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ON THE ORIGINS OF STEREOSELECTIVITY IN THE AMINOCATALYTIC REMOTE ALKYLATION OF 5-ALKYLFURFURALS

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In the manuscript, computational studies on the remote alkylation of 5-alkylfurfurals proceeding via formation of the corresponding trienamine intermediate are presented. By the means of density functional theory (DFT) calculations and the symmetry-adapted perturbation theory (SAPT) method, interesting insights into the mechanism of the reaction have been provided explaining the influence and contribution of different molecular interactions on the observed reactivity as well as on the enantio- and diastereoselectivity of the process. The studies have been extended to the thiophene analogue of the starting furfural derivative and the results obtained verified experimentally.

Introduction

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Understanding of reaction mechanism leading to the identification of key factors determining observed reactivity and selectivity is a longstanding goal in contemporary organic chemistry. It allows the rational design of new reactions proceeding according to novel reactivity schemes. Its profound importance is particularly visible in the field of asymmetric catalysis where the stereoselectivity of a given transformation constitutes the main challenge. Explanation on how the chiral catalyst interacts with substrates and directs the reaction enabling access to enantiomerically enriched products is of major significance in this area of research and leads to the identification of new transformations as well as allows new catalysts design. Computational chemistry is a very powerful tool providing insights into organic reaction mechanisms.1 Organic chemists working in the field of asymmetric catalysis² more and more eagerly employ it in their research. This trend is particularly noticeable in the field of asymmetric organocatalysis³ with many important mechanistic and stereochemical rationalizations being confirmed by means of computational studies.⁴ However, in most of the cases, conclusions are made by the comparison of energies between plausible reaction transition states and no direct information on contributions of different types of molecular interactions involved are available. Therefore, further development in this field is directly correlated with the possibility to employ more sophisticated

computational techniques enabling deeper insights into interactions between catalyst and reactants in a given transition state, thus providing information on the molecular recognition profile.

Dearomatizative processes constitute a very powerful means for the functionalization of aromatic frameworks with increasing popularity observed in the past few years.⁵⁻⁹ Such transformations can proceed according to two main pathways: (1) permanent dearomatization reactions resulting in the formation of dearomatized molecules from aromatic starting materials;6 (2) temporary dearomatization reactions proceeding through the formation of dearomatized intermediates that may rearomatize in subsequent reactions.7-9 Recently, the latter approach has been utilized as a design principle for new, aminocatalytic reactions of (hetero)aromatic compounds.7-⁹ In such a setup compounds bearing both an (hetero)aromatic framework and aldehyde (or ketone) moiety that are directly connected (or through one sp³ carbon linker) are employed. Condensation of the aminocatalyst with such a starting carbonyl compound to give iminium ion and subsequent deprotonation results in the polyenamine intermediate formation that is of key importance for further functionalization of starting (hetero)aromatic system.

Recently, we have developed a novel, dearomatizative approach for the functionalization of 5-alkylfurfurals (Scheme 1).⁹ It involved the initial condensation of the starting furfural derivative **1** with the aminocatalyst **2** bearing an H-bonding unit in the side-chain. Subsequent deprotonation of the benzylic position in the alkyl chain of the corresponding iminium ion resulted in the formation of the trienamine intermediate **3**. It was postulated that it preferentially existed as the *anti-Z,Z,Z* isomer.

Herein, we present the theoretical computations on the aminocatalytic remote alkylation developed that have been performed in order to understand the origins of enantio- and

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^{*} Supplementary Information (ESI) available: Gibbs free energy profiles and energies and Cartesian coordinates of all structures reported herein (PDF).

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diastereoselectivity of the process. These studies have been further extended to predict the chemical and stereochemical behaviour of the thiophene analogue of **3** which has been experimentally verified. Furthermore, the symmetry-adapted perturbation theory (SAPT) method has been used to provide insights into different molecular interactions taking place in the postulated transition states, thus enabling a better understanding of the developed organocatalytic transformation. Surprisingly and to the best of our knowledge, this highly useful tool has never before been employed to study the mechanisms of organocatalytic reaction. The results obtained have been directly correlated with the chemical behaviour of molecules in the transition state and used to predict enantio- and diastereoselectivity of the process.





