + 1phthal), 7.3 (3H, t, J = 7.5 Hz, aro), 7.19 (1H, t, J = 8.1 Hz, phthal), 6.97 (1H, t, J = 7.8 Hz, phthal), 6.10 (1H, d, J = 7.8 Hz, phthal), 1.47 (3H, s, CH_3), 1.29 (6H, s, CH_3). ^{13}C NMR (DMSO-d_6, 323 K, 126 MHz): δ_C 173.2, 169.1, 165.0, 146.5, 141.6, 136.7, 134.8, 133.8, 132.0, 131.5, 130.4, 129.5, 127.8, 124.4, 124.0, 123.0, 122.4, 24.2.

X-ray Crystallography for 1Bi. Crystallographic details have already been reported in ref 17. Crystal data [$C_{54}H_{41}BiN_8O_6 \cdot 3H_2O \cdot 1.5(C_5H_5N)$]: M = 2664.31, triclinic, space group $P\bar{1}$, a = 12.7605(1) Å, b = 13.8671(2) Å, c = 15.7654(2) Å, α = 78.693(1)°, β = 89.696(1)°, γ = 77.096(1)°, V = 2664.31(6) Å^3, Z = 2, D_x = 1.595 Mg m^{-3}, λ(Mo Kα) = 0.71073 Å, μ = 33.79 cm^{-1}, $F(000)$ = 1290, T = 120 K. The sample (0.32 × 0.32 × 0.12 mm^3) was studied on a NONIUS Kappa CCD with graphite monochromatized Mo Kα radiation. The cell parameters were obtained with Denzo and Scalepack[18] with 10 frames (psi rotation: 1° per frame). The data collection (Nonius, 1999; $2\theta_{max}$ = 60°, 310 frames via 2.0° omega rotation and 30 s per frame; range *hkl*, *h* 0,16 *k* −18,18 *l* −20,20) gives 71 226 reflections. The data reduction with Denzo and Scalepack[18] leads to 12 259 independent reflections, 11 368 of which have $I > 2.0\sigma(I)$. The structure was solved with SIR-2002,[19] which reveals the non-hydrogen atoms of the structure. After anisotropic refinement, many hydrogen atoms may be found with a Fourier Difference. The whole structure was refined with SHELXH[20] by the full-matrix least-squares techniques (use of F square magnitude; x, y, z, β_{ij} for Bi, O, N, and C atoms; x, y, z in riding mode for H atoms; 707 variables and 11 368 observations with $I > 2.0\sigma(I)$; calc $w = 1/[\sigma^2(F_o^2) + (0.036P)^2 + 6.55P]$ where $P = (F_o^2 + 2F_c^2)/3$ with the resulting R = 0.033, R_w = 0.082, and S_w= 1.077; $\Delta\rho$ < 2.17 eÅ^{-3}). Atomic scattering factors from International Tables for X-ray Crystallography.[21] CCDC reference number 215678. See http://www.rsc.org/suppdata/cc/b3/b309615g/ for crystallographic data in CIF or other electronic format.

