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Unexpected behavior of 6*H*,13*H*-5:12,7:14-dimethanedibenzo[*d*,*i*][1,3,6,8]tetraazecine (DMDBTA) toward phenols

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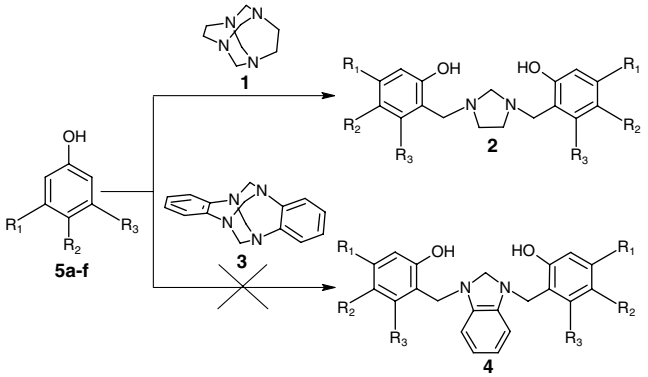
Abstract—A new 20-membered octaazamacrocyclic compound named 1:4,6:9,11:14,16:19-tetramethylentetrabenzo[*b*,*g*,*l*,*q*]-[1,4,6,9,11,14,16,19]octaazaeicocine (TTBOE) (**9**) has been prepared by means of in situ one-pot synthesis between the aminal 6*H*,13*H*-5:12,7:14-dimethanedibenzo[*d*,*i*][1,3,6,8]tetraazecine (DMDBTA) (**3**) and electron-deficient phenols. Otherwise, electron-rich phenols such as 4-chloro-3,5-dimethylphenol or 2-naphthol produce an *ortho*-regioselective aminomethylation resulting in 2-(1*H*-benzimidazol-1-ylmethyl)-4-chloro-3,5-dimethylphenol (**7**) and 1-(1*H*-benzimidazol-1-ylmethyl)-2-naphthol (**8**) in a Mannich type reaction in a basic medium. Moreover, obtainment of 1,1′-methylenbis(1*H*-benzimidazole) (**15**) from TTBOE is discussed.

It is well known that benzyl-benzimidazolines are compounds widely used in medical and pharmaceutical areas since they show analgesic, hypotensive, anti-inflammatory, and anti-convulsive properties.[1] Also, this class of compounds have been used as fungicides,[2] raw materials in dye synthesis,[3] selective reduction of α,β-unsaturated ketones,[4] and coordination chemistry to prepare organometallic compounds for several applications.[5] The benzimidazolines can usually be obtained by reduction of benzimidazole,[6] or by direct condensation of *o*-phenylendiamines and carbonyl compounds.[7]

In a previous work,[8] using a Mannich type reaction in basic medium between the macrocyclic aminal 1,3,6,8-tetraazatricyclo[4.4.1.1^{3,8}]dodecane (TATD) (**1**) and *p*-substituted phenols, we synthesized 1,3-bis(2′-hydroxy-5′-substituted-benzyl)imidazolidines (BISBIAs) (**2**) (Scheme 1). BISBIAs have been utilized as powerful reagents for obtention of salans[9] and hetero-calixarenes.[10]

On the basis of these consideration, we expected that the use of 6*H*,13*H*-5:12,7:14-dimethanedibenzo[*d*,*i*][1,3,6,8]-tetraazecine (DMDBTA)[11] (**3**) and phenols (**5a**–**f**), should give the corresponding 1,3-bis(2′-hydroxy-5′-substituted-benzyl)benzimidazolines (**4**) (Scheme 1).

Surprisingly, the products formed during reaction of **3** with phenols[12] were not the expected benzyl-benzimidazolines (**4**). Moreover, changing reaction conditions



5	R_1	R_2	R_3
a	$-CH_3$	-Cl	$-CH_3$
b	-CH=CH-CH=CH-		-H
c	-H	-H	-H
d	-H	$-CH_3$	-H
e	-H	-Cl	-H
f	-H	$-NO_2$	-H

Scheme 1.

Keywords: Benzimidazoline; Mannich-type reaction; Aminal; DMDBTA.
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such as using different solvents and a different molar ratio of **3** to **5a–f** do not allow finding reaction conditions to obtain the product **4**. Thus, using the electron-rich phenols (**5a** or **5b**), both 1-methylbenzimidazole (**6**) and the respective *ortho* aminomethylation products: 2-(1*H*-benzimidazol-1-yl-methyl)-4-chloro-3,5-dimethylphenol (**7**) or 1-(1*H*−benzimidazol-1-yl-methyl)-2-naphthol (**8**) were obtained.[13] But when electron-deficient phenols (**5c–f**) were used, a cyclodimerization product **9** was isolated (Scheme 2).

