PERKIN 2

Governing organic reactions through secondary orbital interactions. Semiempirical and density functional theory study of catalyzed cycloaddition reactions between pyrrole and ether dienophiles

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A combination of density functional and semiempirical computational studies of cycloaddition reactions with an activated pyrrole and a specially designed dienophile were performed to study electronic interactions and rearrangements that govern cycloaddition reactions. Several very simple principles, such as bond order, uniformity, and secondary orbital interactions were used to follow the reaction paths and the reaction outcomes were determined. It was demonstrated that the localization of double bonds in the ring would increase the reactivity. The reaction should proceed through the transition state that will have the most uniform ring bond order distribution. It was also demonstrated that secondary orbital interactions between reactants, such as hydrogen bonding, could be the curtailing factor that determines the reaction outcome. To obtain a better understanding of the reaction transformations, nonbonding interactions in the reactants' complexes and their isomeric transition states were discussed.

Introduction

From the standpoint of an organic synthetic chemist, the most important questions concerning chemical reactions are: Will the reaction take place under thermal or photochemical conditions?; What is the selectivity of the reaction?; and What kind of catalyst should be used for successful chemical transformation (reaction) under mild conditions?[1] These questions have been answered through generating various models of chemical transformations, better known as reaction mechanisms.[2] Mechanisms do not necessarily reflect real chemical transformations, but rather a model that can fit well into the current knowledge of certain chemical transformations. The most important part of the reaction mechanism is the transition state structure.[3] Through atomic organization in the transition state structure, organic chemists have been able to predict the outcome of the chemical transformations, as well as the reaction conditions needed to enforce these desirable transformations.[4] Although there are various experimental methods that have been used to determine the structural and energetic properties of reactants, intermediates, and products[5] on the potential energy surface, it is still not possible to determine the transition state structures. For many years, chemists have had various indirect evidence that might suggest the structural properties of the transition state structures. Hammond's postulate is probably the most popular method utilized today.[6]

Nowadays, computational methods[7] offer a unique ability for the synthetic organic chemist to generate transition state structures, and through structural and electronic properties of transition state structures, as well as reactants and products, make a decision as to which of the chemical transformations will be used in accomplishing the synthetic task. Because organic chemists are able to predict mechanisms for many chemical transformations, and consequently generate transition state structures, the uncertainty of the computational search for various transition state structures is eliminated. Here we will study the cycloaddition reaction with pyrrole. Using various dienophiles, we will explore the selectivity of cycloaddition reactions as well as catalytic effects of acid and salts.

Computational methodology

All computational studies were performed with the AM1[8] semiempirical method as a part of the MOPAC[9] computational package. Bond orders were computed with the AM1 method as it is incorporated in the MOPAC computational package.[10] The density functional theory computational study was performed with the hybrid B3LYP[11] method with the 6-31G(d,p)[12] basis set as a part of the GAUSSIAN94[13] computational package.

Results and discussion

The acid catalyzed Diels–Alder cycloaddition reactions are some of the most widely used methods for the construction of the CC bond.[14] Aromatic heterocycles seem to be an ideal source of dienes for the Diels–Alder reaction, but are of exceptionally low reactivity.[15] We have performed several computational studies[16] with various five-membered heterocycles, with the goal of elucidating their low reactivity in cycloaddition reactions. From computed magnetic, as well as molecular orbital overlap[17] in the five-membered heterocycles, the aromatic stabilization precludes the heterocycle from participating in the cycloaddition reaction. Pyrrole as a five-membered heterocycle is one that attracts particular attention. It can be obtained from starting material such as cocaine analogs, or isolated from the Ecuadorian poison frog as an alkaloid.[18] Furthermore, due to the presence of the polar NH bond it can easily be deprotonated, or be involved in hydrogen bonding with suitable dienophiles, which may be crucial in the selectivity of cycloaddition reactions. On the other hand, pyrrole formally has an electronic pair located on the nitrogen. Therefore, it can serve as a base or a complexation agent. The complexation of a proton or a metal can not only increase the reactivity of pyrrole as a diene for cycloaddition reactions, but also organize reactions in their complexes in such a way as to lead to the formation of a product that otherwise would not be formed. These interactions are well known in chemistry as secondary orbital interactions (SOI)[19] and have been used for explaining favorable interactions in an *endo* Diels–Alder transition state structure.