Results

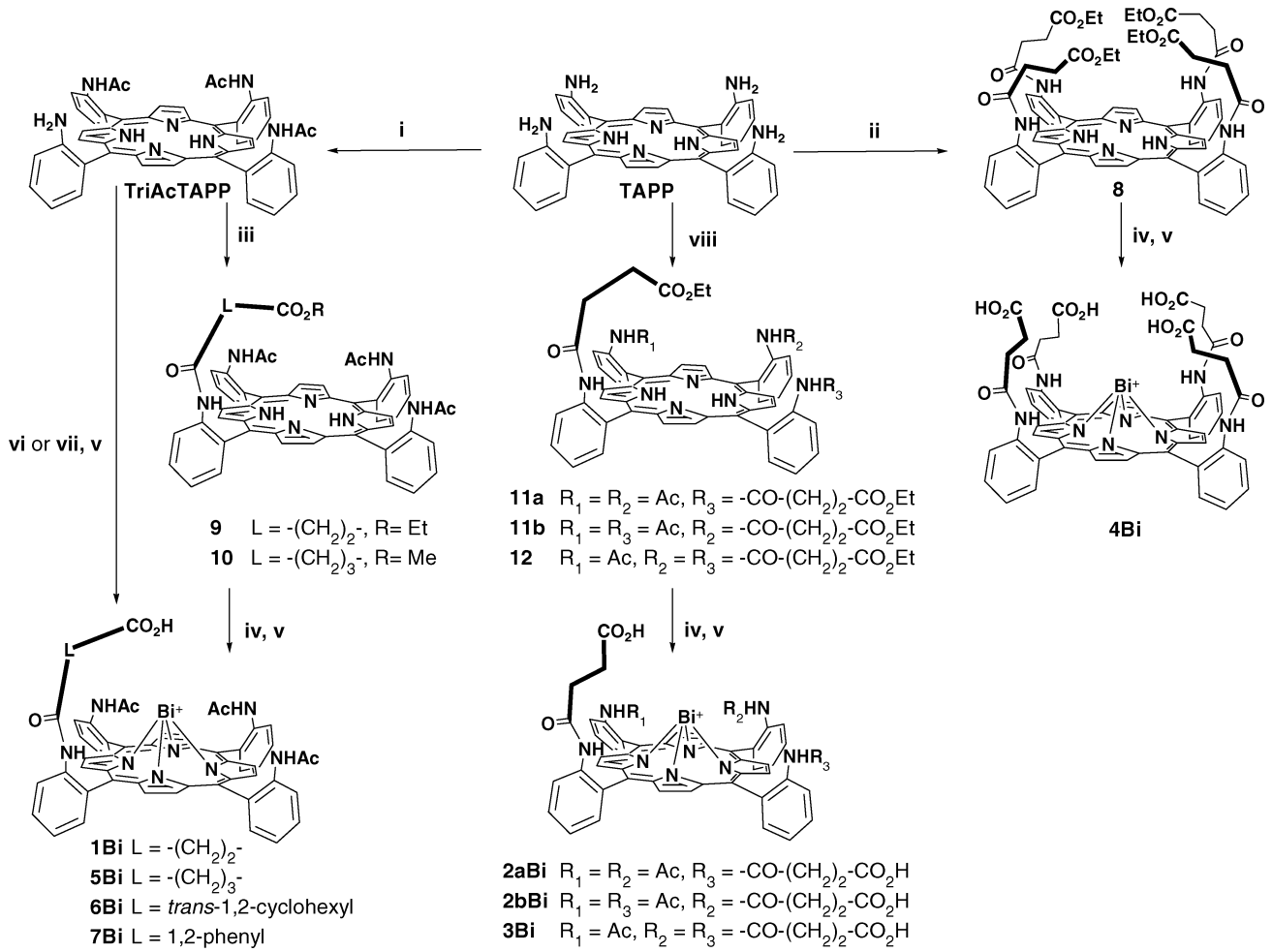
The very first bismuth complex that we investigated to probe the influence of an intramolecular carboxylic picket was porphyrin **1Bi** (Scheme 1) because it was known, from our previous work on ester picket analogues, that the kinetics of metalation were faster for its precursor **9**, which bears one ethyl succinate picket (30 min in pyridine at 50 °C), than those of the four-ester picket analogue **8** (120 min in pyridine at 50 °C).[16] We have attributed this increase in rate to the lack of steric hindrance above the macrocycle making metal insertion faster. Thus, **1Bi** was obtained by metalation of $\mathbf{1H}_2$, which itself results from the reaction of *N*-{2-[15,20-bis-(2-acetylamino-phenyl)-10-(2-amino-phenyl)-porphyrin-5-yl]-phenyl}-acetamide (TriAcTAPP, Scheme 1) with 3-chlorocarbonyl-propionic acid ethyl ester (ethyl succinyl chloride), followed by saponification with potassium hydroxide. Aiming at the same goal, we also isolated the two bis-ethyl succinate picket porphyrins **11a** and **11b** and the tris-ethyl succinate picket porphyrin **12**. These various porphyrins were accessible from the mono-acetyl porphyrin and the two isomeric bis-acetyl porphyrins, for which we have published the full synthesis.[16] Tetra-ethyl succinate picket porphyrin **8** was obtained by the direct acylation of *meso*-tetrakis-2-aminophenyl porphyrin (TAPP). Saponification of **11a**, **11b**, **12**, and **8** led to the corresponding succinic acid picket porphyrins **2a**, **2b**, **3**, and **4**, which were metalated with $Bi(NO_3)_3$ in pyridine at room temperature.

