Ab initio calculations are used to determine the most stable conformation for L-2,4-diaminobutyric acid (L-DABA). Structural characteristics are obtained and compared to γ-aminobutyric acid (GABA). It is found that for L-DABA the extended, partially folded, and cyclic conformations are almost equal in energy.

**INTRODUCTION**

γ-Aminobutyric acid (GABA) is the major inhibitory neurotransmitter of the mammalian central nervous system [1]. Altered synaptic neurotransmission mediated by GABA may play a role in the pathology of epilepsy and seizures [2].

Because diaminobutyric acid (DABA), a structural analog of GABA that contains one more amino group, has been reported to inhibit GABA uptake competitively [3–6], and because the distribution of DABA in nerve terminals mimics that of GABA [5,7,8], it has been suggested that GABA and DABA may be transported by the same high-affinity protein carrier [8–10]. It has also been suggested that DABA, unlike GABA, can cross the blood–brain barrier (BBB) [11].

In vivo studies on mice involving intraperitoneal and intracerebroventricular administration of DABA have yielded results suggesting that DABA acts through several GABA-related mechanisms [12]. Meldrum and co-workers showed that DABA was a neuron-selective transport inhibitor which functioned as a convulsant or proconvulsant after intracerebroventricular injection [13].

Erecinska and co-workers [14] have shown that, in a synaptosomal fraction from rat brain, transport of GABA and DABA is mutually competitive [see also refs. 15 and 16]. pH studies have shown that DABA is transported as a monovalent cation (DABA⁺). In addition, it has been shown that DABA is cotransported with one Na⁺ and its protonated α-amino group on DABA is positioned near the second Na⁺ site on this high-affinity carrier, while GABA in a synaptosomal fraction from rat brain is actively cotransported with two Na⁺ as a neutral molecule across the plasma membrane [17].

Sapse and co-workers have performed ab initio calculations on GABA, determining energies, bond angles, bond lengths, and dihedral angles for various molecular conformations [18]. It appeared to be of interest to perform similar calculations on DABA to see whether the information obtained could provide insights into the similarities and differences in the transport behaviors of GABA and DABA.

This work describes ab initio calculations, performed in order to elucidate the conformations and charge distributions of L-DABA in the gas phase. The gas phase may serve as a good model to mimic the nonhydrated environment of the inner membrane leaflet, which must be traversed in the course of crossing the BBB, or of the hydrophobic receptor-binding site. Ab initio calculations can provide useful information on bond lengths, bond angles, dihedral angles, energies, and molecular conformations that may exist in a
particular model system. The structural characteristics of L-DABA are compared to GABA [18], taurine, and hypotaurine [19] in order to identify the similarities and differences between their lowest energy conformations. The ability of L-DABA to inhibit GABA, taurine, and hypotaurine in high-affinity transport in synaptic somal tissue [16] is correlated with the conformational structures of the compounds.

**METHODS AND RESULTS**

The method of calculation is the ab initio self-consistent field (Hartree-Fock) method, using Gaussian basis sets as implemented by the GAUSSIAN-80 computer program [20,21]. Each system is geometry optimized by allowing all the molecular parameters to relax (subject to the constraints described below) and using the Berny optimization method for obtaining the energetically optimized molecular geometries [22].

The neutral conformations in this study, L-DABA in an extended conformation (1, Figure 1), (2) in a partially folded conformation (2, Figure 2), and in a cyclic conformation (3a–d, Figure 3), have been geometry optimized with the 6-31G basis set [20].

The initial geometries were chosen as follows: in order to obtain an all-extended geometry it is sufficient to set the dihedral angles N2-C4-C3-C2 and C4-C3-C2-C1 at 180.0°. Several partially folded conformations were tried and preliminary optimizations were performed. The conformation that featured the dihedral angle C4–C3–C2–C1 of 90.0° was found to be the most stable and was chosen for further optimization.

The cyclic structure examined features a hydrogen bond between H1 and N2 (Figure 3). In addition, we performed calculations on another cyclic structure, which featured a hydrogen bond between H1 and N1. This cyclic conformation was found to be much higher in energy than the cycle we show in Figure 3 and therefore we did not find it necessary to subject it to complete optimization. To obtain the initial cycle, leading to structure 3', the dihedral angles were given values that insured the formation of the H1–N2 hydrogen bond.

Once these structures were selected, all the parameters of the molecules, including the above-mentioned dihedral angles, were allowed to relax, subject to the following constraints: for the extended and the partially folded L-DABA, all the NH bonds, CH bonds, and H–C–C were kept equal. For the cyclic conformation of L-DABA (where H1 is hydrogen bonded to N2), the parameters of the molecule were allowed to relax, subject to the constraint that the dihedral angle N2–H1–O1–C1 be set at 0.0°. The geometries were then optimized. After optimization was performed, the minima corresponding to Figures 1, 2, and 3 were obtained. All the structures mentioned above are neutral species. The cyclic zwitterion (where N2 is protonated) of L-DABA was also examined performing energy optimization.

![Figure 1. The extended conformation of L-DABA.](image1)

![Figure 2. The partially folded conformation of L-DABA.](image2)