Computational details

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System setup. Initial optimization of all structures was performed at the semi-empirical level using AM1¹⁰ as implemented in Gaussian09 ver. A.01.¹¹ The trienamine 3 can exist as one of four diastereomers, Z,Z,Z, Z,Z,E, E,Z,Z or E,Z,E. The most stable Z,Z,Z-diastereomer was indicated by geometry optimizations with the M06-2X12/6-31+G(d,p)¹³, B3LYP¹⁴/6-31+G(d,p) and MPW1K¹⁵/6-31+G(d,p) density functional theory (DFT) compared with coupled cluster theory with single, doubles and perturbative treatment of triples excitations CCSD(T)¹⁶/6-31+G(d,p) (see Supplementary Information, Table S1). Based on potential energy analysis for diastereomers, the M06-2X/6-31+G(d,p) functional was selected for further investigation with respect to CCSD(T)/6-31+G(d,p). Subsequently, a number of one-dimensional scans of potential energy surfaces (PESs) along with reaction coordinates have been calculated. The polarized continuum solvent model (PCM)¹⁷ of dichloromethane (DCM) was applied using the self-consistent reaction field (SCRF).¹⁸ Structures of the stationary points were confirmed by vibrational analysis (3N-6 real normal modes of vibrations indicate local minimum, while one imaginary frequency corresponds to the transition state) to be either

reactant complex (RC) transition state (TS) or the product complex (PC). Intrinsic reaction coordinate¹⁹ (IRC) hallysis/allowed1t6 concatenate stereoisomers with the corresponding TS geometries. Due to the fact that dispersion may play a crucial role in stabilizing reacting complex, the geometries of the corresponding TS obtained at M06-2X/6-31+G(d,p) level of theory were re-optimized. Minnesota functional M06-2X was not parametrized directly to support dispersion correction, which was required by the studied system. Hence, we decided to use B97D/6-31+G(d,p) functional of Grimme, that includes dispersion correction with the original D3 damping function as implemented in G09.²⁰

Symmetry-Adapted Perturbation Theory (SAPT). SAPT²¹ method constitutes a valuable tool to study non-covalent interactions between monomers. It allows to determine the interaction energy without computing the total energy of monomers or dimer. SAPT ensures the interaction energy decomposition into physically meaningful terms such as electrostatic, $E_{elst}^{(10)}$, exchange, $E_{exch}^{(10)}$, induction, $E_{ind,resp}^{(20)} + E_{exch-ind,resp}^{(20)} + \delta_{HF}^{(2)}$, and dispersion, $E_{dist}^{(20)} + E_{exch-disp}^{(20)}$, components written as:

$$E_{SAPT0} = E_{elst}^{(10)} + E_{exch}^{(10)} + E_{ind,resp}^{(20)} + E_{exch-ind,resp}^{(20)} + E_{disp}^{(20)} + E_{exch-disp}^{(20)} + \delta_{HF}^{(2)}$$

where subscript resp corresponds to orbital relaxation effects, and $\delta_{\scriptscriptstyle HF}^{(2)}$ term describes higher-order induction effects computed from the Hartree-Fock (HF) interaction energy. First electrostatic term, $E_{elst}^{(10)}$, describes Columbic multipole-multipole-type interactions of charge clouds. Exchange interactions term, $E_{exch^\prime}^{\left(10\right)}$ corresponds to repulsive forces. Electrostatic and exchange terms constitute the first-order term. Induction term, $E_{ind,resp}^{(20)}$ + $E_{exch-ind,resp}^{(20)} + \delta_{HF}^{(2)}$, covers both polarization and charge-transfer effects, while dispersion, $E_{dist}^{(20)} + E_{exch-disp}^{(20)}$, is an attractive force from electron-electron dynamic correlation. The second-order term is composed of induction and dispersion forces. Due to a large number of atoms in a studied system the SAPTO²² method was used as implemented in Psi4²³ software. The systematic studies of Sherrill and co-workers²² recommend using the aug-cc-pVDZ²⁴ basis set with a SAPTO method. Moreover, to study crucial interactions in TS the diffusion functions added to angular momentum should be included in basis set, as it is in the case of 'aug-' basis sets. However, usage of pVDZ basis causes underestimation of the dispersion component by approximately 10-15%, but for the qualitative description should serve well enough.

