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Article

Acid-Catalyzed Esterification of Betaines: Theoretical Exploration of the Impact of the Carbon Chain Length on the Reaction Mechanism

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Abstract: Betaine derivatives, especially esters, are compounds of interest for the development of a more sustainable fine chemistry, as they are widely available from biomass and currently produced as side-products from various industries (among which, sugar production). In this publication, we studied the impact of carbon chain length on three considered reaction mechanisms for the esterification of $(\text{CH}_3)_3\text{N}(\text{CH}_2)_n\text{CO}_2$ betaine ($n = 1, 2, 3$) with glycerol under acid catalysis. DFT calculations show that the mechanism proposed by Bachmann–Frapper et al. may also be active here, but it can interestingly be seen as an avatar of the former proposition by Watson. Conversely, Ingold's proposition is in this case too energetically prevented. Overall, lower activation barriers and higher reaction exergonicity are reported, suggesting esterification of longer carbon-chain based betaines is more readily achieved.

Keywords: reaction mechanism; DFT calculations; biomass valorisation



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1. Introduction

The rarefaction of fossil resources and their adverse impact on the environment have led to the search for alternative carbon sources for chemistry [1–3]. In this respect, biomass appears as a credible alternative, already offering various platform molecules for synthesis.

Present in a variety of plants (beetroot, wheat, spinach) [4,5], animals and micro-organisms, glycine-betaine (*N,N,N*-trimethylglycin) plays an important role in cell resistance by stabilizing proteins and membranes [6,7]. It is thus no surprise that this molecule and its derivatives are of a particular interest for pharmaceuticals and cosmetics industry [8–10].

Currently, betaines are co-products from the sugar industry (beetroot molasses), and are industrially produced by DuPont (in Finland) [11,12]. Their valorization is thus potentially achievable and desirable [13].

Esterification of glycine betaine **1** (see Figure 1) with glycerol was rather recently achieved under an acidic catalysis, and computational studies showed that the reaction mechanism is not following the two “classical” esterification mechanisms, i.e., the mechanisms of Watson and Ingold [14,15]. Indeed, Bachmann, Frapper and co-workers showed that protonated reaction intermediates involved in both mechanisms are not stable, owing to a small separation of two positive charges along the organic chain, leading to a strong intramolecular Coulombic repulsion. Instead, a sequential mechanism was proposed, thereafter called the Bachmann–Frapper mechanism, in which undissociated acid molecules are acting as proton relays, in a Grothuss-like way [16].