On one hand, and mostly for comparison purposes, it was decided to prepare by the same synthetic pathway **5Bi**, the glutaryl analogue of **1Bi**. On the other hand, to probe the influence of the pre-organization of the picket delivering the carboxylate group to the metal, we also chose to tether on TriAcTAPP *trans*-1,2-cyclohexyl dicarboxylic acid or 1,2-phenyl dicarboxylic acid, thereby leading to **6Bi** or **7Bi**, respectively, after bismuth insertion. Indeed, these two motifs formally possess two carbon atoms between their two acid functions but should exhibit different degrees of rigidity because of the existence of either the cyclohexyl or the phenyl ring. An illustration of the influence of the 1,2-cyclohexyl skeleton versus the 1,2-ethyl skeleton is the higher affinity of *trans*-cyclohexylenediamine tetraacetic acid (CDTA) for most metal ions than that of ethylenediamine tetraacetic acid (EDTA), because the bridging cyclohexylene group holds the two $N(CH_2CO_2H)_2$ chelate groups in a specific arrangement.[22] Thus, to synthesize **6** and **7** with an average yield of 80%, the synthetic method consists of opening either *trans*-1,2-cyclohexyl anhydride or 1,2-phenyl anhydride at room temperature via nucleophilic attack by TriAcTAPP.

Bismuth insertion was then achieved for all porphyrins bearing at least one carboxylic acid picket (with the exception of **7**) by mixing 1 equiv of $Bi(NO_3)_3 \cdot 5H_2O$ with the free-base porphyrin in pyridine at room temperature for 10 min. Indeed, in the case of **7**, 3 equiv of the metallic salt were required to achieve quantitative metalation in only 10 min. This increase in the kinetics of bismuth insertion, compared either to unfunctionalized porphyrins or to ester pendant-arm porphyrins, could be rationalized by the fact that the carboxylate functions around the coordination site can probably "precomplex" the bismuth cation by counteranion

(18) Otwinowski, Z.; Minor, W. Processing of X-ray Diffraction Data Collected in Oscillation Mode. In *Methods in Enzymology Macromolecular Crystallography, Part A*; Carter, C. W., Sweet, R. M., Eds.; London: Academic Press, 1997; Vol. 276, pp 307−326.
(19) Burla, M. C.; Camalli, M.; Carrozzini, B.; Cascarano, G.; Giacovazzo, C.; Polidori, G.; Spagna, R. *Acta Crystallogr.* **2000**, *A56*, 451−457.
(20) Sheldrick, G. M. *SHELX97: Program for the Refinement of Crystal Structures*; University of Göttingen: Germany, 1997.
(21) *International Tables for X-ray Crystallography*; Wilson, A. J. C., Ed.; Kluwer Academic Publishers: Dordrecht, 1992; Vol. C.
(22) de Sousa, A. S.; Croft, G. J. B.; Wagner, C. A.; Michael, J. P.; Hancock, R. D. *Inorg. Chem.* **1991**, *30*, 3525−3529. Brechbiel, M. W.; Gansow, O. A.; Pippin, C. G.; Rogers, R. D.; Planalp, R. P. *Inorg. Chem.* **1996**, *35*, 6343−6348.

Scheme 1. Synthetic Route Leading to Various Acid Picket Bismuth Porphyrins[a]



[a] Conditions: (i) 3 equiv of CH_3COCl, THF, NEt_3; (ii) 5 equiv of $EtO_2C-(CH_2)_2-COCl$, THF, NEt_3; (iii) 1.2 equiv of $MeO_2C-(CH_2)_3-COCl$, THF, NEt_3; (iv) KOH, MeOH, 55 °C; (v) $Bi(NO_3)_3$, pyridine, rt; (vi) *trans*-1,2-cyclohexyl anhydride, AcOH; (vii) phthalic anhydride, CH_2Cl_2, aluminum oxide; (viii) (see ref 16 for further details) 2 steps, 1.8 equiv of CH_3COCl, THF, NEt_3, chromatography and then $EtO_2C-(CH_2)_2-COCl$, THF, NEt_3 (as the bismuth counteranion was unambiguously shown to be the carboxylate group only for **1Bi**, the various complexes are noted as Bi^+ complexes).

exchange, delivering the bismuth close to the porphyrin coordination site.

