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Synthesis and conformational analysis of 9,10-bis-aminomethyl-11,12-dicarboxy-dibenzobarrelene derivatives ☆

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Abstract—The synthesis of bis-γ-amino acid dibenzobarrelene derivatives (9,10-bis-aminomethyl-11,12-bis-carboxy-dibenzobarrelene) is presented. Bromomethylation of anthracene followed by azide substitution gave 9,10-bis-azidomethylanthracene. Azide reduction, *N*-Boc protection, and Diels–Alder cycloaddition in DMAD furnished the protected 9,10-bis-aminomethyl-11,12-dicarboxy-dibenzobarrelene derivative, which was further converted into the bis-γ-amino acid methyl ester, the *N*-Boc-protected bis-γ-amino methyl amide, and a bis-γ-lactam. Monte Carlo simulations and X-ray analysis of the 9,10-substituted dibenzobarrelenes revealed an exposed hydrophobic surface surrounded by amino and carboxy groups.

The use of artificial receptors is receiving increased attention for studying biomolecular interactions[1–6] at a molecular level, due to their well-defined chemical and structural features and to their ease of manipulation through chemical modifications. Protein binding sites commonly employ nonpolar aromatic amino acid side chains for ligand binding via for example, van der Waal's, hydrophobic, Π–Π, and cation–Π interactions, which are complemented by polar and charged side chains allowing for hydrogen bonding or salt bridges with the ligand. Thus, the presence of both polar and nonpolar interactions in a geometrically well-defined manner is critical.[7] Henceforth, in our ongoing search for biomimetic artificial receptors, a rigid molecular backbone possessing a nonpolar area surrounded by polar groups was desired. Within this context, the 9,10-disubstituted dibenzobarrelene framework appeared interesting, because it has the desired hydrophobic surface, as well as sites for modification at C-9 and C-10, and is thus ideally suited as an amphiphilic scaffold molecule. In a series of studies, Dougherty and co-workers used the dibenzobarrelene backbone structure in macrocycles as synthetic receptors in water, however, with a 2,6-disubstituted pattern.[8–12] Furthermore, Otto and co-workers used 2,6-disubstituted dibenzobarrelenes for the synthesis of a dynamic combinatorial library of macrocycles as water-soluble receptors for hydrophobic ammonium ions.[13,14] The 2,6-disubstituted dibenzobarrelenes provide more extended structures, in comparison to the 9,10-disubstituted examples, and would hence give different receptor characteristics and geometry.

Electrophilic aromatic substitutions provide a convenient entry into symmetrically 9,10-disubstituted anthracenes. The synthesis of 9,10-bis-azide **1** was readily performed via bromomethylation of anthracene[15] followed by substitution with sodium azide under phase-transfer conditions (Scheme 1). Problems were encountered upon attempted purification of the intermediate bis-bromide: it was not stable on silica and decomposed during crystallization attempts. Instead, subjecting the crude bis-bromide immediately to azide substitution conditions gave the stable azido compound **1**[16] in superior overall yield. The azide **1** was transformed into the Boc-protected amine **2** in one step with trimethylphosphine and Boc–ON.[17] Synthesis of the dibenzobarrelene **3** was achieved by Diels–Alder reaction with **2** in neat dimethylacetylene dicarboxylate (DMAD) at 90 °C. Attempts to use co-solvents were made with poor results. Unreacted excess DMAD was easily removed by vacuum distillation.

Keywords: Dibenzobarrelene; Ethenoanthracene; γ-Amino acid; Peptide turn.
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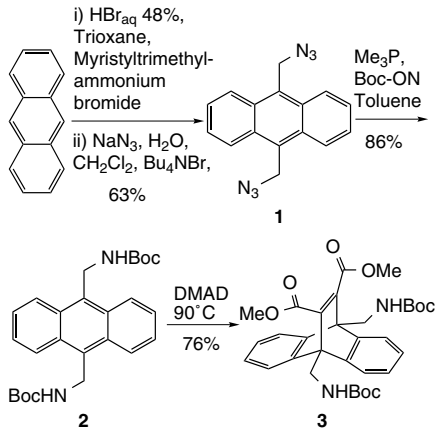
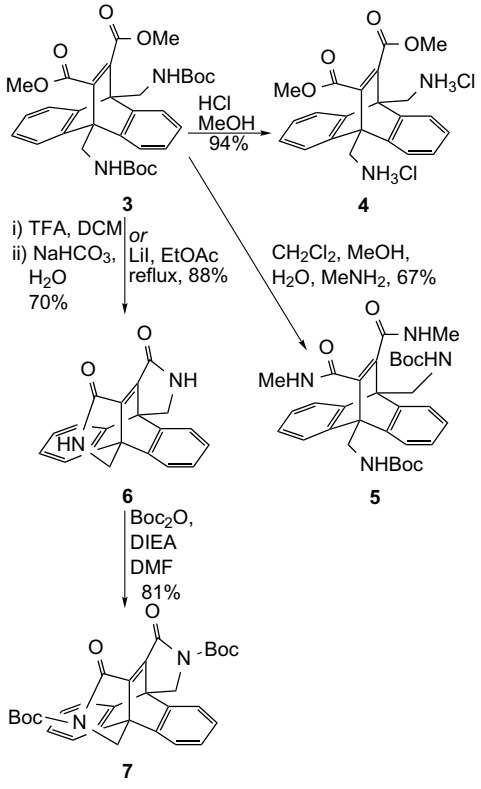


Scheme 1.

