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Experimental and quantum mechanical studies on the ion–pair of levocetirizine and bromocresol green in aqueous solutions

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ABSTRACT

In the present work, levocetirizine dihydrochloride (LEV) was found to interact with bromocresol green (BCG) via ion–pair formation. UV–vis and FTIR spectroscopy were used to validate the data obtained from quantum mechanical calculations (QMC). The electrostatic potential maps show that the reaction is preferred through the interaction of the sulfonic acid group of BCG and the quaternary ammonium group of LEV. The optimized geometry of the product shows that there are six different intermolecular hydrogen bonds between the studied molecules resulting from the ionic attraction between the oppositely charged groups. The UV–vis spectra suggest the formation of an ion–pair. This finding is contradicting with the previous charge–transfer hypothesis.

1. Introduction

Levocetirizine dihydrochloride (LEV), shown in Scheme 1(a), is named by the IUPAC as [2–[4–[(R)–(4–chlorophenyl) phenylmethyl]–1–piperazinyl] ethoxy] acetic acid dihydrochloride. It has a molecular formula of $C_{21}H_{25}ClN_2O_3 \cdot 2HCl$. It is a third generation non sedative antihistaminic drug derived from the second generation antihistaminic drug cetirizine. It prevents the binding of histamine molecules released from mast cells to the histamine receptors in order to prevent inflammation. This effect reliefs the symptoms of allergy such as flares, redness and irritation [1,2].

Bromocresol green (BCG), shown in Scheme 1(b), molecular formula $C_{21}H_{14}Br_4O_5S$, is a well known acid dye for analytical chemists because it is used as a pH indicator. It belongs to the triphenylmethane family (also called sulfonephthaleins). The IUPAC name of BCG is 2,6–dibromo–4–[7–(3,5–dibromo–4–hydroxy–2–methyl–phenyl)–9,9–dioxo–8–oxa–9λ6–thiabicyclo[4.3.0] nona–1,3,5–trien–7–yl]–3–methyl–phenol. In aqueous solutions, it is deprotonated to yield the yellow monoanionic form that can be deprotonated at high pH to give the blue dianionic form [3].

Different researchers propose spectrophotometric methods for determining organic drug molecules containing quaternary ammonium groups by reacting them with triphenylmethane acid dyes [4]. These methods depend on the formation of a yellow product in organic solvents which is subsequently measured with the aid of a spectrophotometer. However, we have found that triphenylmethanes themselves give the same yellow color when treated with hydrochloric acid in aqueous solutions 0 [5]. This fact encouraged us to study the type of interaction between these compounds in aqueous media to make sure whether there is a reaction between LEV and triphenylmethanes or it is only the effect of the pH change which causes the variation in color. This study is critical for analytical chemists who use the reaction under investigation to estimate drugs containing quaternary ammonium groups [5–14] because the nature of interaction is an important factor which affects the selectivity and sensitivity of the analytical method. However, no previous studies are devoted to the way of bonding of any of these drugs with triphenylmethanes. On the other hand, there are different hypotheses in the literature that the reaction occurs by charge–transfer [12], proton–transfer [5] and ion–pair [5–7,13,14] formation without any clear evidence.

According to the above facts, it is necessary to investigate this type of interaction to make sure that sulphonephthalein acid dyes can be used as chromogenic reagents in spectrophotometric analysis of some pharmaceutical compounds with reasonable selectivity. BCG acid dye was taken as an example during the study. The present work relies on the use of spectroscopic tools such as UV–vis and FTIR spectroscopy to support the theoretical quantum mechanical calculations. The experimental spectra were scanned and compared with the calculated ones to prove our hypothesis.

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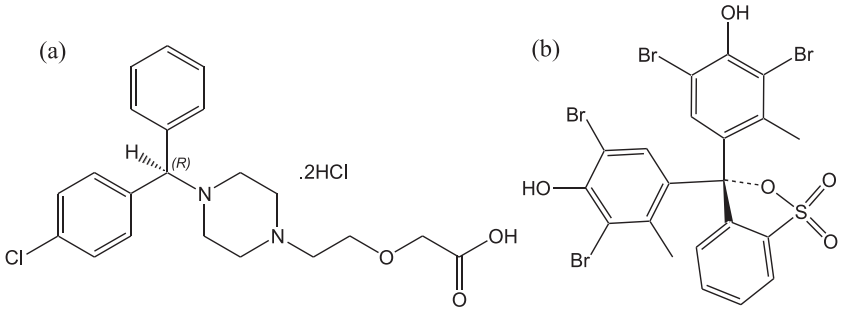

Scheme 1. Chemical structure of LEV (a) and BCG (b).