Interestingly, we could obtain crystals suitable for X-ray study by the diffusion of water into a solution of **1Bi** in pyridine. This represents, so far, the only X-ray structure of a monomeric bismuth porphyrin.[17] All other structurally characterized bismuth porphyrins reported to date crystallize as dimers, bridging through the counterions. As depicted in Figure 1, **1Bi(H_2O)$_2$·H_2O·py** comprises a monomeric structure with the counteranion delivered by the single pendant succinate arm. Indeed, the two oxygen atoms of the carboxylate group (O4 and O5) bound to the metal center (Bi−O4 = 2.697(3) Å and Bi−O5 = 2.869(3) Å) are stabilized by the two hydrogen bonds with the neighboring NH groups from the amide linkage, N7 and N8, respectively. With both C−O distances of the carboxylate group being equal (C46−O4 = 1.262(5) Å and C46−O5 = 1.269(5) Å), the carboxylate binds bismuth in an η^2-carboxylato complex. The two other coordination sites are occupied by two water molecules (O7 and O8) with Bi−O7 = 2.920(3) Å and Bi−O8 = 2.715(3) Å. The two coordinated water molecules are also included in a hydrogen bonding net. The first one, O7, is hydrogen bonded to O5 from the carboxylate group and to N5 from an acetamide residue. The second one, O8, is hydrogen bonded to N10 from a solvated pyridine molecule (not represented for the sake of clarity) and to a noncoordinated water molecule, O9, which is itself hydrogen bonded to N6 from an acetamide residue. The bismuth is eight-coordinate and lies 1.145 Å above the N4 plane and 1.239 Å above the 24-atom mean porphyrinic plane. The mean Bi−N bond length is 2.343(2) Å, nearly identical to the corresponding one in **4Bi(NO_3)** (2.340(2) Å).[15] The bismuth atom is coordinated in a distorted antiprismatic geometry, and the porphyrin plane adopts a "saddle-shaped" and ruffled conformation[23] (see ref 17 for further details).

To the best of our knowledge, this type of deformation of the macrocycle has never been reported for bismuth porphyrins. More precisely, the deviations from the mean porphyrin plane of the four C*m* atoms are 0.297, −0.150, 0.243, and −0.164 Å (positive and negative values indicate deviations toward and away from Bi, respectively), leading to an average value of 0.213 Å. They are quite substantial

(23) Shelnutt, J. A.; Song, X. Z.; Ma, J. G.; Jia, S. L.; Jentzen, W.; Medforth, C. J. *Chem. Soc. Rev.* **1998**, *27*, 31−41.

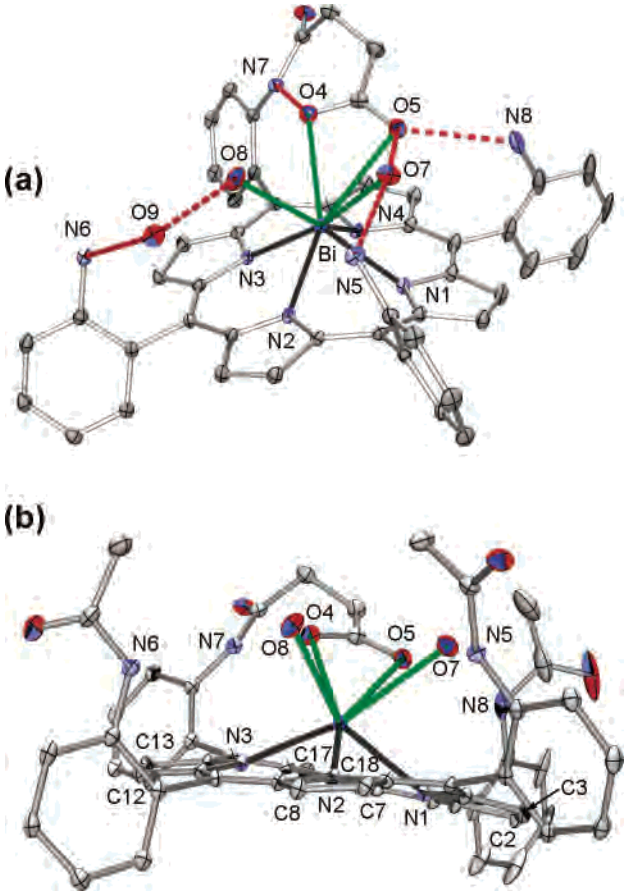


Figure 1. Molecular structure of **1Bi** (30% thermal ellipsoids). (a) Perspective view. For the sake of clarity, the three acetyl groups are not represented on N5, N6, and N8. (b) Side view along the N2−N4 axis. (Black, Bi−N bonds; green, Bi−O bonds; red, hydrogen bonds.)