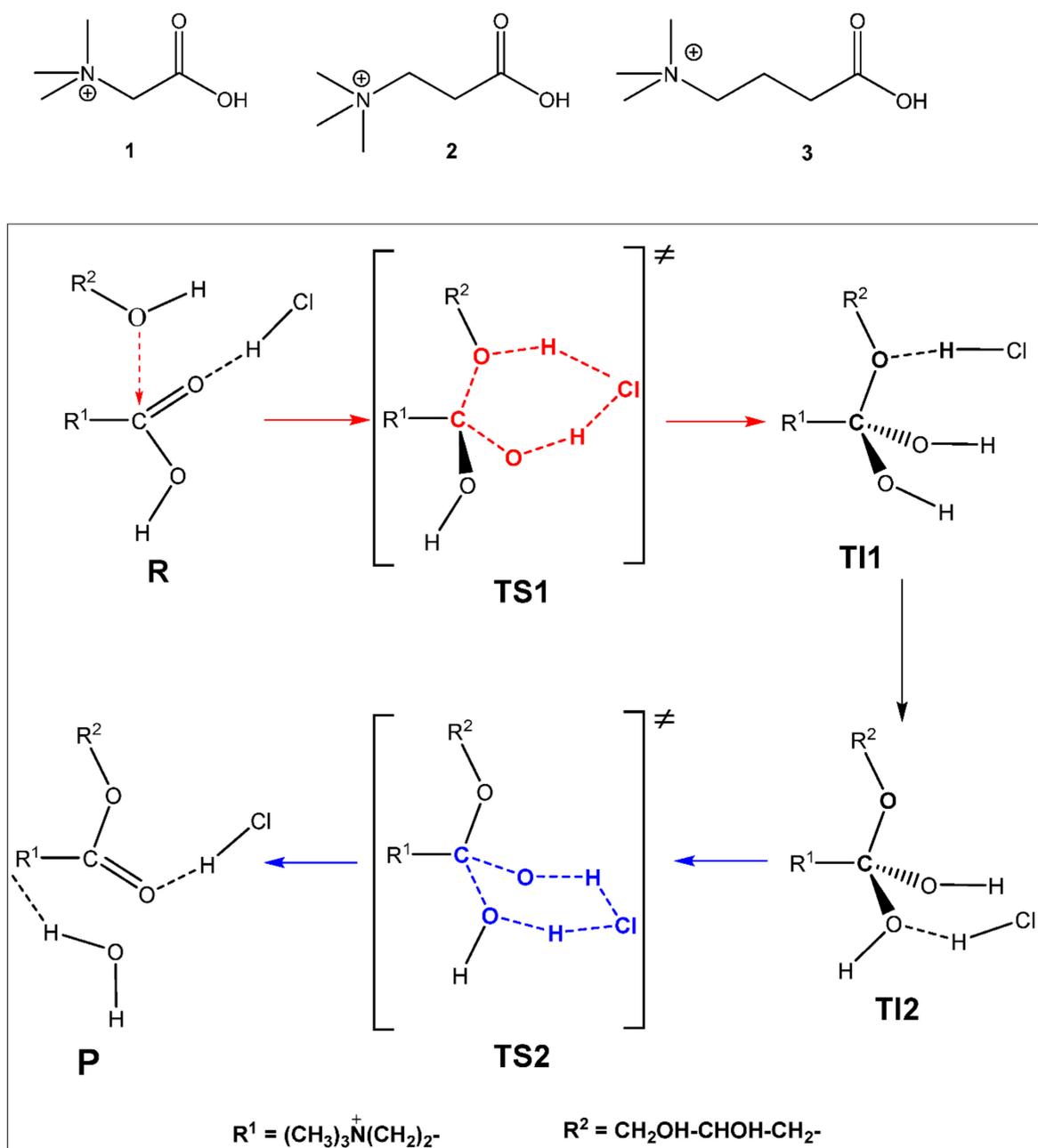


Figure 1. Structure of protonated betaines 1 (top left), 2 (top middle) and 3 (top right) and Bachmann–Frappier mechanism of esterification (bottom).

In the present work, we studied whether the extension of the internal carbon chain of the betaine (betaines 2 and 3) would lead to a drastic change in the reaction mechanism. Indeed, Coulombic repulsion is expected to decay with distance, and one may wonder if the addition of one or two C–C simple bonds would suffice to allow the formation of Watson or Ingold’s intermediates.

In the first section, we present the theoretical methods used in this study. Then, in a second section we study the possible formation of Watson and Ingold intermediates. Interestingly, although both intermediates are associated to stable geometries (unlike what was reported for glycine betaine 1), their formation appear rather unlikely in experimental conditions.

As such, the Bachmann–Frappier mechanism appears to be a more realistic alternative, which we explore in the third section. Remarkably, the associated activation and reaction

energies for water elimination are found to be lower compared to betaine **1**, indicating a higher propensity to react for the longer carbon-chain betaines, supporting the experimental viability of this esterification route for the valorization of betaines. Some elements are put forward to account for this observation.

2. Computational Details

All density functional calculations were performed using Gaussian 09 rev. C.01 [17]. In line with the previous work undertaken by one of the present authors, the hybrid functional B3LYP [18] was employed with the 6-31+G(d,p) basis set. [19] The B3LYP coordinates of reactants, transition states (TS) and products are given in the ESI. All presented geometries were fully optimized without constraint. Frequency calculations were then undertaken at 298.15 K to both characterize the nature of each stationary point on the potential energy surface and to compute thermodynamical corrections to the energy. Transition states optimization were guided using the Synchronous Transit-guided Quasi-Newton method QST2 [20]. Associated geometries were then subjected to Intrinsic Reaction Coordinate (IRC) calculations to ensure they indeed connect to the desired reagents and products [21,22]. All geometries and energies (Table S1) are provided in Supplementary Materials.