Table 1 Bond order uniformity as computed with AM1 semiempirical models

Heterocycle	BO_{12}	BO_{23}	BO_{34}	BO_{45}	BO_{51}	ABO	SDABO
Pyrrole	1.181	1.555	1.285	1.555	1.181	1.351	0.814
H^+–pyrrole	0.923	1.853	1.047	1.853	0.922	1.320	2.134
Li^+–pyrrole	1.224	1.524	1.171	1.524	1.224	1.333	0.762
N-Formylpyrrole	1.088	1.648	1.204	1.649	1.079	1.334	1.260

BO_{nm} = bond order between the pyrrole ring atoms *n* and *m*; ABO = average ring bond order computed as sum of all rings' bond orders deviation by number of ring's atom (in our case it is five); SDABO = sum of ring's bond order deviation from an average bond order.

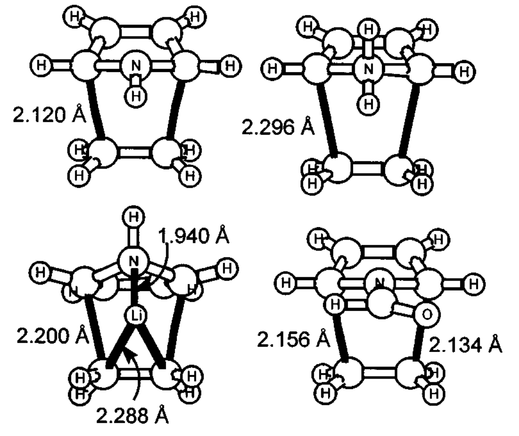

Fig. 1 Transition state structures for ethylene addition to pyrrole and its derivative computed with B3LYP/6-31G(d,p) theory model.

Table 2 Total energies (a.u.) for reactants and transition state structures, and activation barriers (kcal mol^{-1}) for ethylene addition to activated pyrrole

Diene	E_{diene}	E_{TS}	ΔE
B3LYP/6-31G(d,p)//B3LYP/6-31G(d,p)			
Pyrrole	−210.1763393	−288.7214768	30.5
N-Formylpyrrole	−323.5075871	−402.0555782	28.7
H–pyrrole	−210.4963309	−289.0733222	10.6
Li–pyrrole	−217.5350725	−296.0677264	38.4
B3LYP/6-31G(d,p)//AM1			
Pyrrole	−210.1738200	−288.7153600	32.5
N-Formylpyrrole	−323.5040316	−402.0480950	30.9
H–pyrrole	−210.4929739	−289.0674826	11.8
Li–pyrrole	−217.5350725	−296.055371	45.8

Total energy of ethylene is −78.5938056 a.u. computed with B3LYP/6-31G(d,p) and −78.5933158 computed with B3LYp/6-31G(d,p)/AM1.

Recently, we have utilized bond orders for the determination of SOI through hydrogen bonding of cyclopropene as a diene in the transition state with butadiene[20] and furan,[21] respectively. In the case of furan (O–H interaction), the *exo* product is preferred, while in the case of butadiene (n–H interaction) the *endo* product is preferred. Both computational preferences are in agreement with the experimental data. We would like to further explore SOI with their reaction outcomes using pyrrole as the dienophile and using the catalytic effects of acids and salts on the cycloaddition reaction with pyrrole.