but are smaller than those observed for highly distorted nickel porphyrins, for instance.[24]

However, this structural description deserves some comments. First, it is worth mentioning that the distances between the bismuth atom and the oxygen atoms of the two "bonded" water molecules are particularly long. A geometry optimization was carried out at the B3LYP/SDDAll level of theory (see the Computational Details section) on a simplified model of **1Bi** (the pyridine molecule hydrogen bonded to O8 was discarded to reduce computational efforts) to analyze the role of these water molecules in the coordination sphere of bismuth. The computed structure is overall in good agreement with the experimental data. The computed Bi−N bond lengths, for instance, which range from 2.293 to 2.383 Å (average value of 2.340 Å), compare rather well with the experimental values, which are measured between 2.330 and 2.362 Å (average value of 2.343 Å, see above). The deviations of the *meso* carbon atoms from the mean porphyrin plane are also well reproduced (−0.180, 0.286, −0.160, and 0.292 Å).

Analogous to the X-ray structure, the distances between the two oxygen atoms of the carboxylate group and the Bi atom differ somewhat. A substantial difference of 0.352 Å was computed in the model, twice larger than experimentally measured (0.172 Å), which may be related to the fact that the Bi−O (carboxylate) bonding contacts are rather weak.[25] Importantly, the "saddle-shaped" and twisted conformation of the porphyrin macrocycle is kept during the optimization process. This indicates that such a distortion cannot be attributed to crystal packing forces but rather is due to intramolecular forces. Interestingly, the coordination number of the bismuth atom diminishes from eight to seven due to an increase of the Bi−O7 distance from 2.92 Å (experimental) to ∼4.03 Å (computed). However, the corresponding water molecule remains hydrogen bonded to the same atoms, that is, an oxygen atom from the carboxylate and a hydrogen atom from the acetamide residue located on the opposite *meso* aromatic cycle of the porphyrin. Such a result indicates that one of the two water molecules is very loosely bonded to the bismuth center in **1Bi**.

To investigate its role in the geometry of complex **1Bi**, this *spectator* water molecule was removed and the structure was re-optimized. It is noteworthy that the deformation of the porphyrin is then strongly reduced. Indeed, the deviation distances of the four C*m* atoms from the mean porphyrin plane decrease, on average, to 0.06 Å. This suggests that the two hydrogen bonds involving the aforementioned water molecule and connecting both *meso* positions of the porphyrin macrocycle via N5 and O5 should be considered as being mainly responsible for the resulting distorted conformation of **1Bi**.

Similar conclusions were drawn from the geometry optimization of a model of **5Bi** derived from **1Bi** by substituting a glutaryl motif for the succinyl motif. It appears, therefore, that the length of the picket and the coordination of the carboxylate to the metal atom in **1Bi** do not play the major role in the reported experimental deformations of the porphyrin. In particular, it is noteworthy that very weak deviations of the *meso* carbon atoms from the mean porphyrin plane are computed (0.05 Å on average) in the absence of one water molecule.

To experimentally verify the actual influence of the length of the arm on the distortion of the macrocycle, porphyrin **5** was also studied for its ability to complex bismuth rapidly. In the latter, the succinate motif was substituted by the glutarate motif, which possesses one more carbon, but actually, no significant difference was observed for the kinetics of the metalation of **1** or **5** by bismuth nitrate. On the other hand, **5Bi** proved to be much less stable than **1Bi** in acidic medium.