3. Results

3.1. Formation of Ingold and Watson Protonated Intermediates

As stated before, Bachmann, Frapper and co-workers could show through DFT calculations that the formation of Watson's (double protonation of the carboxyl group, leading to a formal $C(OH)_2^+$ moiety) and Ingold's (formation dehydration of the former, leading to an acylium CO^+ group) intermediates was impossible for betaine **1** because of strong electrostatic repulsion between the positive charge and that of the ammonium group $N(CH_3)_3^+$.

When moving to a longer carbon chain (addition of a C-C single bond on the chain, see Figure 2), these "intermediates" now become stable points on the potential energy surface (no imaginary vibration mode, no self-dissociation). The corresponding structures for betaine **2** are depicted in Figure 2.

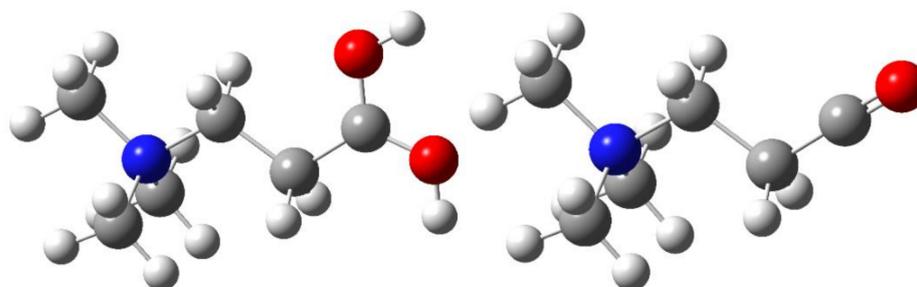


Figure 2. Active species in Watson (**left**) and Ingold (**right**) mechanisms in the case of betaine **2**. Color scheme: gray, C; blue, N; red, O; white, H.

As expected, the Watson intermediates present a formally hypovalent, positively charged carbon atom in a trigonal planar environment (AX_3E_0 according to VSEPR). Similarly, Ingold's intermediates exhibit a hypovalent, positively charged carbon atom in a linear environment (AX_2E_0) [23].

Both intermediates could then be potentially involved in the esterification reaction, provided that their formation is kinetically and thermodynamically achievable.

Formally, Watson's intermediates stem from the protonation of the betaines. The associated reaction with HCl (acid catalyst) should thus be at most slightly endothermic if Watson's mechanism is to be invoked. Here, calculations reveal that the free enthalpy of reaction between betaines and HCl is strongly positive (+226 kcal/mol for betaine **2**, +215 kcal/mol for **3**), hence forbidding the formation of Watson's intermediate. One may surmise that this very strong destabilization of Watson's intermediates is in this case too due to a quite strong electrostatic repulsion between the two positively charged moieties on the

molecular backbones. Natural Population Analysis (NPA) [24,25] conducted on Watson's intermediates indeed reveal a strong positive charge on both the NMe_3 and $\text{C}(\text{OH})_2$ moieties, respectively, +0.721 e and +0.916 for betaine 2, 0.719 e and +0.969 e for betaine 3. Hence, although the increase in carbon chain length stabilizes Watson's intermediate (genuine minimum on the potential energy surface) by reducing the Coulombic repulsion between the positively charged groups, the stabilization is not sufficient to make this species a plausible reaction intermediate.

Formally, Ingold's intermediates derive from Watson's by the elimination of a water molecule. As we just saw, Watson's intermediates formation is itself highly unlikely. Nevertheless, provided that their dehydration was strongly exothermic, formation of Ingold's intermediates could still be thermodynamically plausible. Calculations here reveal that the associated reaction free enthalpies are largely positive (+30 kcal/mol for betaine 2, +25 kcal/mol for betaine 3), hence discarding this mechanism, too.