The rigid dibenzobarrelene **3** has two pairs of sites possessing orthogonal reactivity and routes towards an amino ester **4**, a methyl amide **5**, and a rigid polycyclic bis-lactam structure **6** were developed (Scheme 2). The Boc-protecting groups of **3** were readily removed with HCl in methanol to form the amino ester **4**. The primary amide **5** was obtained from **3** by treatment with methylamine. Cleaving the Boc-groups of **3** with TFA in dichloromethane followed by base treatment, resulted in spontaneous cyclization to afford the rigid polycyclic bis-lactam **6**. Alternatively, refluxing **3** in ethyl acetate in presence of LiI overnight removed both the methyl esters and the Boc groups to give the bis-lactam **6** as a precipitate. Subjecting the precipitate of **6** to Boc_2O in the presence of a base resulted in the formation of the N-protected bis-lactam **7**.



Scheme 2.

Monte–Carlo conformational searches[18,19] of **3** and **6** showed that the dibenzobarrelene backbone is indeed very rigid. The carbamates of **3** and amino groups of **4** fall into two different positions, either between two aromatic rings or between one aromatic ring and the etheno moiety. In their respective minimum conformations, the carbamates of **3** and amino groups of **4** are positioned one on each side of the etheno moiety (Fig. 1). These conformations are, according to ab initio calculations[20] both in water and in gas-phase, favored by approximately 5 kcal/mol over the conformations having both 9,10-substituents placed between the aromatic rings. Alignment of dipoles in the favored conformation could possibly explain the calculated energy differences, because no large differences in steric interactions were detected. The low-energy conformation of **3** with the two carbamate groups placed one on each side of the dicarboxy moiety was confirmed by X-ray studies[21] (Fig. 2). Thus, the large concave hydrophobic surface presented by the aromatic rings appears to be exposed even in water. The bis-lactam **6** was, as expected, found to be more or less totally rigid.

In conclusion, we have developed short and high-yielding syntheses of novel *C*2-symmetric and 9,10-bis-func-

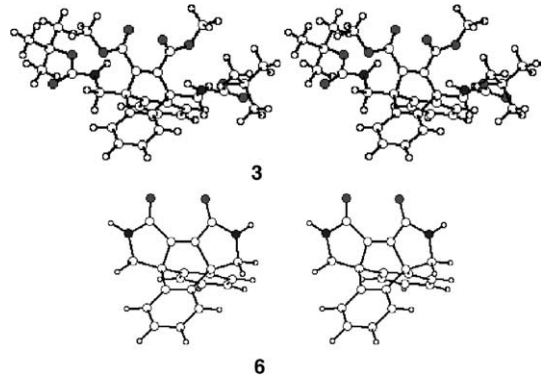


Figure 1. Stereo representations of the low-energy conformations obtained from Monte–Carlo calculations of **3** and **6**.

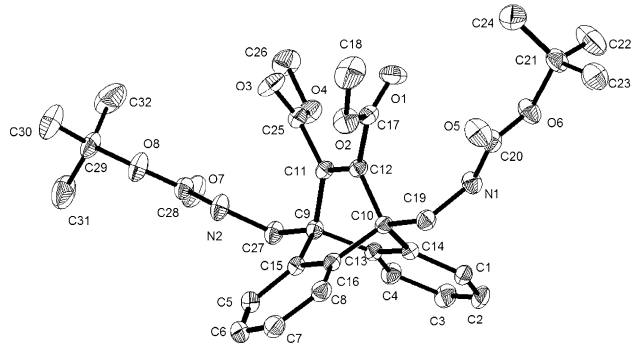


Figure 2. DIAMOND drawing of **3** with atomic numbering. Hydrogen atoms are omitted for clarity. The ellipsoids denote 30% probability. Selected torsion angles (°) with estimated standard deviations: N2–C27–C9–C11 = 55.0 (2), N1–C19–C10–C12 = 58.0 (2).

tionalized dibenzobarrelene structures, which have potential as core structures for the synthesis of biomimetic artificial receptor molecules as they are water-soluble and expose a large concave hydrophobic surface even in water according to calculations. Moreover, the bis-amino acid derivatives **4** and **5** are rigid bis-GABA derivative, which can be incorporated into two peptide chains to create a 'back-to-back' novel type of double peptide turn with potential in the preparation of novel turn mimetica.

Acknowledgements

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