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ORIGINAL RESEARCH

Conformational analysis of *N*-isopropylbenzohydroxamic acids: crystal structure, DFT, and NMR studies

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Abstract X-ray crystal structure determinations together with density functional theory (DFT) calculations in vacuo and NMR studies in solution have been carried out for 4-$MeOC_6H_4CONPr^iOH$ **2a** and 3,5-$(NO_2)_2C_6H_3CONPr^iOH$ **2b**. The results were compared with that for the respective *N*-methyl benzohydroxamic acids. For crystal structures as well as for DFT-optimized geometries of **2** (both isomers) in vacuo, the effect of substituents in aromatic ring manifested by changing of charges is inconspicuous. Studies of potential energy surfaces showed that libration barrier around $\omega_1 = 0°$ is low enough to make electron conjugation feasible, and that for **2b** rotation barrier around C(O)N bond is higher by 6 kcal/mol and additionally, that rotation around N–C bond is hindered. A careful analysis of low-temperature ^{1}H NMR spectra confirmed the greater stability of *Z*-**2a**, the greater rigidity of *E*-**2b** and the influence of solvent on both isomers population. Despite solvent-dependent conformational alteration, both **2a** and **2b** crystallize exclusively as *E* isomers from ethyl acetate solution. Correlations of absolute ^{1}H, ^{13}C, and ^{15}N shielding calculations with experimental data were also analyzed.

Keywords Hydroxamic acids · X-ray structure · DFT calculations · Substituent effects · Conformations · Absolute nuclear shieldings

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Introduction

N-Hydroxyamide unit is the main function of microbial hydroxamate siderophores. Natural as well as synthetic hydroxamic acids play a diverse biological activity, including antibacterial, antifungal, and antitumor profiles [1]. They are specific inhibitors of wide spectrum of metalloenzymes due to their strong chelating properties [2]. The conformational behavior of hydroxamic acids in solution connected with $Z \leftrightarrows E$ isomerization is well recognized by NMR spectroscopy. It was found that *N*-methyl benzohydroxamic acids **1** exist as mixtures of both isomers with the slight domination of the *Z* one in chloroform [3] and in dichloromethane ($K_{Z/E} = 1.86$–2.74; $\Delta E_{rot} = 12.0$–14.8 kcal/mol) [4]. It was found that the electronic character of *para* substituent have no influence on a *Z/E* ratio and the *Z* isomer population strongly depends not only on the solvent used but also on concentration [4]. Until now, ab initio methods were applied only for the simplest formohydroxamic and acetohydroxamic acids [5]. Calculations showed that *E* isomers are nearly always more stable. However, sometimes hydrated *Z* isomers have lower energy. It is still believed that the use of high level methods and large basis sets are necessary for compounds having an N–O bond, because none of the used methods describes the hydroxamic acid structure satisfactory [6].

N-Methyl-4-methylbenzohydroxamic **1a** and *N*-methyl-4-metoxybenzohydroxamic acids **1b** are the only representatives of crystal structures of *N*-alkylbenzohydroxamic acids reported in the Cambridge Structural Database (CSD version 5.29, with Nov 2007 updates [7]). Like most secondary hydroxamic acids they exist as *E* isomers that is apparently due to a strong intermolecular hydrogen bonding. It should be added that some *N*-aryl hydroxamic acids are essentially present as *Z* isomers in solid-state. Recently [8],