3.2. Study of Bachmann-Frappier's Mechanism

Watson's and Ingold's intermediates being discarded, we then evaluated the feasibility of the Bachmann-Frappier mechanism. The latter consists of two steps: first, the nucleophilic addition of a primary alcohol function from glycerol on the carboxyl group of betaine, followed by the elimination of a water molecule. In both steps, an undissociated HCl molecule acts as a proton shuttle (6-centres intermediate), which plays an important role in lowering the activation barriers.

Satisfactorily, a very similar mechanism could be delineated for betaines 2 and 3, as shown in Figures 3 and 4. In line with the case of betaine 1, the first transition state (associated to nucleophilic addition) exhibits in both cases two OH bond distances nearing 1 Å (1.003 and 1.020 Å for betaine 2, 1.007 and 1.039 Å for betaine 3), thus bearing a significant $\text{C}(\text{OH})_2^+$ character in both cases. This is further evidenced by the calculated charges of the carboxylic carbon atoms, ca. 0.856 e in both cases, according to NPA.

In a way, this mechanism can thus be conceived as an extension of Watson's mechanism, in which the carbocation is no longer a reaction intermediate but a transitory species—its instability arising from Coulombic repulsion.

However, more interestingly, the energy profiles in these cases differ quite significantly from what was observed with glycine betaine 1. Indeed, although the activation barriers for the first step are all rather close (+22.4, +23.5 and +20.6, respectively, for betaines 1 to 3), the associated reaction free enthalpies are clearly decreasing along the series (+20.4, +13.8 and +13.0 kcal/mol, respectively). The formation of intermediates IR1 is thus significantly eased with 2 and 3.

Additionally, the second reaction step is also facilitated. Transition states for this step are all found around +11–12 kcal/mol above intermediates IR2, but in the case of betaines 2 and 3 these intermediates are significantly stabilized compared to betaine 1 (+11.5 and +12.7 kcal/mol in relative free enthalpy for 2 and 3, against +19.4 for betaine 1). The associated TSs are thus found at a much lower relative energy for betaines 2 and 3 than for betaine 1. Additionally, the free enthalpy of reaction for this second step also seems to be preserved when moving from betaine 1 to 3: in all cases products are found approximately 14 kcal/mol lower in energy than the corresponding intermediate IR2. In the case of betaines 2 and 3, this renders the overall reaction slightly exergonic (−1.6 and −1.1 kcal/mol), while it is clearly endergonic for betaine 1 (+5.9 kcal/mol).

Hence, although the global mechanism of reaction remains preserved when moving from 1 to 2 and 3, the energetic features of the reaction are quite strongly altered. The significant easing in the second reaction step (water elimination), which should translate to an overall faster rate of esterification, suggests it could be performed at lower temperatures—helping to reduce the energy cost of the total valorization process. Additionally, the more pronounced exergonicity suggests that water trapping in experimental conditions may no longer be required, reaction tending towards spontaneity (no need to displace the chemical equilibrium).