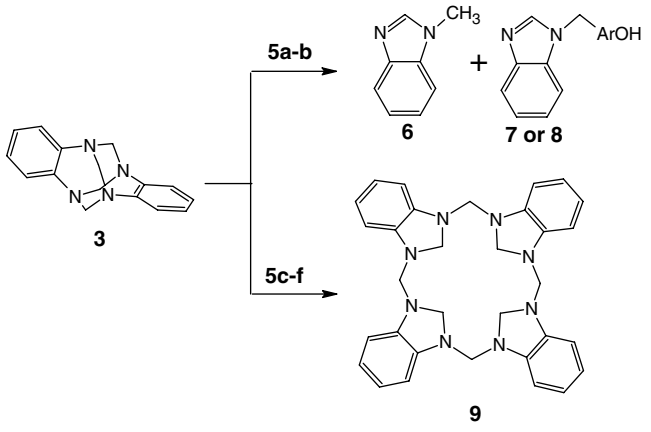
The question arises as to why only the products of *ortho* aminomethylation were isolated in the cases of 4-chloro-3,5-dimethylphenol (**5a**) and 2-naphthol (**5b**). An explanation of this fact is shown in Scheme 3, where hydrogen bonding between the phenolic hydrogen and any nitrogen atom of the aminal **3** would be expected to precede the formation of the six-membered cyclic transition state, which would then bring the reactive methylene group into position for electrophilic attack on the aromatic ring in the *ortho*-position, resulting in adduct **10**. Protonation of **10** is likely accompanied by a ring opening of a strained cycle with a nitrogen lone-pair *anti* to the breaking of the C–N bond providing some assistance. In the resulting structure **11**, the lone-pair *anti* to the C–N bond may labilize that bond regarding cleavage forming iminium ion **12** and benzimidazoline **13**. Formation of **6** from **12** involves an intra-molecular hydride transfer to the iminium ion generating the N–Me group, as it occurs in other cyclic aminals.[14] **13**—a plausible intermediate—afforded benzimidazole derivatives[15] (**7** or **8**) by atmospheric oxygen oxidation being capable of transferring a hydride.[16]

On the other hand, 1:4,6:9,11:14,16:19-tetramethyl entetrabenzo[*b*,*g*,*l*,*q*][1,4,6,9,11,14,16,19]octaazaeicocine (TTBOE) **9**, a tetramer of benzimidazoline, was obtained when electron-deficient phenols **5c–f** were reacted with DMDBTA.

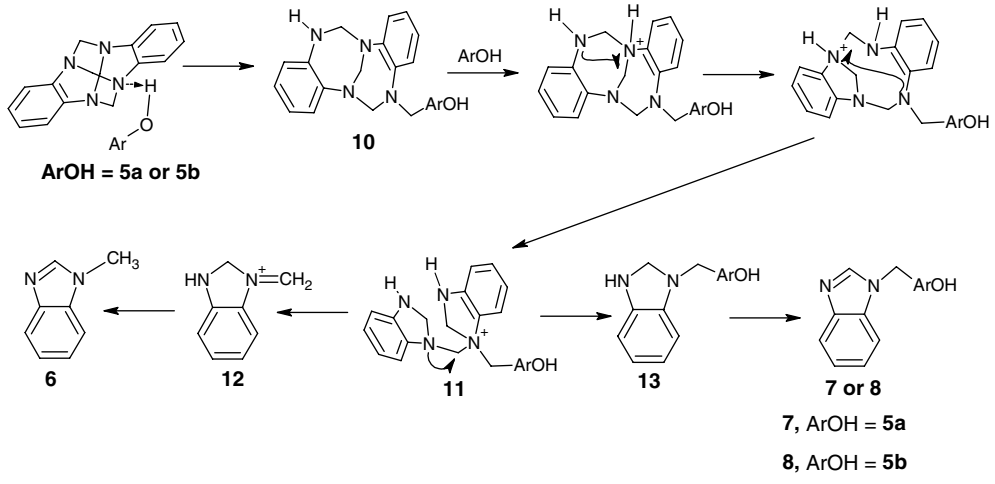
The possible mechanism for formation of the macrocycle **9** is indicated in Scheme 4. As discussed above, firstly, the hydroxyl group of phenol forms a hydrogen bond O–H···N with any one of the N-atoms of **3**, which polarize adjacent methylenes. Secondly, the partially charged methylenes suffer a nucleophilic attack by any nitrogen atom from other DMDBTA molecules. It is reasonable to assume that this reaction is faster than ring aminomethylation. In fact, electron-deficient phenols afford a corresponding Mannich-type product in low yields[17] and even strongly acid phenols did not form aminomethylation products.[18]

