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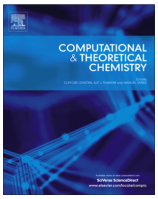

Quantum chemical study of the impact of protective association on the chemoselective synthesis of carboxybetaine from 2-(dimethylamino) ethanol and acrylic acid

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ABSTRACT

Targeted carboxybetaine synthesis is an important process that one can apply to prepare polymeric materials with various unique properties or low molecular weight products, such as deep eutectic solvents based on acrylic acid formulated for the specific tasks. Analyzing the mechanism of carboxybetaine formation, it was found that with an excess of amine, the H-bond formed between amine nitrogen and the acidic proton of the acrylic acid was strong enough to protect the intermediate obtained after carbanion protonation from the interaction with acrylate anion, thus facilitating the formation of quaternary ammonium salts as the final product at the beginning of the reaction instead of the desired carboxybetaine. Similarly, a threefold excess of acrylic acid should also lead to the preferential formation of the quaternary salt due to the protection of the half-product from the interaction with acrylate anion via cyclic dimer formation with two strong H-bonds. From the other side, calculations revealed that a twofold excess of acrylic acid should provide formation of carboxybetaine as the dominant product. The discussed energy profiles were supplemented with extensive natural bond order analysis in the course of which delocalization energies were calculated and used to discuss the strength of intermolecular donor–acceptor interactions within the considered molecular systems.

1. Introduction

Carboxybetaines constitute a unique class of zwitterionic compounds receiving attention due to the variety of their applications in chemistry and biology, the most attractive of which were discovered in the field of polymer chemistry. Poly(carboxybetaines) and their copolymers were used as hydrogels and nonfouling materials [1–5], for protein immobilization [6], sensors [7,8], and were also introduced to promote the stability of quantum dots with targeting capability [9]. Thus, it was demonstrated that films of poly(carboxybetaine methacrylate), grafted onto microetched gold slides are effective in preventing nonspecific adhesion of cells of different types [10]. Polyurethane with zwitterionic side chains based on a poly(carboxybetaine) analogue was developed for marine coatings and biomedical applications. Excellent long-term nonfouling property, healing capability through self-regeneration, superior mechanical properties (such as hardness and elasticity), and good adhesiveness as a paint on both polar and nonpolar substrates were demonstrated [11]. One of the interesting features of the zwitterionic polymers discovered in recent years is the rare ability to demonstrate upper critical solution temperature (UCST) and even dual-stimuli-responsive phase transitions in aqueous solutions [12,13]. These peculiarities make it useful to employ zwitterionic polymers as base for the design of modern thermosensitive polymeric catalysts that allow one to solve a complex task of carrying out reactions with high rate and conversion under homogeneous reaction conditions from the one side and to remove catalyst from the system after the completion of the process from the other side. This idea is supported with recent advances in usage of ammonium betaines as efficient ionic nucleophilic catalysts for the ring-opening polymerization of l-lactide and cyclic carbonates [14]. It was demonstrated that some of the tested betaines combine the positive aspects of both nucleophilic and hydrogen-based systems in terms of kinetics and selectivity.

One of the potential areas of application that is unexplored to date is the use of low molecular weight carboxybetaines as components of environmentally friendly solvents of a new type, such as deep eutectic solvents (DES), the application of which in various areas has gained increasing attention, especially in the fields of sustainable chemistry [15–18]. It is desirable to use carboxybetaines with additional functional groups similar to the hydroxymethyl group in choline chloride (typical DES component). In

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line with the sustainable chemistry concept, this strategy will make it possible to obtain valuable products from cheap raw chemicals and even waste products that require special methods of disposal.

In addition, the advantage of betaines is the simplicity of their preparation, including the protocols when no solvent is employed. Thus it usually takes from several minutes to a few hours for the synthesis to complete in nearly quantitative yield of the corresponding betaine at ambient temperature. The appropriate synthetic procedures for the preparation of 3-((2-hydroxyethyl) dimethylammonio)propanoate discussed in this paper are described in the Supporting Information.

Despite the widespread use of carboxybetaines, the reaction mechanism leading to their production, especially when the tertiary amines used contain an additional functional group capable of interacting with intermediates at certain stages of the reaction, and the distribution of possible reaction products, are poorly studied. This situation is exacerbated by the complexity of clear distinction between betaine and quaternary ammonium products in the resulting mixture using conventional laboratory methods especially in the case when additional functional groups such as OH-group of the 2-(dimethylamino)ethanol are present. Therefore, the development of theoretical foundations based on the calculations of the energy paths leading to the formation of various products at the beginning of the reaction and recommendations for the synthesis of carboxybetaines based on acrylic acid (AA) and 2-(dimethylamino)ethanol is the goal of this study.