Results and discussion

Finding the most stable diastereomer of trienamine 3. Studies were initiated with the goal of a finding the most stable isomer of the corresponding trienamine intermediate **3.** The analysis of the total energy confirmed that among possible isomers of trienamine reactant **3**, the *Z*,*Z*,*Z*-configured intermediate with an *anti*-conformation around the C-N bond is the most thermodynamically stable and is anticipated to participate in the developed reaction (see

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Supplementary Information, Table S1) as previously correctly predicted.⁹ The *anti-Z,Z,Z*-trienamine **3** may be approached by the β -nitrostyrene **4** from either the upper or bottom side. Furthermore, the Michael acceptor **4** can position itself synperiplanar (with respect to the phenyl ring in *anti-Z,Z,Z*-trienamine **3**) or anticlinal. Given these considerations, the formation of four different iminium ions, namely *R,S, R,R, S,S* and *S,R* can be expected.





particular case are compensated by the π -stacking stabilization. The highest energy barrier was obtained for the brack of the stabilization of the stabil

Scheme 2. Stereodetermining step in the aminocatalytic remote functionalization of 5-alkylfurfural 1

Energy barriers for TS structures with furan-derived trienamines 3. Therefore, four TSs for the reaction of *anti-Z,Z,Z*-trienamine **3** with β nitrostyrene 4 have been located, as presented in Figure 1. For each TS geometry, the energy barriers (ΔG^{\dagger}) were computed using B97D/6-31+G(d,p). The obtained energies of activation indicate that the most favourable reaction goes through the pro-R,S-TS with the lowest energy barrier equalling to 6.8 kcal·mol⁻¹. In this case, the electrophile 4 approaches anti-Z,Z,Z-trienamine 3 from the upper side, and the corresponding pro-R,S-TS has two types of stabilization: by hydrogen bonds (formed between the nitro moiety of electrophile **4** and the sulphonamide group in **2**) and by π -stacking interactions between the phenyl ring in **4** and the conjugated π -system in **3**. Higher energy barriers were obtained for pro-*R*,*R*-TS (8.6 kcal·mol⁻¹) and pro-S,S-TS (8.6 kcal·mol⁻¹) geometries. Both pro-R,R-TS and pro-S,S-TS maintain the π -stacking stabilization, however, in contrast to pro-R,R-TS, the pro-S,S-TS lacks the hydrogen bond stabilization. However, given the results it should not be claimed that the hydrogen bond stabilization is less important than the π -stacking stabilization. No difference in energy barriers obtained for pro-R,R-TS and pro-S,S-TS should be considered as a result of weaker π stacking stabilization occurring in the pro-R,R-TS that in this

Figure 1. Four possible transition state geometries pro-*R*,*S*-TS, pro-*R*,*R*-TS, pro-*S*,*S*-TS and pro-*S*,*R*-TS, with the participation of the furan analogue **3**, located with B97D/6-31+G(d,p) with their energy barriers (ΔG^{\ddagger}) and key distances reported in kcal·mol⁻¹ and Å, respectively

Energy barriers for TS with thiophene analogue 7. Four TS geometries of Z,Z,Z-trienamine reactant with sulfur in the heteroaromatic ring corresponding to four possible products R,R-8, R,S-8 or S,R-8, S,S-8 have been located, as presented in Figure 2. For each TS the energy barriers (ΔG^{\ddagger}) were computed using B97D/6-31+G(d,p). The obtained energies of activation indicate that the most favourable reaction, for reactant complex with thiophene analogue goes through the pro-R,S-TS with the energy barrier that equals to 8.9 kcal·mol⁻¹. The pro-*R*,*S*-TS is stabilized by both hydrogen bonds and π -stacking interactions, in contrast to other located TS geometries, where the activation energies are higher and equal to 11.0 kcal·mol⁻¹ (for pro-R,R-TS), 10.7 kcal·mol⁻¹ (for pro-S,S-TS) or 14.0 kcal·mol⁻¹ (for pro-S, R-TS). As presented in Figure 2, more interactions result in lower energy barriers. The energy barriers obtained for complexes with thiophene analogue are higher than those obtained for the furan-derived system. The difference

