Computational and Theoretical Chemistry 988 (2012) 63–74

Contents lists available at SciVerse ScienceDirect

Computational and Theoretical Chemistry

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

Exploring the unexpected pyridine- and 4,4′-bipyridine-catalyzed isomerization of maleic acid: A DFT approach

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ARTICLE INFO

Article history:
Received 22 December 2011
Received in revised form 20 February 2012
Accepted 22 February 2012
Available online 3 March 2012

Keywords:
Maleic acid
Isomerization of maleic acid
Cis–trans isomerization
DFT calculations
4,4′-Bipyridine-catalyzed *cis–trans* isomerization

ABSTRACT

DFT at B3LYP/6-31G(d,p) and B3LYP/6-311+G(d,p) levels calculations for the pyridine- and 4,4′-bipyridine-catalyzed isomerization of maleic acid demonstrated that the mechanism involves four steps: (1) a proton transfer from one of maleic acid carboxyl groups onto the amine nitrogen (pyridine or 4,4′-bipyridine) to yield an ion pair INT1. (2) Proton transfer from INT1 to the C–C double bond to give INT2. (3) Rotation about the central C–C single bond followed by proton abstraction by an amine molecule to yield INT3, and (4) proton transfer from the ammonium cation into the carboxylate anion of the fumarate thus formed to furnish the *trans* isomer, fumaric acid. Moreover, the calculations revealed that an abstraction of a proton from INT2 (step 3) was found to be the rate limiting step. However, the activation energy difference between steps 2 and 3 was not significant. Furthermore, it was found that the solvent dielectric constant has a profound impact on both the isomerization activation energy and the free energy difference between the *cis* and *trans* isomers (maleic and fumaric acids). While, polar solvents such as DMSO tend to lower the isomerization activation energy and to increase the free energy difference between the two isomers, apolar solvents such as chloroform behave in an opposite manner. In addition, linear correlation was found between the activation energy and the solvent dielectric constant.

1. Introduction

Maleic acid is a synthetic organic compound and it is highly useful as an intermediate in the industrial preparations of polyester resins, plasticizers, copolymers, and agricultural chemicals. Its *trans* isomer, fumaric acid, is a naturally occurring organic acid. It was first isolated from the plant *Fumaria officinalis*, from which it derives its name. Many microorganisms produce fumaric acid in small amounts, as it is a key intermediate in the citrate cycle. Fumaric acid is used by cells to produce energy from food. Human skin naturally produces fumaric acid when exposed to sunlight. Fumaric acid is a food additive commonly included in sweet foods such as baked goods and dairy-based desserts and it is also used as an intermediate in the synthesis of certain polyester resins, furniture lacquers, paper sizing chemicals and aspartic acid [1].

The major industrial use of maleic acid is its isomerization to fumaric acid. This isomerization, is catalyzed by a variety of reagents, such as mineral acids and thiourea. Maleic acid and fumaric acid do not spontaneously interconvert because rotation around a C–C double bond is restricted. However, isomerization of the *cis* isomer into the *trans* isomer is possible by photolysis in the presence of a catalytic amount of bromine. Light converts bromine into a bromine radical, which attacks the alkene in a radical addition to a bromo-alkane radical which allows a single bond rotation. The bromine radicals recombine and fumaric acid is formed. In another method, maleic acid is transformed into fumaric acid through the process of heating the maleic acid in hydrochloric acid solution. Reversible addition of proton leads to free rotation about the central C–C bond and formation of the more stable isomer, fumaric acid. In earlier studies a mechanism was proposed for the acid and salt catalyzed isomerization of maleic acid to fumaric acid. The mechanism assumed the formation of an intermediate which involves both a proton donor and an electron donor (anion) [2–6].

Another interest in maleic and fumaric acids comes from the medical field. Recent studies showed that fumaric acid can be used to treat psoriasis, but there are risk factors involved upon ingestion of this pharmaceutical. It has been also documented that fumaric acid could be used as a cure for the inflammatory disease multiple sclerosis (MS). However, its use as a medicine for a chronic disease was not an ideal. It causes flushing and some unpleasant gastrointestinal side effects. Recently, researches began developing fumaric acid derivatives that maximized efficacy while minimizing side effects. One of these was dimethyl fumarate, however its bioavailability was very low due to fast degradation upon exposure to physiological environments [7–10].

Cocrystal solid forms have received considerable attention during the past few years because of the utility of the cocrystallization

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doi:10.1016/j.comptc.2012.02.030

process in affecting the physical properties such as dissolution rate of a material without affecting its intrinsic chemical structure. The cocrystallization process has been used in the pharmaceutical industry to obtain solid forms of active ingredients with enhanced physical properties. Other solid forms can be chosen to optimize the physical properties of active ingredients including polymorphs, solvates, and salts. For example, the dissolution rate of the α polymorph of chloramphenicol palmitate is different from that of its β polymorph. Hence, the bioavailability of the two different polymorphs is different. Other examples are theophylline and erythromycin by which the hydrate forms have different dissolution rates and bioavailability when compared to their anhydrous forms [11–15].