The pre-organization of the linear substrate into a folded conformer is forced by the lone pair repulsion in the 1,1-diamine units ('rabbit ears' effect[19]), which brings the proximity of the reactive centers in **14** and enhances the chance of a productive interaction suitable for ring closure. It is interesting to notice that high-dilution conditions were not necessary for a ring-closing step since the cyclization was successfully produced using up to 0.1 mol/L concentrations without contamination detection by polymers or larger ring systems. The reaction proceeds smoothly and clearly produces **9** in acceptable yield depending on the phenol employed (Table 1). In addition, by using a large excess of **3** (10 equiv), only **9** was formed with similar yields.

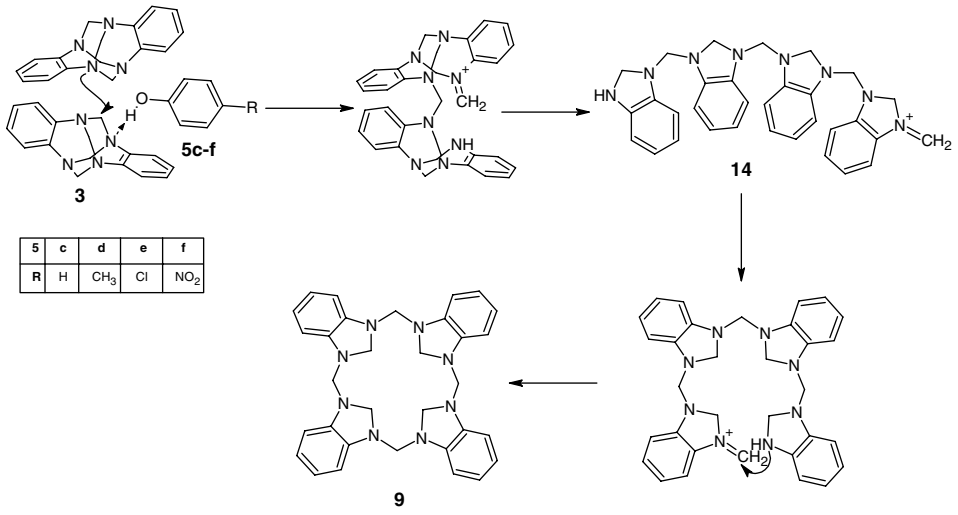
Besides, our experiments showed that a reaction occurs exclusively with phenols, because by adding acetic acid,



Scheme 2.



Scheme 3.



Scheme 4.

Table 1.

Entry	Phenol	Reaction time (h)	Yield TTBOE (%)
5c	Phenol	12	13
5d	4-Methyl phenol	10	19
5e	4-Chlorophenol	4.5	47
5f	4-Nitrophenol	2	65

p-toluensulfonic acid, or mineral acids in place of phenol, in all cases, *o*-phenylendiamine and formaldehyde were obtained.

On the other hand, **9** is poorly soluble in most solvents including dimethyl sulfoxide, but a sample of enough concentration in chloroform-d_1 was obtained by NMR spectroscopy.[20] The ^{1}H NMR spectrum of **9** in this solvent shows two signals distinctive for aminal's resonance at δ 4.52 and 4.55, as well as the aromatic protons. However, the data from ^{1}H NMR are insufficient to design the possible conformer: cone (I), partial cone (II), 1,2-alternate (III), and 1,3-alternate (IV). Preliminary conformational analysis per-formed through computational calculations using Gaussian 98 software,[21] B3-LYP-3-21G basis set, showed that the most stable conformation for TTBOE is the 1,3-alternated ring of benzimidazoline (IV) (Fig. 1).

Under strict exclusion of air and moisture, **9** is thermally stable and can be stored indefinitely, but decomposition in dissolution occurs. Thus, by registering again spectrum ^{1}H NMR from **9** over 1–2 days in chloroform-d_1, the spectrum showed marked differences compared with those formerly taken. As observed, aminal signals at 4.52 and 4.55 for **9** were decreased in intensity and replaced by signals at δ 8.18 and 8.05. Over the same period, aromatic proton signals of **9** were replaced by new multiplet sets. Then a sample of **9** dissolved in $CDCl_3$ was monitored by ^{1}H NMR. In measures on chloroform-d_1 after 5 min of preparation, the spectrum showed small quantities of 1,1′-methylenbis(1*H*-benzimidazole) (**15**) and 1-methylbenzimidazole (**6**) in almost equal amounts. After 3–4 h, the same solution contained **6** and **15** in substantially increased amounts as the predominant species detected. The tetramer **9** was not observed.

