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Theoretical study of the regioselectivity of the Huisgen reaction

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Abstract From the structure of a series of spiro (pyrrolidine-2,3′-oxindole) derivatives synthesized by Huisgen reaction of isatin, α-amino acids, and different olefins, different regioselectivities were found. The possible mechanism of the Huisgen reaction of oxindole azomethine ylide and the substituent of olefins was investigated using a B3LYP/6-311G* level of theory, and the results show that the regioselection depends on the energy barrier between the stacking state and the regioisomer. This mechanism can also be applied to the illumination of other Huisgen reactions.

Keywords Huisgen reaction · Regioselectivity · Regioisomer · π–π Stacking · Theoretical study

Introduction

The Huisgen reaction, also known as the 1,3-dipolar cycloaddition, provides a direct and straightforward entry for the synthesis of many five-membered heterocyclic compounds [1], such as pyrrolidines, pyrrolines, and pyrroles, among which spiro-oxindole has received the attention of biochemists because of its therapeutic and biochemical activities [2, 3]. The spiro-oxindole system is the core structure of several natural alkaloids and pharmacological agents, e.g., spirotryprostatin A [2], pteropodine [3], and isopteropodine [4], which have shown important biological

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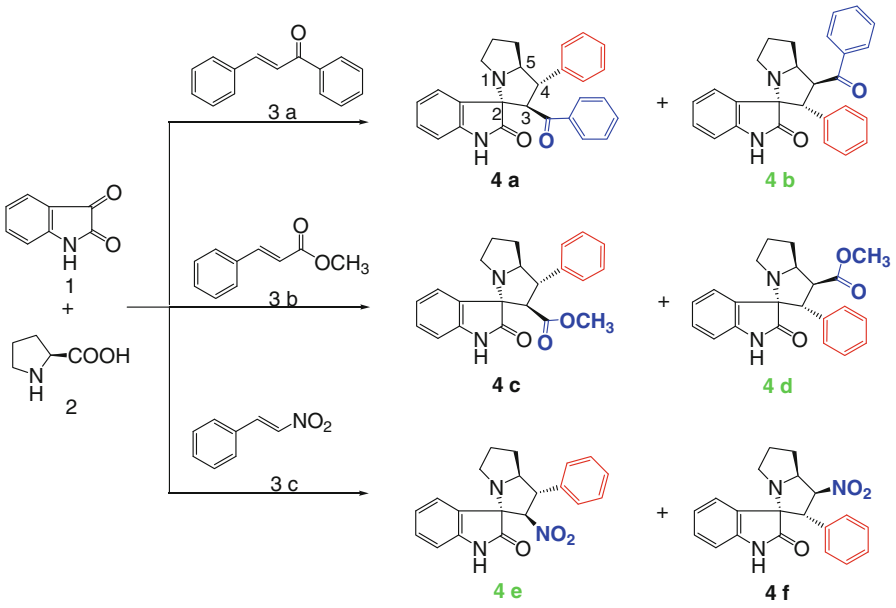
activity, with potential use in antibacterial, antiprotozoal, and anticancer. Because of their remarkable biological activity, significant effort has been devoted to the synthesis of natural product-like spiro-oxindole derivatives [2, 3, 5–7]. Olefins, such as chalcone [4], acrylate, maleimide [2], maleic anhydride 2-arylidene-1-tetralone, and arylidenemalononitrile derivatives [3], have been used efficiently as trapping dipolarophiles in high yield and high regio- and stereoselectivity. Due to the interesting bioactivities of spiro-oxindole compounds, many spiro-oxindole derivatives have been synthesized in our work [7–10]. The Huisgen reactions, with the reactant of isatin, α-amino acids and olefins (chalcone/methyl cinnamate/(*E*)-*β*-aryl-nitro-olefins), are in good yield and high regio- and stereoselectivity. But it was found that the regioselectivity is quite different with different trapping dipolarophiles. So, in this work, we will report the theoretical study of the regioselectivity in the synthesis of spiro-oxindole compounds by the Huisgen reaction.

Results and discussion

Our previous work is summarized in Scheme 1. In each Huisgen reaction of isatin, α-amino acids, and chalcone/methyl cinnamate, only one product was obtained (4a and 4c), and the other isomer, 4b and 4d, cannot be obtained. Based on the NMR and MS spectrums, a conclusion can be drawn that the regioselectivity of the reactions is the same: in the product (4a and 4c), the electron-withdrawing groups (EWG) of olefins (ester and benzoyl groups) always connect with the C-3 of the newly-constructed pyrrolidine, and the phenyl groups always connect with the C-4. While, in the reactions of isatin, α-amino acids, and (*E*)-*β*-aryl-nitro-olefins, two isomers were obtained (4e and 4f), and what is most interesting is that the major product (4f) showed different regioselectivity from the reported spiro-oxindole derivatives. In the major product, the nitro group shows the correlation with C-4 of the newly constructed pyrroline and the phenyl groups connects with the C-3. For these olefins with similar structure, ester, benzoyl, and nitro groups are the EWG, and the other group is the same one, phenyl. Why is the regioselectivity quite different, and how does it work?