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between pro-R,S-TS for a furan derivative and pro-R,S-TS for thiophene derivative is 2.1 kcal·mol⁻¹.



pro-S,R-TS 14.0

Figure 2. Four possible transition state geometries pro-*R*,*S*-TS, pro-*R*,*R*-TS, pro-*S*,*S*-TS and pro-*S*,*R*-TS, with the participation of thiophene analogue **7**, located with B97D/6-31+G(d,p) with their energy

barriers (ΔG^{\dagger}) and key distances reported in kcal;mol⁻¹ and Å respectively DOI: 10.1039/C9OB00914K

SAPT results for TS geometries for reactions involving furan-derived trienamine 3. To get a deeper insight into key interactions that influence TS stabilization, the SAPTO/ aug-cc-pVDZ method was used to obtain different interaction energy terms. Results are collected in Table 1. The lowest energy barrier was expected to be obtained for the TS that is stabilized to the highest degree by molecular interactions. Indeed, the strongest attraction is observed for the pro-R,S-TS structure with the lowest total interaction energy, calculated as a sum of electrostatic, exchange, induction, and dispersion terms, that equalled to -75.2 kcal·mol⁻¹. It is not surprising that pro-R,S-TS and pro-R,R-TS are characterized by the strongest electrostatic attraction with -80.4 and -78.8 kcal·mol⁻¹, respectively, which probably comes from the hydrogen-bonding interactions between the nitro moiety of electrophile 4 and the sulphonamide group in 2. The lack of hydrogen-bond attraction results in weaker electrostatic interaction observed for pro-S,S-TS and pro-S,R-TS with energies equalling to -67.5 and -68.7 kcal·mol⁻¹, respectively. The exchange term, describing the repulsion forces, is the highest in pro-S,S-TS case and equals to 149.6 kcal·mol⁻¹. Repulsion forces play also an important role in the geometries of pro-R,S-TS (141.1 kcal·mol⁻¹) and pro-R,R-TS (137.9 kcal·mol⁻¹). However, for these cases, they are compensated by electrostatic attraction resulting from H-bonding interactions. For all TSs, the first-order term (a combination of electrostatic and exchange terms) is repulsive, and the inclusion of second-order induction and dispersion terms provides system stability. It is worth to note that the second-order induction is attractive. In general, based on the literature examples, in the case of the hydrogen-bonded complexes, the dispersion term constitutes half of the total interaction energy, while in the π -stacking systems the dispersion term is usually bigger than overall total interaction energy.²⁴ Interestingly, for the studied system, the second-order dispersion term exceeds half of the total interaction energy. However, it is still lower than the whole total interaction energy. It means that both hydrogen-bond and π -stacking characters overlap.

Table 1. The components contributing to the interaction energy in the corresponding TS computed using SAPTO for located TS geometries with the participation of furan-derived trienamine **3**. The values are reported in kcal·mol⁻¹

| | pro-R,S- | pro- <i>R,R</i> - | pro-S,S- | pro-S,R- | |
|-----------------------------|----------|-------------------|----------|----------|--|
| | ΤS | ТS | ΤS | TS | |
| Electrostatic | -80.4 | -78.8 | -67.5 | -68.7 | |
| Exchange | 141.1 | 137.9 | 131.6 | 149.6 | |
| Induction | -83.8 | -82.4 | -72.2 | -91.7 | |
| Dispersion | -52.1 | -50.1 | -46.9 | -46.9 | |
| Total interaction energy | -75.2 | -73.4 | -55.0 | -57.7 | |

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Thermodynamically, the most possible reaction goes through the pro-*R*,*S*-TS with the lowest energy barrier equalling to 6.8 kcal·mol⁻¹ and leads to the formation of *R*,*S*-configured product **6**. The pro-*R*,*S*-TS has the strongest stabilization that comes from hydrogen bonds and π -stacking interactions. Moreover, in order to study such systems, the second-ordered corrections are required to ensure the proper description of interactions and the total energies.