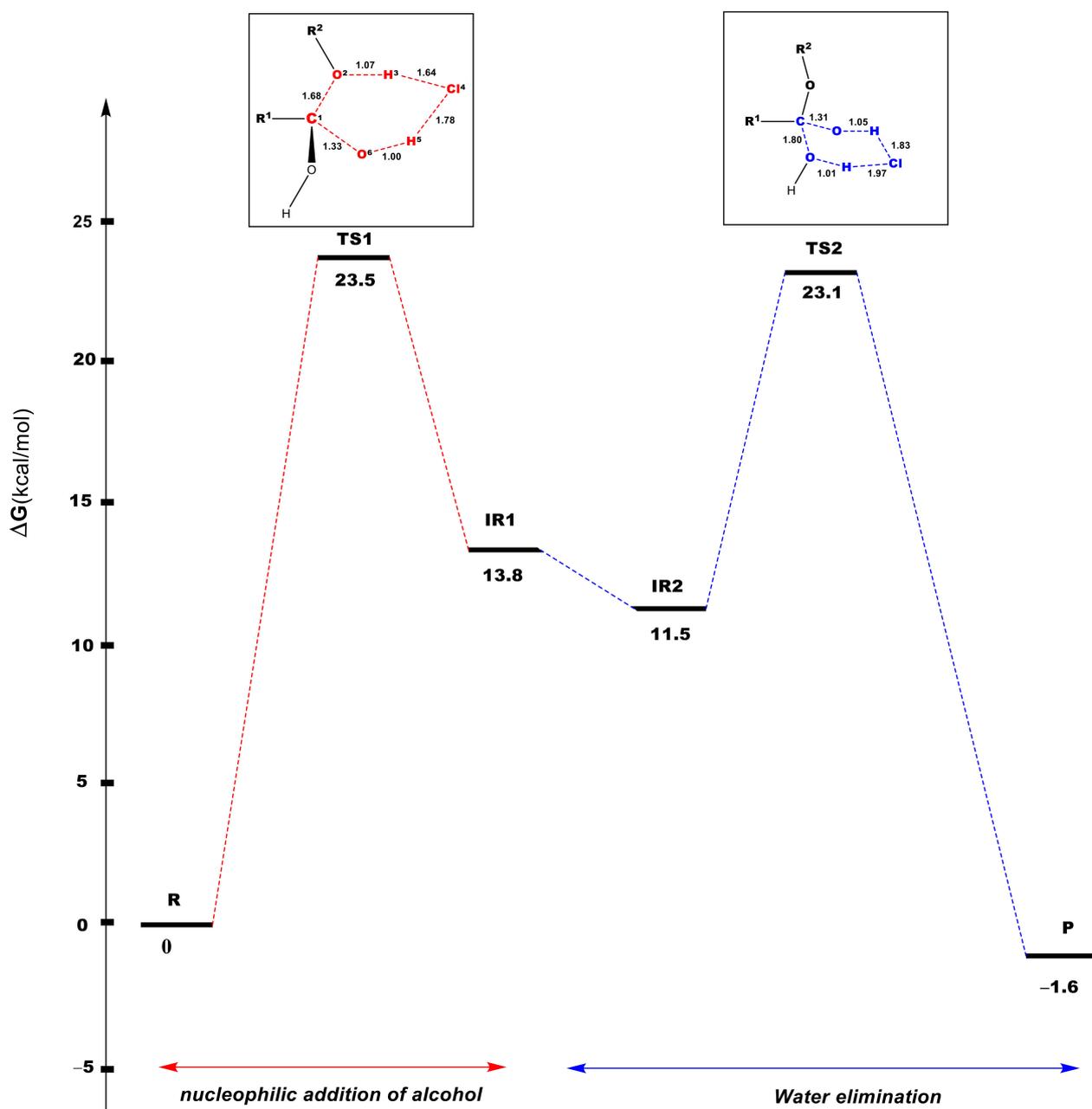


Figure 3. Computed reaction profile for betaine 2, at the B3LYP/6-31+G(d,p) level.