These experiments suggested that upon dissolution in chloroform, **9** began a rearrangement in two cyclic structures. ^{1}H NMR[22] spectrum showed peculiar benzimidazole resonances at δ 8.18 for **15** and δ 8.05 for **6** (Scheme 5). Thus we suggest that TTBOE is decomposed by traces of oxygen present in chloroform,[23] which induces a dealkylation of the cyclic tertiary amine function making therefore the generation of **15** and formaldehyde on a similar fashion to aromatic N-replaced amines. Later, a slower stage involves a decomposition of **15** by an oxide-reduction reaction with

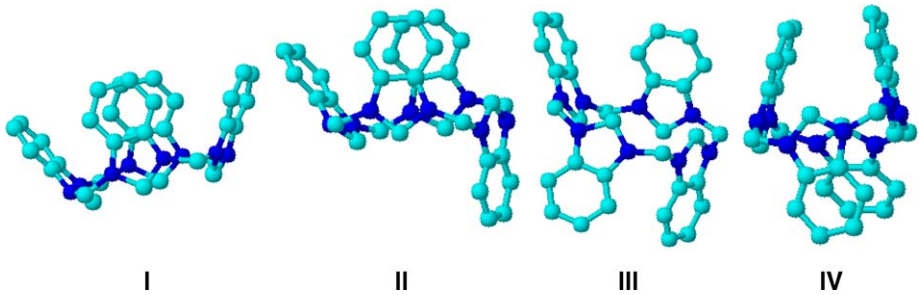
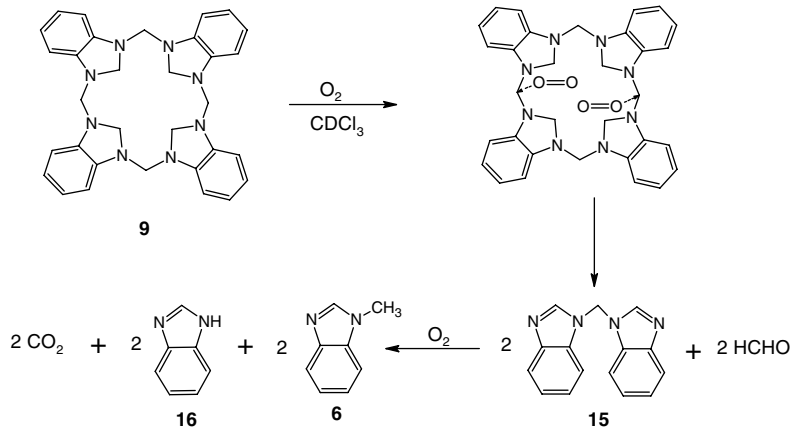


Figure 1. Four main conformations of TTBOE: cone (I), partial cone (II), 1,2-alternate (III), 1,3-alternate (IV).



Scheme 5.

formaldehyde formed participation to produce carbon dioxide, 1-methylbenzimidazole **6**, and benzimidazole **16**.

In conclusion, we discovered an innovative route for an efficient one-pot synthesis of 1:4,6:9,11:14,16:19-tetramethylentetrabenzo[*b*,*g*,*l*,*q*][1,4,6,9,11,14,16,19]octaazaeicocine (TTBOE) (**9**) from DMDBTA and phenols. Depending on the phenol employed, Mannich-type bases could be obtained instead of **9**. Now that the utility of this methodology for synthesis of TTBOE and some derivatives has been established, further studies are underway to investigate the role of phenols in the reaction and to explore its applications in synthesis of benzimidazole derivatives.

