Journal of Molecular Structure 1093 (2015) 8–12

Contents lists available at ScienceDirect

Journal of Molecular Structure

journal homepage: www.elsevier.com/locate/molstruc

Intramolecular interactions contributing for the conformational preference of bioactive diphenhydramine: Manifestation of the *gauche* effect

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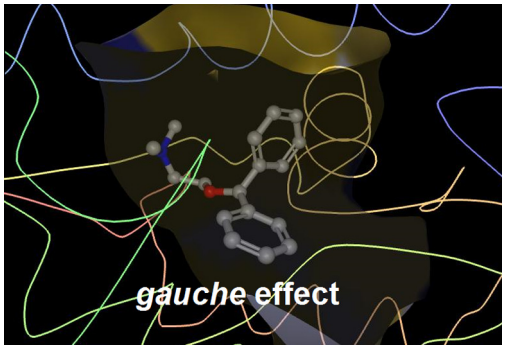
HIGHLIGHTS

- Neutral and protonated diphenhydramine exhibits the *gauche* effect.
- The *gauche* effect in diphenhydramine is due predominantly to hyperconjugation.
- The cation experiences hydrogen bond, hyperconjugation and electrostatic attraction.
- The main conformation of calculated diphenhydramine matches its bioactive geometry.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 28 January 2015
Received in revised form 5 March 2015
Accepted 23 March 2015
Available online 27 March 2015

Keywords:
Diphenhydramine
Gauche effect
Hyperconjugation
Electrostatic effects
Hydrogen bonding

ABSTRACT

Diphenhydramine is an antihistamine used to treat some symptoms of allergies and the common cold. It is usually marketed as the hydrochloride salt, and both the neutral and cation forms have the O–C–C–N fragment. The *gauche* effect is well known in fluorine-containing chains, because its main origin is hyperconjugative and the σ^*_{C-F} is a low-lying acceptor orbital, allowing electron delocalization in the conformation where F and an adjacent electronegative substituent in an ethane fragment are in the *gauche* orientation. Our experimental (NMR) and theoretical findings indicate that diphenhydramine exhibits the *gauche* effect, since the preferential conformations have the O–C–C–N moiety in this orientation due especially to antiperiplanar $\sigma_{C-H} \rightarrow \sigma^*_{C-O}$ and $\sigma_{C-H} \rightarrow \sigma^*_{C-N}$ interactions. This conformational preference is strengthened in the protonated form due to an incremental electrostatic *gauche* effect. Because the *gauche* conformation matches the bioactive structure of diphenhydramine complexed with histamine methyltransferase, it is suggested that intramolecular interactions, and not only induced fit, rule its bioactive form.

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Introduction

The *gauche* effect was introduced by Wolfe [1] to indicate the tendency of some species in adopting a structure which has a maximum number of *gauche* interactions between the adjacent electron pairs and/or polar bonds. Organofluorine compounds, *e.g.* the milestone 1,2-difluoroethane, are known to exhibit the *gauche* effect, because they have low-lying σ^*_{C-F} orbitals and, therefore, antiperiplanar hyperconjugative electron donation from relatively good donor orbitals (σ_{CH} for 1,2-difluoroethane) to the electron acceptor σ^*_{C-F} orbital stabilize the *gauche* conformation, overriding steric or electrostatic repulsions between the adjacent electronegative substituents in an ethane fragment [2–4]. The origin

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http://dx.doi.org/10.1016/j.molstruc.2015.03.033
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of the *gauche* effect in fluorinated compounds can also be due to electrostatic interactions [5–7], in which the negatively charged fluorine interacts with the positive nitrogen in β-fluoro-*N*-ethylpyridinium/ammonium salts [8–10], or due to hydrogen bonding, in which the proximity of *gauche* fluorine and hydroxyl groups allows the establishment of hydrogen bonds [11]. However, the *gauche* effect in non-fluorinated compounds has been less explored, despite the prospective framework of some relevant molecules to exhibit this effect, *i.e.* molecules containing the 1,2-disubstituted ethane fragment (substituents = electronegative atoms or groups), such as the O–C–C–N moiety.

Diphenhydramine is an example of drug molecule containing the O–C–C–N moiety in its chemical structure; the oxygen and nitrogen atoms are oriented in *gauche* arrangement in both ligands of the histamine methyltransferase enzyme (Fig. 1). In order to investigate whether such arrangement is due to induced fit or not, diphenhydramine was searched in solution using NMR coupling constants, as well as in the gas phase and implicit solution using theoretical calculations. In addition, the protonated diphenhydramine was experimentally and theoretically studied to give insight about the role of the electrostatic *gauche* effect in this cation, and also because it is not explicit in the crystal if the bioactive compound is protonated or not [12]. The outcomes from this study can be useful to understand the role of intramolecular interactions as governing factors of the conformational preferences in a biological environment, since an earlier work showed that the bioactive conformation of 2,4-dichlorophenoxyacetic acid (2,4-D), an herbicide that binds the TIR1 ubiquitin ligase enzyme, does not match the structure of the calculated most stable conformer [13].

Experimental

Diphenhydramine hydrochloride (**1**) was commercially available, while its neutral form (diphenhydramine, **2**) was prepared by deprotonation of **1** using powder zinc in diethyl ether [14], as confirmed by infrared spectroscopy. The NMR experiments were carried out at 60.0 and 499.9 MHz for H-1, for *ca.* 20 mg mL^{-1} solution in $CDCl_3$.