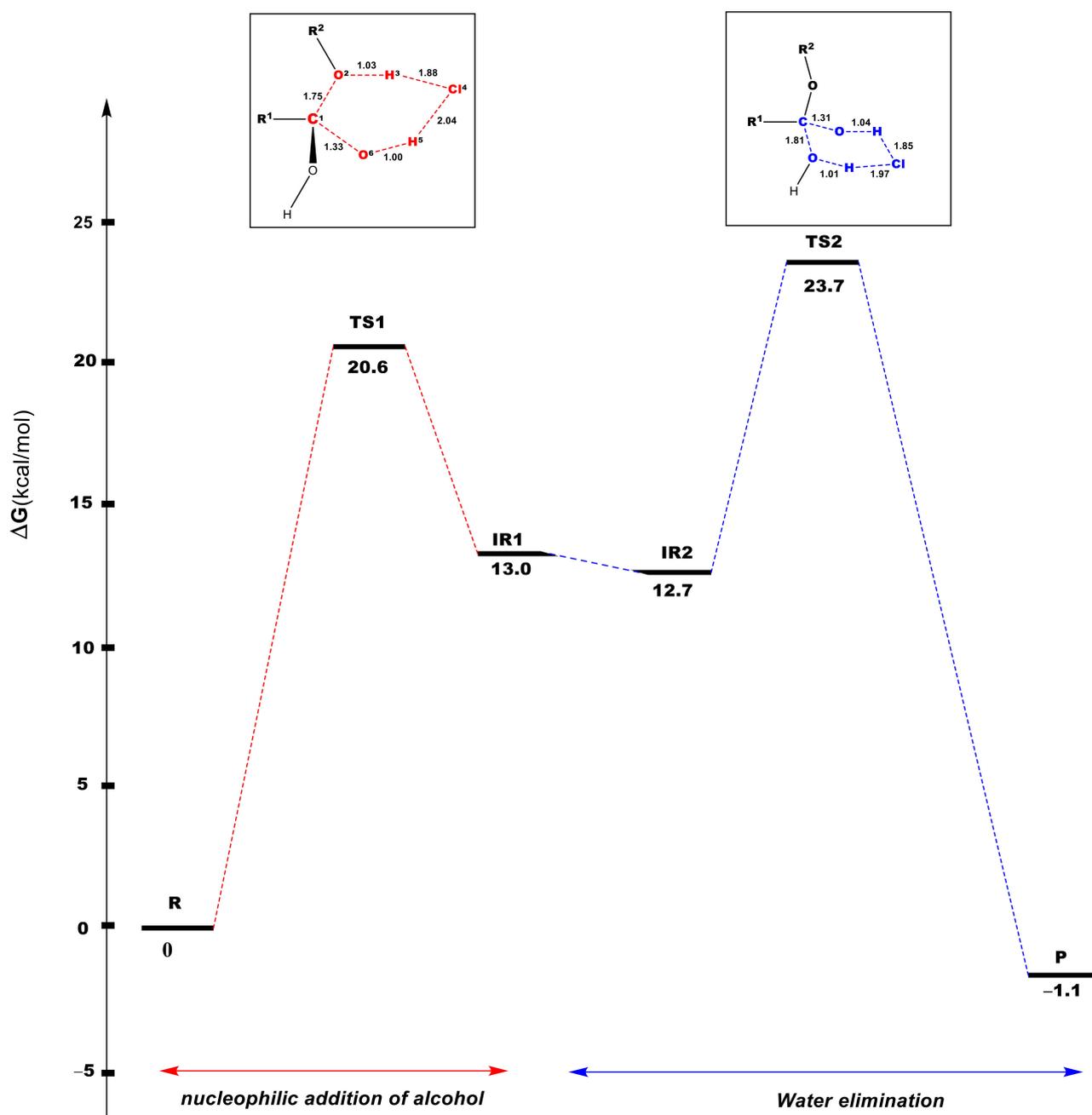


Figure 4. Computed reaction profile for betaine 3, at the B3LYP/6-31+G(d,p) level.

Nevertheless, a question remains: what is the fundamental cause of that reduction in energy cost? A further look at the reaction profiles on Figure 5 suggests the difference starts to manifest itself after the first transition state, that is when going down from TS1 to the reaction intermediates IR1 and IR2. Indeed, IR1-2 and IR1-3 appear to be more stabilized with respect to TS1-2 and TS1-3 than IR1-1 is with respect to TS1-1, by approximately 7 kcal/mol. This difference remains stable along the rest of the reaction path: overall, it appears that the second step for betaines 2 and 3 is simply shifted downwards by 7 kcal/mol.