To further address this question, we undertook a study of the decomplexation of bismuth from these two chelates bearing acid pickets differing only by one carbon atom. The absorption at 470 nm that is characteristic of the metalated porphyrin[26] was monitored while the complex was exposed to 2500 equiv of trifluoraocaetic acid (TFA). A typical result

(24) Richard, P.; Rose, E.; Boitrel, B. *Inorg. Chem.* **1998**, *37*, 6532−6534.

(25) The bonding energy between the carboxylate group and the bismuth atom was computed to be equal to ∼45 kcal mol^{-1}. This value was estimated by positioning the carboxylate group "below" the porphyrin, followed by a full geometry re-optimization of the new conformation.

(26) Sayer, P.; Gouterman, M.; Connell, C. R. *Acc. Chem. Res.* **1982**, *15*, 73−79.

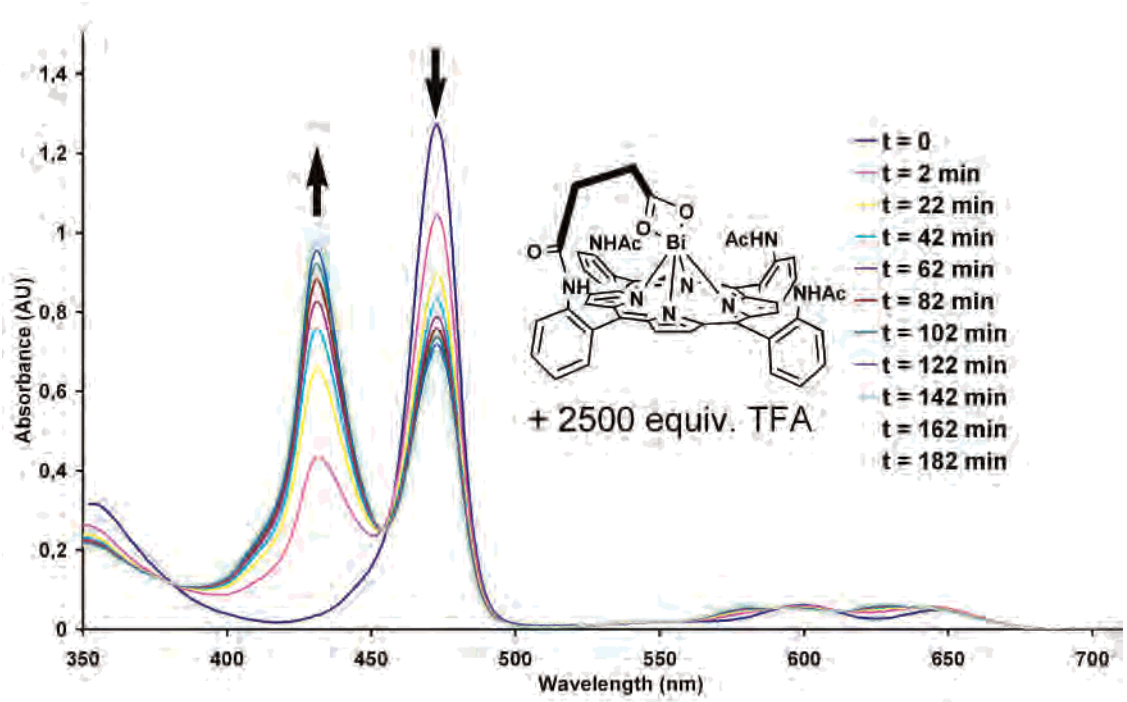


Figure 2. UV−vis monitoring of the demetalation reaction of **1Bi** in methylene chloride in the presence of 2500 equiv of TFA.