Rao and coworkers have studied the structures of hydrogen bonded adducts obtained by co-crystallization of some aliphatic dicarboxylic acids with the expectation of forming interesting hydrogen bonded supramolecular assemblies. They examined the structures of the adducts obtained from the cocrystallization of maleic acid with 4,4′-bipyridine, in different solvents. Cocrystallization of maleic acid and 4,4′-bipyridine was obtained when the solvent used was acetone, chloroform, ethylacetate and methanol but co-crystallization in dimethylformamide and dimethylsulfoxide gave an adduct where maleic acid had isomerized to fumaric acid [16]. Recently, Tocher and coworkers have investigated the two-component crystals formed from pyridine or 4-dimethylaminopyridine with maleic, fumaric, phthalic, isophthalic, or terephthalic acids by X-ray diffraction method. Their study demonstrated that the two-component solid forms involving pyridine included both salts and cocrystals, while 4-dimethylaminopyridine crystallized exclusively as a salt, in agreement with the differences in the p*K*a values. In addition, they reported that an *in situ* base catalyzed isomerization of maleic acid was observed in cocrystallization experiments involving pyridine [17].

Continuing our studies on the design and synthesis of prodrugs for certain drugs that have low dissolution rates and poor bioavailability we sought to investigate the pyridine- and 4,4′-bipyridine-catalyzed isomerization of maleic acid into its *trans* isomer, fumaric acid in order to utilize the former as a prodrug for the latter [18–23]. Unraveling the mechanism of the isomerization might shed light on the kinetics of this conversion and might lead to a potential prodrug system capable of delivering the parental drug with higher bioavailability than the current direct administration of fumaric acid or its mono- and di-esters.

2. Methods

The Becke three-parameter, hybrid functional [24] combined with the Lee, Yang, and Parr correlation functional [25], denoted B3LYP [26], were employed in the calculations using density functional theory (DFT). All calculations were carried out using the quantum chemical package Gaussian-2009 [27]. Calculations were carried out based on the restricted Hartree–Fock method [27]. The starting geometries of all calculated molecules were obtained using the Argus Lab program [28] and were initially optimized at the HF/6-31G level of theory followed by optimization at the B3LYP/6-31G(d,p) and B3LYP/6-311+G(d,p). Second derivatives were estimated for all 3N-6 geometrical parameters during optimization. An energy minimum (a stable compound or a reactive intermediate) has no negative vibrational force constant. A transition state is a saddle point which has only one negative vibrational force constant [29]. Transition states were located first by the normal reaction coordinate method [30] where the enthalpy changes was monitored by stepwise changing the interatomic distance between two specific atoms. The geometry at the highest point on the energy profile was re-optimized by using the energy gradient method at the B3LYP/6-31G(d,p) and B3LYP/6-311+G(d,p) levels of theory [27]. The "reaction coordinate method" [30] was used to calculate the activation energy for maleic acid in the presence of 4,4′-bipyridine and pyridine (Scheme 2). In this method, one bond length is constrained for the appropriate degree of freedom while all other variables are freely optimized. The activation energy values for the first step in the process (proton transfer from one of the carboxylic groups of maleic acid onto the pyridine or 4,4′-bipyridine nitrogen, Scheme 2) were calculated from the difference in energies of the global minimum structures (*Cis*) and the derived transition states (TS_1 in Scheme 2). Similarly, the activation energies for step 2, a proton transfer from the pyridinium or 4,4′-bipyridinium cations to the C–C double bond to form INT2 were calculated from the difference in energies of the global minimum structures (*Cis*) and the corresponding transition states (TS_2 in Scheme 2). The activation energy values for step 3, an abstraction of a proton from INT3 by a pyridine or 4,4′-bipyridine molecules were calculated from the difference in energies of the *Cis* and the corresponding transition states (TS_3 in Scheme 2). The activation energy values for step 4 (proton transfer from a pyridinium or 4,4′-bipyridinium cation to the carboxylate anion, step 4 in Scheme 2) were calculated from the difference in energies of the global minimum structures (*Cis*) and the corresponding transition states (TS_4 in Scheme 2). Verification of the desired reactants and products was accomplished using the "intrinsic coordinate method" [30]. The transition state structures were verified by their only one negative frequency. Full optimization of the transition states was accomplished after removing any constrains imposed while executing the energy profile. The activation energies obtained from the DFT at B3LYP/6-31G(d,p) and B3LYP/6-311+G(d,p) levels of theory for maleic acid in the presence of 4,4′-bipyridine and pyridine were calculated with and without the inclusion of solvent (water, chloroform, dimethylsulfoxide, methanol and acetone). The calculations with the incorporation of a solvent were performed using the integral equation formalism model of the Polarizable Continuum Model (PCM) [31–34]. In this model the cavity is created via a series of overlapping spheres. The radii type employed was the United Atom Topological Model on radii optimized for the PBE0/6-31G(d) level of theory.

3. Results and discussion

3.1. General consideration

Because the energy of carboxylic acid is strongly dependent on its conformation especially on its ability to be engaged either inter- or intramolecularly in hydrogen bonding, we were concerned with the identification of the most stable conformation (global minimum) for each of maleic acid/4,4′-bipyridine, maleic acid/pyridine, fumaric acid/4,4′-bipyridine and fumaric acid/pyridine adducts calculated in this study. This was accomplished by 36 rotations of each of the two carboxyl groups of maleic acid about the C5–C6 bond in increments of 10° (i.e. variation of the dihedral angles O2/C4/C5/C6 and O9/C7/C6/C5, see Chart 1) and calculation of the energies of the resulting conformers.

In the DFT calculations of the reactions of maleic acid in the presence of 4,4′-bipyridine and pyridine two types of conformers were considered: one in which the two carboxylic carbonyl groups are perpendicular each to other (Chart 1a) and another in which they are 180° each to other (Chart 1b). It was found that the global minimum structures exhibit conformation by which the two carbonyl groups exist perpendicularly each to other (Chart 1a). Further, the calculations revealed that maleic acid and fumaric acid exist in conformations by which the hydroxyl proton of their carboxyl groups is engaged in a hydrogen bonding with a molecule