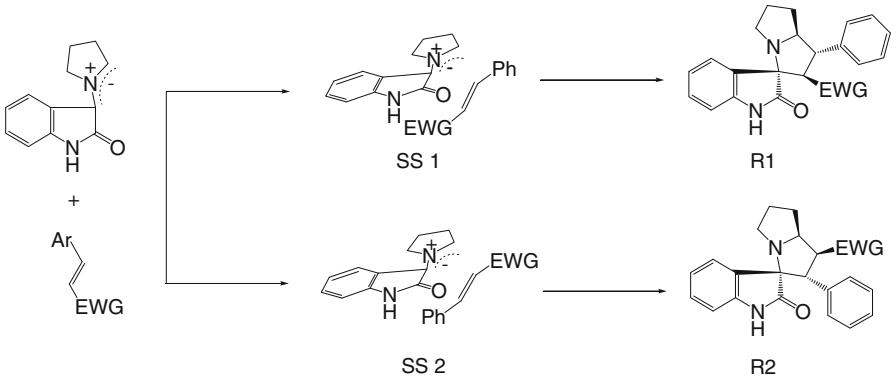
Several researchers have reported Huisgen reactions giving two regioisomers, but few have studied the mechanism [11, 12]. It is a common view that the azomethine ylide, firstly generated in situ via decarboxylative condensation of isatin with α-amino acids, can be trapped smoothly by olefin to form spiro-oxindole derivatives [13, 14]. Geometry optimization of the azomethine ylide generated from isatin and proline indicates that it has a planar structure. The pyrrolidine ring, instead of having an envelope shape, is planar and coplanar with the isatin moiety [15]. Since the azomethine ylide and olefin are two conjugated systems with rich π electrons, we proposed that there is an interaction, π–π stacking [9], between the azomethine ylide and olefin before reacting (as shown in Scheme 2). So there are two stacking states (SS 1 and SS 2) in the presence of chalcone, methyl cinnamate or (*E*)-*β*-phenyl-nitroolefin as olefin, which will lead to two regioisomers. Scheme 2 describes the possible reaction process. It is common sense that a lower energy barrier between the stacking state and the transition state will lead to the single or



Scheme 1 The 1,3-dipolar cycloaddition reactions between isatin, proline, and different olefins

main product. Based on this proposal, the regioselection of 1,3-dipolar cycloaddition reactions between isatin, amino acid, and olefins can be illuminated reasonably.

In order to get more information on the mechanism, we utilized computer assistance. All structures were optimized using Gaussian 03 at the B3LYP level of theory, and with the B3LYP/6-311G* basis set, and the following results (Figs. 1, 2, 3) were obtained. Inspection of Fig. 1 shows that the energy flows at 21.3 kJ/mol from the reactant to the stacking state (SS-4a), in which benzoyl group (EWG) and oxindole group are located ipsilaterally, and 17.2 kJ/mol for the reactant to the other



Scheme 2 The possible process of the Huisgen reaction

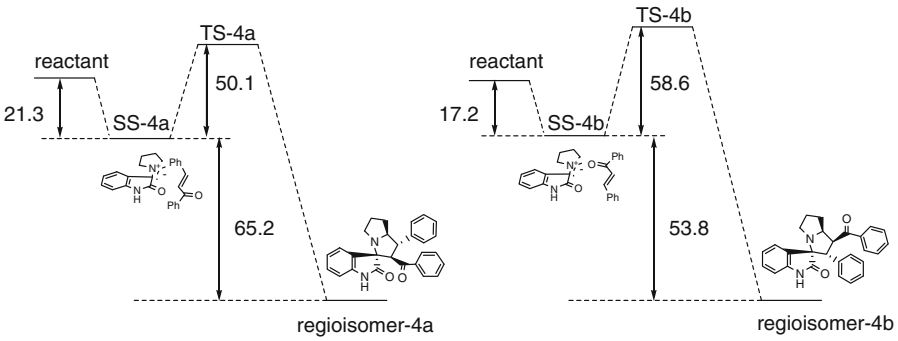


Fig. 1 The energy change of the Huisgen reaction between isatin, L-proline, and chalcone

stacking state (SS-4b) of phenyl group and oxindole group ipsilateral; the energy barrier between SS-4a and regioisomer-4a is 50.1 kJ/mol, while the barrier between SS-4b and regioisomer-4b is 58.6 kJ/mol. It is obvious that SS-4a is more stable than SS-4b and regioisomer-4a is easier to be formed than regioisomer-4b, so it is obtained as the single regioselected product in the reaction. The same result can be found from Fig. 2. But the instance changes in Fig. 3: the energy of SS-4e, in which the nitro group and the oxindole group are located ipsilaterally, flows at 11.4 kJ/mol, which is less stable than that of the other stacking state (SS-4f, 26.9 kJ/mol); the energy barrier of the former (56.7 kJ/mol) is higher than the latter (50.7 kJ/mol). So it is clear that regioisomer-4f would be the regioselected product. From all these data above, we can find that the regioselection depends on the energy of a π–π stacking state between azomethine ylide and olefin, and the energy barrier between the stacking state and the regioisomer, and all these calculated results accord perfectly with the experimental results. In addition, the stability of the stacking state of different conjugated systems with the oxindole group can be concluded from the calculations as: benzoyl group > ester group > phenyl group > nitro group.