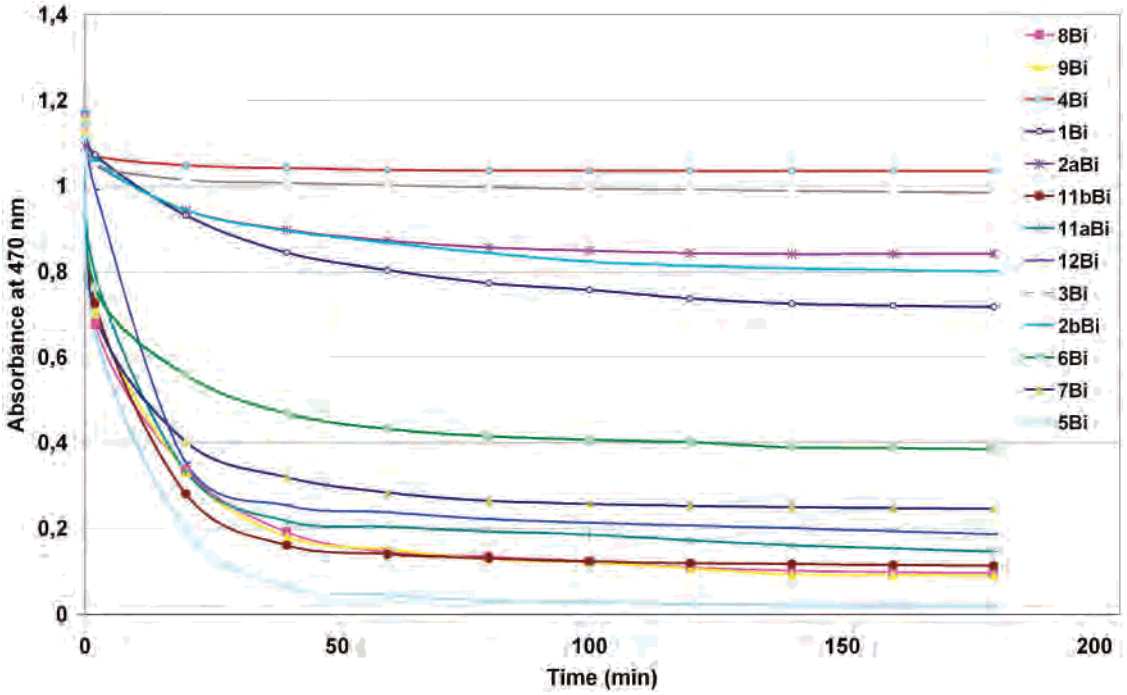


Figure 3. Relative stability of 13 bismuth complexes in methylene chloride in the presence of 2500 equiv of TFA.

is illustrated in Figure 2 for the bismuth complex **1Bi**. In this particular example, once the equilibrium was reached after 3 h, only 37% of the complex (Soret at 470 nm) was transformed to the free-base porphyrin (Soret at 420 nm) by bismuth decomplexation.

Thus, this method was also applied to the other studied complexes with a direct comparison with their precursors bearing ester pendant arms as it represents a simple way to compare the stability of metal complexes which are not water-soluble (Figure 3).

Clearly, the various complexes can be classified into two main groups. The first group of complexes, for which the decomplexation of the bismuth cation is evaluated to be around 80−90% after 3 h in acidic medium, is composed of the following molecules in order of decreasing stability: **7Bi** (79%), **12Bi** (84%), **11aBi** (88%), **11bBi** (90%), **8Bi** (92%), **9Bi** (92%), and **5Bi** (98%). The second group is composed of the five porphyrins bearing from one to four succinic acid picket(s), for which the percentage of demetalation remains below 40%, in order of decreasing stability: **4Bi** (7%), **3Bi**

(14%), **2aBi** (23%), **2bBi** (32%), and **1Bi** (37%). (The proportion of bismuth decomplexation was evaluated after 180 min according to the decrease of the Soret band of the bismuth complex at 470 nm with the following formula: 100 − (Abs180/Abs0) × 100. For each complex, this proportion is given in parentheses. Indeed, preliminary studies have shown that, for all the bismuth complexes studied, such a period of time was long enough to reach a new equilibrium.) The bismuth complex **6Bi** (67%) is located midway between these two groups. Actually, the first group, which represents the least stable complexes, is mainly composed of all the pendant ester picket complexes (from **12Bi** to **9Bi**). However, as already mentioned, a striking result comes from complex **5Bi**, which is the direct analogue of **1Bi**, having the glutaryl motif instead of the succinyl motif. Indeed, from the distortion of the macrocycle observed in the X-ray structure of **1Bi** and independently of the theoretical calculations, it was resonable to think that an analogous complex able to release this distortion would be more stable than **1Bi**. Although we do not have any structural evidence for **5Bi**, we hypothesized that elongating the pendant arm by one atom of carbon should release this distortion.