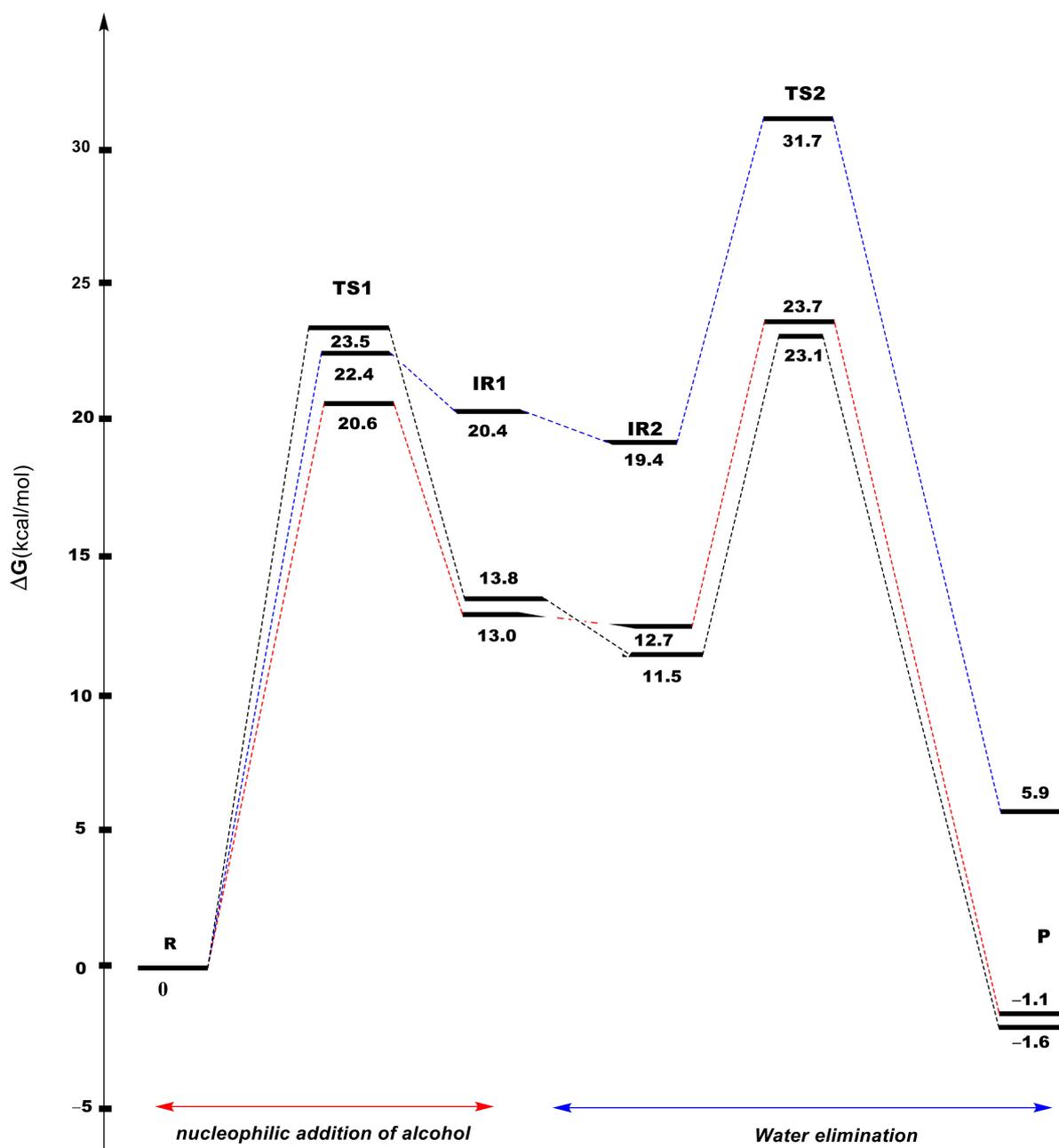


Figure 5. Comparison between the energy profiles for Bachmann–Frappier’s reaction mechanism computed for betaines 1 (blue curve), 2 (black curve) and 3 (red curve). Free enthalpies are given relative to the pre-reacting complex (betaine + glycerol + 2 HCl).

We may surmise that the key factor here is again a modulation of the electrostatic repulsion between two positively charged sites in the molecule (here, in all species, starting from IR1), induced by the increase in the carbon chain length when moving from 1 to 2 and 3. NPA conducted on IR1-1 and IR1-2, indicate that the “orthoester” C atom indeed bears a significant positive charge: +0.820 e in IR1-1, +0.844 e in IR1-2, +0.836 e in IR1-3. A significant repulsion may then be expected with the N-trimethylammonium moiety, which also bears a positive charge: +0.617, 0.613 and +0.597 e, respectively, for IR1-1, IR1-2 and IR1-3. However, for IR1-1, these two positive charges are separated by 3.184 Å, while the separation increases to 4.450 Å for IR1-2 and to 5.267 Å for IR1-3.