Acknowledgements

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11. DMDBTA is obtained by direct condensation between *o*-phenylendiamine and formaldehyde.
12. General procedure for the synthesis of **7**, **8**, and **9**: A solution of 6*H*,13*H*-5:12,7:14dimethanedibenzo[*d*,*i*][1,3,6,8]-tetraazecine (DMDBTA) (**3**) (0.25 mmol) and the appropriate phenol (**5a**–**f**) (0.5 mmol) in 15 mL of propan-2-ol was placed in a round-bottomed flask equipped with a water-cooled condenser. The reaction mixture was heated at 74 °C for different times (see Table 1). In all cases, the precipitates were collected by filtration and washed with propan-2-ol. The solids residues **7** or **8** were chromatographed on a column of silica gel with ethyl acetate as eluent solvent. The crude product **9** was purified by recrystallization from propan-2-ol.
13. *2-(1H-benzimidazol-1-ylmethyl)-4-chloro-3,5-dimethylphenol* (**7**): Mp 232–235 °C (uncorrected), yield 35%; ^{1}H NMR (400 MHz, CD_3OD) δ: 2.34 (6H, s, –CH_3), 5.49 (2H, s, N–CH_2–Ar), 6.77 (1H, s, H–C6′), 7.27 (1H, t, $J = 6$ Hz, H–C6), 7.30 (1H, t, $J = 6$ Hz, H–C7), 7.63 (1H, d, $J = 6$ Hz, H–C5), 7.66 (1H, d, $J = 6$ Hz, H–C8), 7.94 (1H, s, N=CH–N). ^{13}C NMR: (100 MHz, CD_3OD) δ: 19.7 (–CH_3), 40.5 (N–CH_2–Ar), 110.3 (C5), 115.0 (C6′), 118.6 (C8), 119.1 (C2′), 122.0 (C7), 122.7 (C6), 125.4 (C3′, C5′), 133.7 (C4), 136.3 (C4′), 137.6 (C9), 142.9 (C2), 154.4 (C1′). *1-(1H-benzimidazol-1-ylmethyl)-2-naphthol* (**8**): Mp 180–182 °C (uncorrected), yield 46%. ^{1}H NMR (400 MHz, CD_3OD) δ: 5.88 (2H, s, N–CH_2–Ar), 7.24 (1H, d, $J = 7.4$ Hz, H–C13), 7.27 (2H, t, $J = 6.6$ Hz, H–C7 and H–C8), 7.32 (1H, dt, $J_1 = 8.92$ Hz, $J_2 = 0.9$ Hz, H–C19), 7.46 (1H, dt, $J_1 = 8.6$ Hz, $J_2 = 1.1$ Hz, H–C18), 7.62 (1H, d, $J = 7.1$ Hz, H–C6), 7.76 (1H, dd, $J_1 = 8.32$ Hz, $J_2 = 1.1$ Hz, H–C20), 7.81 (1H, d, $J = 7.44$ Hz, H–C14), 7.83 (1H, d, $J = 6.9$ Hz, H–C9), 7.95 (1H, d, $J = 9$ Hz, H–C17), 7.97 (1H, s, H–C2). ^{13}C NMR: (100 MHz, CD_3OD) δ: 38.9 (N–CH_2–Ar), 110.5 (C20), 111.8 (C11), 117.3 (C13), 118.5 (C6), 122.0 (C19), 122.7 (C7), 122.7 (C8), 126.9 (C18), 127.4 (C17), 128.5 (C14), 129.0 (C16), 130.6 (C9), 133.3 (C5), 133.9 (C15), 142.5 (C4), 143.0 (C2), 154.2 (C12).
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20. *1:4,6:9,11:14,16:19-tetramethylentetrabenzo[b,g,l,q][1,4,6,9,11,14,16,19]octaazaeicocine (TTBOE)* (**9**): Mp 213–215 °C (uncorrected). ^{1}H NMR ($CDCl_3$) δ: 4.52 (8H, s, N–CH_2–N bridge), 4.55 (8H, s, N–CH_2–N cyclic); 6.33 (8H, dd, $J = 8.48$, $J = 2.76$, Ar), 6.52 (8H, dd, $J = 8.48$, $J = 2.76$, Ar). ^{13}C NMR ($CDCl_3$) δ: 57.4 (N–C–N), 71.4 (N–C–N), 105.4, 119.3, 140.2; HRMS calcd for $C_{32}H_{32}N_8$ (M^+) 528.65, found 528.60.
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22. *1,1′-Methylen-bis(1H-benzimidazole)* (**15**): Mp 134–136 °C (uncorrected), yield 42%. ^{1}H NMR (DMSO-d_6) δ: 6.89 (2H, s, N–CH_2–N); 7.21 (2H, t, $J = 7.20$ Hz, H–C7); 7.29 (2H, t, $J = 7.16$ Hz, H–C6); 7.65 (2H, d, $J = 8.3$ Hz, H–C5); 7.88 (2H, d, $J = 8.00$ Hz, H–C8); 8.18 (2H, s, H–C2). ^{13}C NMR (DMSO-d_6) δ: 52.9 (N–CH_2–N); 111.1 (C8); 120.2 (C5); 122.2 (C7); 123.6 (C6); 133.1 (C9); 143.9 (C4); 144.8 (C2).
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