But it turns out that this change in length does not induce the expected effect as it leads to the least stable bismuth complex of this series! The stability of **5Bi** is even lower than that of the complex with one ethyl ester picket, namely **9Bi**. A plausible explanation could be that the glutaryl motif with three methylene groups does not readily allow the coordination of the intramolecular carboxylic acid function due to the arrangement of dihedral angles along the propyl skeleton. This observation is consistent with the conclusions drawn from the theoretical calculations; that is, the distortion of the macrocycle is mainly due to the presence of water molecules in the bismuth surroundings rather than the length of the carboxylate picket.

A second approach consisted of investigating the influence of the pre-organization with the two-methylene motif of the succinyl picket while increasing the rigidity of the picket. This increase of rigidity is *a priori* satisfied in compounds **6** and **7**. However, it was disapointing to observe that none of the resulting bismuth complexes gain stability in comparison with **1Bi**. Actually, **6Bi** and **7Bi** are just slightly more stable than the ester picket porphyrins. In these two examples, it is clear that too much pre-organization can disfavor the stability of the bismuth complex. In the case of **6Bi**, the dihedral angles between the two methylene groups joining the amide and the carboxylic acid are dictated by the cyclohexyl ring and the *trans* configuration. If the "coordinating carboxylate" is not properly located, the possibility of movement to adjust its position is smaller than that in **1Bi**.

For its aromatic analogue **7Bi**, the pre-organization is even stronger for two reasons. First, the "coordinating carboxylate" is expected to be conjugated with the aromatic cycle of the picket; such an orientation does not favor the coordination in the η^2-carboxylato mode. Second, in most of the known X-ray structures reported, in which a phthalic acid is conjugated with an aniline just as in porphyrin **7**,[27] the two aromatic cycles are almost orthogonal but not coplanar. This conformation is supposed to locate the "coordinating carboxylate" away from the center of the porphyrin.

In the second group composed of all the succinic acid picket porphyrins, from **4Bi** to **1Bi**, the percentage of decomplexation of the bismuth increases from 7% for **4Bi** up to 37% for **1Bi**. In the series, it appears that the stability of the bismuth porphyrin is almost proportional to the number of succinic acid pickets of the ligand. As in the precursor series concerning the ethyl succinic ester picket porphyrins **11a** and **11b**, the 5,10 isomer is more stable than the 5,15 isomer, but the difference between them is even more pronounced in the acid series, **2a** and **2b**.

Conclusions

In this study, we have shown that porphyrins bearing succinic acid pickets as chelators for bismuth(III) cation are efficient both in terms of the kinetics of complexation (time required to observe a significant metal insertion) and their stability in acidic medium. Indeed, in comparison with their ester picket precursors, they complex bismuth at room temperature in 10 min, leading to fairly stable complexes. We have also demonstrated that, serendipituously, the succinyl motif leads to the most efficient ligands in comparison with either the longer glutaric acid or pre-organized diacids, such as *trans*-1,2-cyclohexyl dicarboxylic acid or phthalic acid, all of which lead to less stable bismuth complexes.

So far, we do not know how the four carboxylate pickets of the most stable complex that we obtained interact with the bismuth. As in the X-ray structure of the single acid picket bismuth porphyrin, they may interchange with one another in the first coordination sphere of the metal or they might be stabilized by hydrogen bonding to water molecules bound to bismuth. They could also bind bismuth by different modes: one picket in an η^2-carboxylato complex and one (or two) picket(s) as a neutral ligand(s), via a lone pair of

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the acid carbonyl. However, this hypothesis needs further structural characterization to be definitively confirmed. Nevertheless, for medical applications in alpha-radioimmunotherapy that require linking of the chelate to a biomolecule, the three-succinic acid picket porphyrin appears to be optimal so far.

Computational Details

Density functional theory calculations were performed using Becke's three-parameter hybrid gradient-corrected exchange functional[28] and the gradient-corrected correlation functional of Lee, Yang, and Parr[29] (B3LYP). Stuttgart/Dresden effective core potentials were employed for all atoms.[30] Geometries were optimized without constraints using the Gaussian03 (revision B.4) package.[31]

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Supporting Information Available: NMR and spectroscopy data for porphyrin ligands (**2a**, **2b**, **3**, and **4**) and bismuth complexes (**2aBi**, **2bBi**, and **3Bi**). Supplementary material for Figure 3. This material is available free of charge via the Internet at http://pubs.acs.org.

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