Calculations were first carried out by scanning the possible energy minima of **1** and **2** through the Monte Carlo distribution method at the AM1 semi-empirical method [15], using the Spartan program [16]. The obtained conformers were optimized (frequency calculations included) at the HF/6-31g(d,p) level [17] to verify the absence of imaginary frequencies and, subsequently, the ten (in the gas phase) or eleven (in implicit solution) different geometries found for **1** and thirteen for **2** were further optimized at the ωB97X-D/6-31++g(d,p) level [18] (for the gas phase and using implicit solvents – chloroform and acetonitrile – according to the polarizable continuum model, PCM [19]). Natural bond orbital (NBO) analysis [20], including deletion of all antibonding and Rydberg orbitals, and NMR coupling constant calculations were carried out at the same DFT level. These calculations were performed using the Gaussian 09 program [21]. Quantum theory of atoms in molecules (QTAIM) [22] calculations were performed to search for possible hydrogen bonds using the AIMAll program [23].

Results and discussion

Both diphenhydramine (**2**) and its protonated form (cation **1**) of Fig. 2 were submitted to conformational scanning using the Monte Carlo approach at the AM1 semi-empirical level, giving more than 100 geometries, but many were coincident. Indeed, up to 11 different conformers for **1** and 13 for **2** were found for the gas phase and solution (implicit $CHCl_3$ and acetonitrile), according to DFT ωB97X-D/6-31++g(d,p) calculations (Supplementary Material). This theoretical level includes dispersion effects and has shown good agreement with CCSD results for aromatic systems [24]. The *gauche* effect is evident for **1** after analyzing the energy results of Table 1 (in agreement with solid-state data available in the literature [25]), where only a single high energy conformer (two in solution) appears with *anti* geometry along with the O–C–C–N torsional angle. Indeed, the remaining *gauche* conformers are more stable than *anti* ones independent of the medium, despite diphenhydramine hydrochloride is supposed to have different conformation in crystals and solutions [26].

According to earlier studies for compounds containing the F–C–C–N^+ fragment [8–10,27–31], the preferred *gauche* arrangement along this fragment has strong contribution from the electrostatic attraction between the electronegative fluorine substituent and the positively charged nitrogen. According to NBO analysis, the *gauche* conformers are far more stabilized by hyperconjugation than the *anti* geometries (Table 1), whose important contribution comes from $\sigma_{CH} \rightarrow \sigma^*_{CO}$ and $\sigma_{CH} \rightarrow \sigma^*_{CN}$ hyperconjugative interactions (Table 2). Decomposition of the full energy of each conformer into non-Lewis (hyperconjugation) and Lewis-type (steric and electrostatic interactions) contributions indicates that *gauche* conformers are generally destabilized by steric repulsion in comparison to *anti* conformers, but possibly less than expected if electrostatic attraction between *gauche* F and N^+ was not present (because $\Delta E_{\text{Lewis }(\mathbf{1g1}-\mathbf{1a1})} < \Delta E_{\text{Lewis }(\mathbf{2g1}-\mathbf{2a1})}$). In addition, the low-energy conformers $\mathbf{1g_1}$–$\mathbf{1g_5}$ present the N–H hydrogen oriented toward the oxygen atom, giving rise the possibility to form intramolecular hydrogen bond. Indeed, the global minimum $\mathbf{1g_1}$ exhibits a bond path between H(N) and O according to QTAIM analysis, indicating conformer stabilization due to intramolecular hydrogen bond, which is characterized by the electronic density along with the O···HN pathway (ρ, that should fall within 0.004 and 0.04 au), its

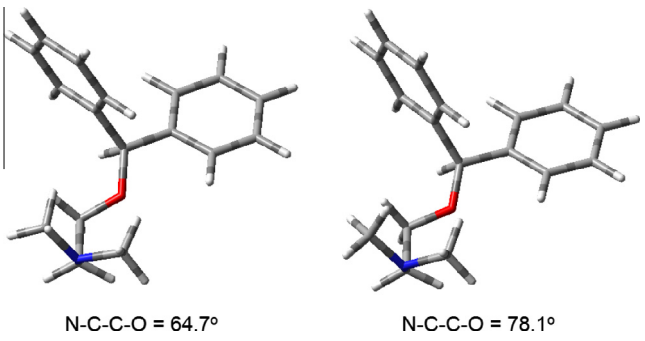

Fig. 1. Chemical structures of two diphenhydramine molecules complexed with the histamine methyltransferase enzyme (PDB code: 2AOT). The H(N) hydrogen can be omitted.

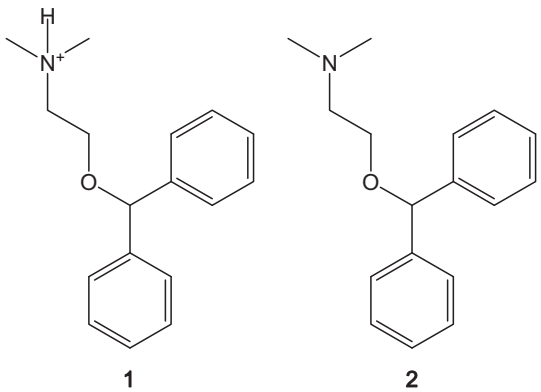

Fig. 2. The chemical structures of protonated (**1**) and neutral (**2**) diphenhydramine.

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