Electrostatic repulsion is thus expected to decrease strongly as the carbon chain length increases, and thus we may expect intermediates to be stabilized accordingly.

In fact, if we assume this repulsion is the only factor in play, using NPA charges and distances within a simple Coulomb model, it can be expected that the stabilization of IR1-2 and IR1-3 with respect to IR1-1 should be of 15 and 22 kcal/mol, respectively.

It is quite plain that such a simple model overestimates the stabilization of intermediates, but it is noteworthy that the order of magnitude is quite correctly grasped. Electrostatic repulsion may thus be expected to play a significant part in the easing of the second reaction step for the longer carbon chain betaines. The fact that the reaction profile for betaine 3 lies close in energy to that of betaine 2 (and not lower as would be expected from the electrostatic model) still indicates that other phenomena are active here. In fact, the trimethylammonium moiety in IR1-1, IR1-2 and IR1-3 is found quite close to a formal chloride anion (N-Cl distances of 3.780, 3.870 and 3.972 Å, respectively), which is itself interacting with an acidic H (H-bond with a neighboring OH group). These two interactions are expected to be quite stabilizing; hence, it is not surprising that they should be observed here. Interestingly, in order to allow for these interactions to take place, in IR1-3, a certain folding of the betaine backbone is necessary (see Figure S1 in Supplementary Materials), which does not appear for 2 and 3. Such a folding likely requires energy (strain or deformation energy, which unfortunately cannot be expressed here) [26], which may explain why the reaction profiles for 2 and 3 are eventually found at close relative energies.

4. Conclusions

In this study, we examined the impact of the elongation of the carbon chain of a simple betaine on the mechanism of its esterification reaction with glycerol, under an acidic catalysis. Using DFT calculations, in combination with simple electronic structure analysis (NPA), we showed that the “classical” mechanisms of Watson and Ingold were unlikely to occur here, as the active species they involve are strongly destabilized by electrostatic repulsion between their positively charged groups.

Interestingly, the increase in the carbon chain length did not impact much the first activation barrier, associated with the nucleophilic addition of glycerol on the carboxyl group. Conversely, the remaining of the reaction path was much more impacted: starting from the first reaction intermediates, all species on the reaction paths for 2 and 3 were found at a lower relative energy (approximately of 7 kcal/mol). This stabilization could be accounted for by the decrease in the Coulombic repulsion between the positively charged sites as the carbon chain elongates, which is tempered in the case of betaine 3 by a necessary folding (and thus, straining) of the molecular backbone. In the end, water elimination appeared to be much easier for longer chain betaines, and the overall reaction exhibited a significantly increased exergonicity—which may allow it to become spontaneous.

Altogether, this suggests that such a chemical valorization of betaines with longer carbon chains should prove experimentally feasible, and easier to perform than that of glycine betaine, both in terms of energy costs (lower barriers allowing lower reaction temperatures) and experimental procedure (exergonicity suggesting removal of water would no longer be an issue). We hope these theoretical results will stimulate further experimental investigations.

Supplementary Materials: The following are available online at <https://www.mdpi.com/article/10.3390/physchem1030022/s1>: Table S1: Total electronic energies (E_e), zero-point corrected electronic energies (E_{ZPE}), enthalpies (H_{298}) and Gibbs free energies (G_{298}) for gas phase structures involved in the reaction profiles, Figure S1: Structure of the IR1 intermediate species for betaines 1, 2 and 3, showing the molecular backbone folding in IR1-3, geometries (given in Cartesian coordinates) for all species on the reaction paths for betaine 2 and 3.

Author Contributions: Conceptualisation: G.F.; methodology: G.F. and F.G.; data production and treatment: R.D.M.-K.; writing: R.D.M.-K., J.-M.O., S.N., G.F. and F.G.; supervision: F.G. and G.F. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

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