2. Theoretical methods

Quantum mechanics calculations were performed using the Gaussian 03 program [19]. All geometry parameters of the studied systems were fully relaxed by searching for the energy minimum. Minnesota hybrid M06-2X DFT functional based on the meta-GGA approximation [20–22] with the 6-31+G(d,p) basis set was used for local minima and transition state calculations. A preliminary optimization procedure with the B3LYP/3-21G* level of theory was conducted in some cases. A relaxed potential energy scan was employed prior to transition state calculations. This approach was used to find the geometry of the complex with the maximum energy close to the transition-state structure. Lengths of the Intermolecular bonds such as hydrogen bonds (H-bonds) were used as scanning variables. Individual molecules and the appropriate complexes were optimized both by a condensed-phase simulation using a polarizable continuum model [23,24] with propanoic acid as the solvent ($\varepsilon = 3.44$) as implemented in Gaussian 03. Vibrational frequency calculations were conducted to confirm the transition states (one imaginary frequency) and local minima (all vibrational frequencies are positive). The intrinsic reaction coordinate (IRC) method was used to confirm that a located saddle point lies on the minimum energy path between two appropriate minima [25,26]. The application of the natural bond orbital (NBO) analysis applied in this study has been described by Weinhold et al. [27–32]. The mathematical and historical background of NBO methods can be found elsewhere [31]. On the basis of the NBO conception, H-bond strength was determined as delocalization energy (e.g., electron transfer from donor to acceptor orbital) by the second-order perturbation theory. Charges were calculated via natural population analysis (NPA) [28]. NPA charge assignments were found to exhibit excellent numerical stability with respect to variations of basis extension and wave function form, as well as a gratifying agreement with empirical structure–function relationships and other well-known measures of charge distribution in physical organic chemistry [20,33]. Wiberg bond indexes which reflect the superposition of electron density between two interacting atoms was used to measure the bonds strength [34]. Along with NBO second-order perturbation theory used to analyze the existence of intermolecular interactions topological properties of the electron density were characterized using the "atoms in molecules" (AIM) methodology and used to verify H-bond formation [35,36]. Bond critical points (BCPs) were located as extrema in the electron density where the gradient vector vanishes. This method has already been successfully employed to study noncovalent interactions such as conventional hydrogen bonds [37–39] and also dihydrogen bonds [40].

3. Results and discussion

3.1. Prereaction complexes in acrylic acid-amine solutions

Stability of the prereaction complexes described in terms of donor-acceptor interactions between bounded molecules is an important quantity that determines the possibility of a certain reaction path. This is also of special interest for the reactions proceeded without direct catalytic activation. Scheme 1 shows the most probable mechanism for the carboxybetaine formation between 2-(dimethylamino)ethanol and acrylic acid (AA) [41]. Analyzing the system prior to the experiment one can note that carboxylic acids in particular AA tend to form strong self-associated dimers in solutions [42–44]. Organic acids also capable to form strong donor-acceptor complexes with amines which, under certain conditions, can be considered as organic salts. The main issue to the reaction shown in Scheme 1 can be the fact that the depicted prereaction complex in which the methylene ($CH_2{=}$) group is located next to the nucleophilic center of the amine should be less stable in comparison with competing complexation formed via —OH···N and —OH···O= interactions as described earlier. Thus the formation of the stable prereaction complex in the arrangement favorable for the nucleophilic attack of the amine seems unlikely. To avoid unfoundedness and to verify the assumptions made, all of the discussed complexes were calculated. The results of optimization of the geometries of the complexes showed that homo- (AA-AA) and heterodimer (AA-amine) poses comparable stabilization energies ($E_{stab} = 59.1$ and 57.1 kJ mol^{-1} respectively). As expected complex formed between AA and amine depicted in Scheme 1 showed the least stabilization energy (15.7 kJ mol^{-1}). The localized character of the natural bond orbitals (NBO) serves as an effective tool for analyzing the donor/acceptor ability of the molecular systems. Calculations revealed that for the prereaction complex shown in Scheme 1 the acceptor orbital is the antibonding NBO of the C=C double bond ($\pi^*_{C=C}$). For the isolated AA $\pi^*_{C=C}$ energy was found to be 0.07071 a.u. In contrast to this reference value complexation with amine leads to the increase in the energy of the corresponding NBO ($\pi^*_{C=C} = 0.08242$ a.u.) and opposite dimerization of AA via two H-bonds leads to the decrease in the energy of the NBO ($\pi^*_{C=C} = 0.06985$ a.u.). The Wiberg bond indexes (WBI) which are the measure of the electron density between two atoms and usually used to measure the bond strength were calculated along with natural atomic charges. These data confirm that AA stabilized with another AA molecule should be more reactive towards nucleophilic attack of the amine nitrogen in comparison with isolated AA and AA associated with another amine molecule. Thus, charge on the $CH_2{=}$ carbon atom for the AA constituting cyclic dimer was calculated to be −0.344 versus −0.372 and −0.349 for the AA H-bonded with amine and isolated AA correspondingly. Complexation energies, WBIs, NBO energies and NPA charges calculated for the complexes shown in Scheme 1 are summarized in Table 1.

Based on the data obtained, it becomes clear that with the participation of only two molecules (hypothetical reaction in the gas phase), the attack of the nitrogen on the methylene group of the