Based on the assumed mechanism and associated with quantum chemical calculation, the regioselection of the Huisgen cycloaddition reaction of isatin,

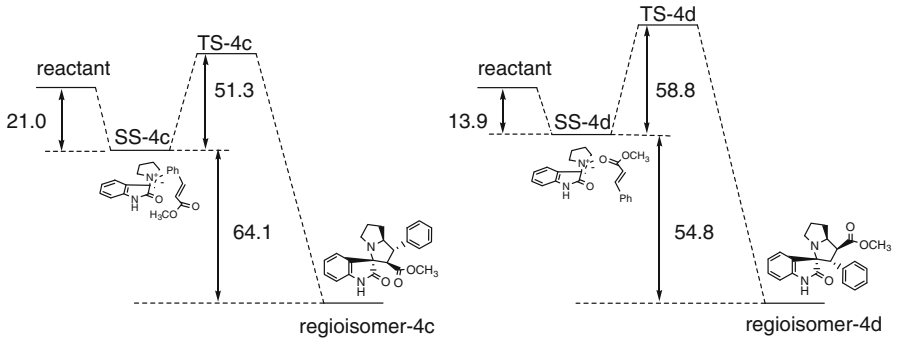


Fig. 2 The energy change of the Huisgen reaction between isatin, L-proline, and methyl cinnamon

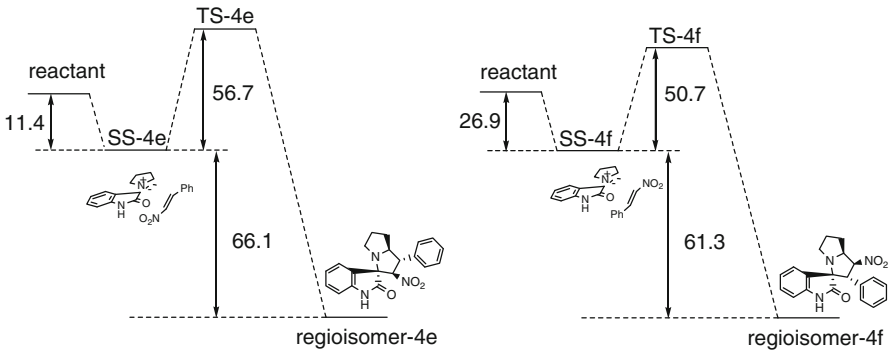


Fig. 3 The energy change of the Huisgen reaction between isatin, L-proline, and (*E*)-*β*-phenyl-nitroolefin

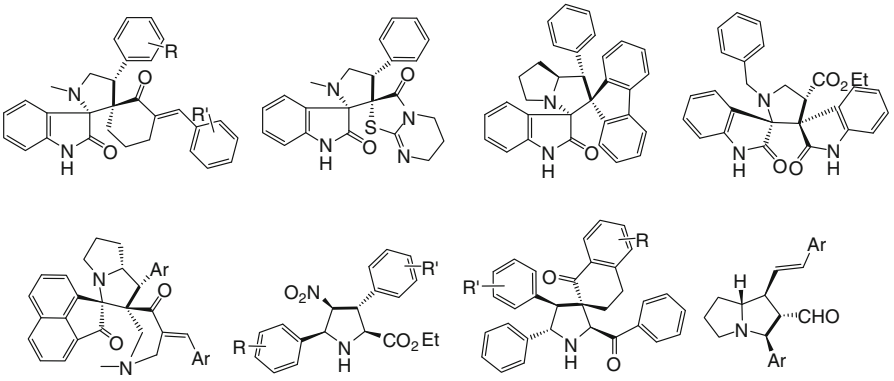


Fig. 4 The products of other kinds of Huisgen reaction. (The *bolder bounds* come from C=C bounds of the olefins)

α-amino acids, and olefins seemed to be well illuminated. The application of a perfect mechanism must be widely applicable, so other kinds of Huisgen reaction were reviewed. From the structure of the products of other kinds of Huisgen reaction (shown in Fig. 4), we find that this mechanism is applicable in all these Huisgen reactions.

Conclusions

In conclusion, the regioselection of the Huisgen reaction is controlled by the energy barrier between the stacking state and the regioisomer. Associated with quantum chemical calculation, the regioselection was well illuminated. This mechanism can be applied to the illumination of other Huisgen reactions. We are also confident that this mechanism will be used in regio-control synthesis for certain molecules.

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