SAPT results for TS geometries for reactions involving trienamine derived from thiophene 7. Analogical analysis for key interactions was carried out for the SAPT results obtained for all TS geometries of reactions involving thiophene-derived systems and values are collected in Table 2. The strongest attraction (82.4 kcal·mol⁻¹) is noticed for pro-*R*,*S*-TS structure, which has the lowest energy barrier equalling to 8.9 kcal·mol⁻¹. The same as in a previously discussed example the first-order term is repulsive for all complexes, and the second-order terms are attractive. The sum of both leads to the final attractive character of interactions. Herein, the dispersion term exceeds half of the total interaction energy but is still lower than overall interaction energy, which is probably a proof of interplay between hydrogen-bond and π -stacking characters.

Table 2. The components contributing to the interaction energy inthe corresponding TS computed using SAPTO for located TSstructures with the participation of the thiophene analogue 7. Thevalues are reported in kcal·mol⁻¹

| | pro- <i>R,S</i> - TS | pro- <i>R,R</i> - TS | pro- <i>S,S</i> - TS | pro- <i>S,R</i> - TS |
|-----------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| Electrostatic | -79.7 | -80.7 | -67.0 | -76.6 |
| Exchange | 144.6 | 144.2 | 132.0 | 146.5 |
| Induction | -93.9 | -89.4 | -74.5 | -88.9 |
| Dispersion | -53.4 | -55.5 | -48.4 | -47.5 |
| Total interaction energy | -82.4 | -81.4 | -57.9 | -66.5 |

In order to verify theoretical data, they were compared with the results of the performed experiments. It was found that a previously proposed mechanistic scenario is in accordance with the calculation. The pre-assumed participation of Z,Z,Z-configured trienamine **3** was unequivocally confirmed by theory. For the developed reaction to proceed in an enantio- and diastereoselective fashion two factors were of key significance. Firstly, the recognition of the electrophile by the H-bonding unit resulting from the catalyst. Secondly, the alignment of β -nitrostyrene **4** with regard to the trienamine intermediate. Performed calculation indicated the importance of two groups of molecular interactions in controlling the stereochemistry of the reaction: (1) recognition of the nitro group by the H-bonding unit of the catalyst; (2) π -stacking interaction between phenyl ring of the β -nitrostyrene **4** and conjugated π -system in **3**. In this context, the results of SAPT analysis clearly indicate the crucial

role of these molecular interactions in recognition of both reaction partners. Furthermore, the model reaction between this partners derived aldehyde **7** with β -nitrostyrene **4** was performed in order to compare the reactivity of both systems (Scheme 3). It was found that sulphur-containing heterocycle was less reactive when compared to oxygen counterpart. This is in accordance with computed energy barriers which were in general higher for the thiophene-derived system. Experimentally observed stereoselectivities were similar confirming the accuracy of obtained values of transition states energies. Notably, the comparison of differences in total interactions energies from SAPT analysis between pro-*R*,*S*-TS and pro-*R*,*R*-TS for furan and thiophene analogues (1.8 kcal·mol⁻¹ vs 1.0 kcal·mol⁻¹) might be an indication of slightly lower diastereoselectivity observed in the latter case.



Scheme 3. Reactivity comparison of furan- and thiophene-derived systems in the aminocatalytic remote functionalization

Conclusions

In conclusion, we have developed theoretical studies on the mechanism of remote functionalization of 5-alkylfurfural derivatives proceeding under aminocatalytic conditions. The reaction involves dearomatization of the central heteroaromatic framework to give trienamine intermediate. The most stable intermediate has been identified and the role of aminocatalyst in providing stabilization of the corresponding transition state explained. Furthermore, by means of SAPT analysis insight into crucial molecular interactions was gained providing valuable information on the reaction mechanism. The reactivity of the thiophene analogue of the starting 5-alkylfurfural derivative has been also theoretically evaluated and the results verified experimentally.

Conflicts of interest

There are no conflicts to declare.

Notes

The authors declare no competing financial interest.

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