The electrostatic potential (ESP) maps were visualized and studied to investigate the reactivity of the studied molecules which will give some information about the preferable sites of interaction. In addition, frontier molecular orbitals (FMOs) were studied to help interpret the electronic transitions together with the reactivity of the studied molecules. Moreover, we used FMOs to prove the origin of the electronic transitions which cause the formed yellow color in aqueous solutions. We have found that LEV interacts with the BCG via the formation of an ion–pair through the negatively charged sulfonic acid group of BCG and the positively charged quaternary ammonium group of the drug. In addition, the formation of a number of hydrogen bonds provide more stability for the formed product. These hydrogen bonds were formed due to the presence of LEV molecule in close proximity to the highly electronegative oxygen atoms of the BCG sulfonic acid group.

2. Materials and methods

2.1. Materials

During this study, highly pure chemicals (HPLC grade) were used. The drug LEV was obtained from BORG Pharmaceutical Industries, Borg El–Arab, Alexandria, Egypt. BCG was purchased from MERCK, Germany. Absolute ethyl alcohol from Sigma–Aldrich Chemie GmbH, Germany was used throughout the work procedures. Double distilled water was used to wash the glasswares during all experiments.

2.2. Preparation of standard solutions

Standard solutions of 0.01 mol/L of LEV or BCG were prepared by accurately weighing 0.4618 or 0.6980 g, respectively, and dissolving it in 100 mL of absolute ethanol in a 100 mL standard measuring flask.

2.3. Apparatus

A Scientech SA 210 balance was used for weighing chemicals. A Perkin–Elmer Lambda 4B UV–vis double beam spectrophotometer equipped with 1.0 cm quartz cells was used for UV–vis spectrophotometric measurements. FTIR spectra were recorded using transmission through KBr pellets with the aid of a Shimadzu FTIR spectrometer, Micro–Analytical Center, Faculty of Science, Cairo University.

2.4. Methods of calculations

Optimization of the molecular geometries and TD–DFT [15] calculations for the studied molecules and their interaction product were carried out using WB97XD [16] method. This method is more accurate than the pure Hartree–Fock level of theory. Moreover, it can describe the π–π* interactions because it takes into account the dispersion energy corrections. The 6–311 ++G(d,p) basis set was used for all geometry optimization calculations. The 6–31G(d,p) basis set was used for all frequency calculations after geometry optimization.

All the calculations were done using the Gaussian 09W software [17] The TD–DFT calculations were carried out for 10 excited states. Gaussview [18] version 5.0.9 and Chemcraft [19] software packages were used for visualization of the optimized geometries, molecular orbitals and electrostatic potential maps.

3. Results and discussion

3.1. Geometry optimization

The fully optimized geometry of LEV is shown in Fig. 1. The energy of the obtained global minimum is shown in Table 1. The two phenyl rings

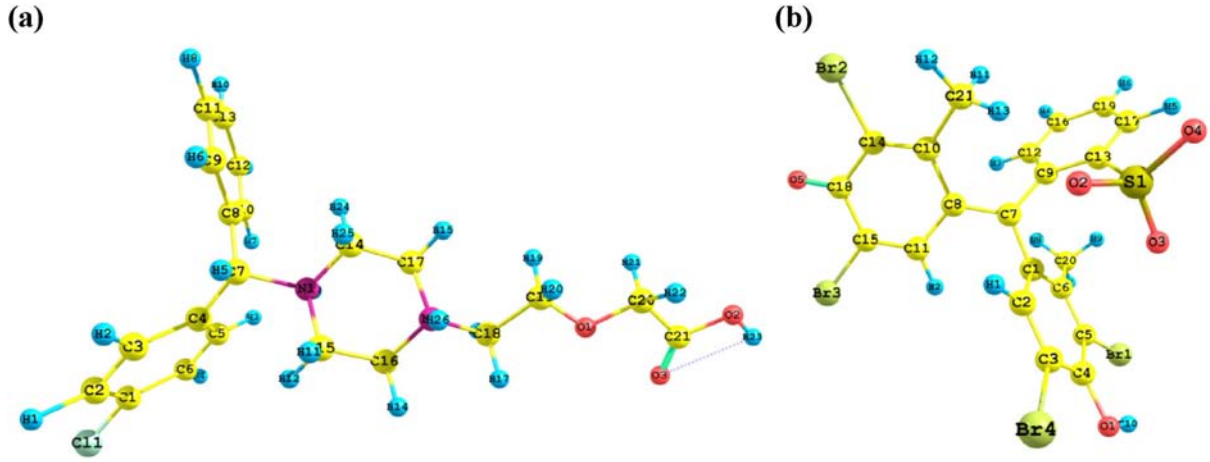

Fig. 1. Optimized geometry of protonated LEV (a) and the quinoid form of BCG (b).