Let us first explore the relative aromatic (resonance)[22] character of pyrrole and its derivatives through bond order uniformity[23] and the frontier molecular orbital (FMO)[24] energy gap[25] computed with the AM1 semiempirical method (Table 1). According to the bond order uniformity approach,[23] the ring systems that have the most uniform bond order distributions are the most stable ones. This can be measured by the sum of bond order deviations from an average bond order (SDABO). The smaller value reflects the more uniform molecular system that is delocalized (aromatic), and hence more stable. According to our computational study, the formation of lithium cation complexes with pyrroles produces more uniform (more aromatic) ring systems. Therefore, one can expect that cycloaddition reactions with pyrrole in the presence of lithium salts are even less likely to occur than cycloaddition reactions in the absence of the lithium salts.

To test our assumption, we have computed transition state structures for the ethylene addition to pyrrole derivatives presented in Table 1 by the semiempirical DFT B3LYP/6-31G(d,p) theory model. The DFT geometries of these transition state structures are presented in Fig. 1. The transition state structures computed with AM1 semiempirical methods are very similar to the ones computed with the DFT method, but the C–C bond in formation is slightly shorter. For instance, the C–C bond distance in the transition state for the ethylene addition in the protonated pyrrole is 2.147 Å. It is well known that the AM1 semiempirical method and the B3LYP hybrid DFT method compute transition state structures for Diels–Alder reactions which are very similar. Therefore, it does not come as a surprise that the B3LYP/6-31G(d) computed activation barriers on the B3LYP/6-31G(d) and AM1 geometries are almost identical.[26] We are again testing this observation based on the evaluation of activation barriers for ethylene additions to pyrrole and activated pyrrole.

With the exception of the lithium cation, the computed energies are 1–2 kcal mol^{-1} higher than the full B3LYP/6-31G(d,p) activation barriers. In fact, these barriers should be much closer to the experimental values if we consider the fact that the B3LYP usually computes activation barriers for cycloaddition reactions that are 1–2 kcal mol^{-1} lower than the experimental values.[27] Consequently, we have demonstrated that the single point energies on the AM1 geometries are a valid approach for the study of cycloaddition reactions.

We will now present our results in Tables 1 and 2, which reflect an astonishing agreement between the computed ring bond uniformity (aromaticity) and computed activation barriers. It was estimated that the most ring bond order uniformity was observed in the lithium complexed pyrrole (which is the least reactive diene). The least uniform ring is the protonated pyrrole, for which the activation barrier in the reaction with ethylene is estimated to be 11 kcal mol^{-1}. Therefore, bond order uniformity is a valid, qualitative approach to determine the reactivities of heterocyclic aromatic compounds. Special attention should be given to the structure of the lithium cation pyrrole complex (Fig. 2). The complex perfectly demonstrates its uniformity in regard to bond order distribution. All Li–C bond distances are identical, indicating identical bond order distributions. Furthermore, the C–N bond distance is shortened and the C2–C3 bond distance is longer in comparison with the uncomplexed pyrrole. This indicates a higher ring bond order uniformity and a lower reactivity in cycloaddition reactions than would be seen in the uncomplexed pyrrole. This correlates with the computed activation barriers (Table 2).

Let us now examine the cycloaddition of activated pyrroles with dienophiles. We use dienophiles that can make nonbonding interactions, because in this way we can determine reaction outcomes. Two dienophiles (Fig. 3) were selected for these studies because of their ability to form hydrogen bonds or

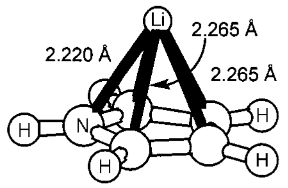

Fig. 2 The B3LYP/6-31G(d,p) computed geometry of the Li$^+$ complex with pyrrole.

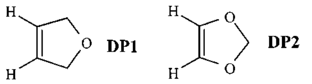

Fig. 3 Structures of two dienophiles with ether linkages necessary for nonbonding interactions in the transition state structure with pyrrole.

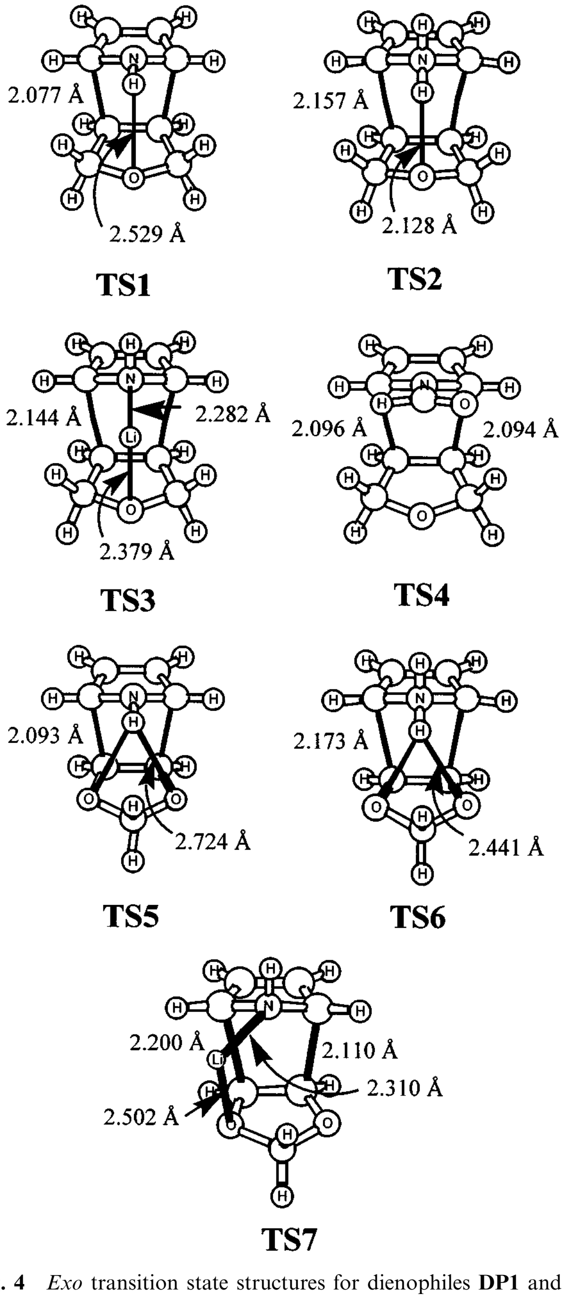

Fig. 4 *Exo* transition state structures for dienophiles **DP1** and **DP2** addition to pyrrole and activated pyrrole.

complex lithium cations of activated pyrroles. Both of them (**DP1** and **DP2**) should be able to make hydrogen-bonding interactions with the protonated pyrrole, as well as complexations of the lithium cation. Furthermore, both the dienophiles are able to form hydrogen bonding or complexes with metal cations. Of course, these interactions can be obtained only in *exo* transition state structures, as presented in Fig. 4. All of these transition state structures are optimized by the semi-empirical AM1 method. All these transition state structures are for the concerted Diels–Alder addition reactions. Almost all of them are symmetrical, therefore, they represent synchronous formation of both CC bonds. If we use the Hammond postulate[6] with the assumption that the potential energy diagram is for reactions that involve transition states **TS1**–**TS4**, rather than the transition state structure with the longest CC bond distance, we should see the geometry which is closest to the reactants and has the lowest activation barrier. According to this approach, the addition of **DP1** to protonated pyrrole has the longest CC bond in formation (2.157 Å), and should have the lowest activation barrier. On the other hand, the inactivated pyrrole should have the highest activation barrier. The lithium cation catalyzed cycloaddition reaction should be close to the activation barrier of the acid (proton) catalyzed reaction. This may not be the case. The major problem is that the reaction potential surface for the protonated and the lithiated pyrrole is substantially different. As we have demonstrated, on the basis of the ring bond order uniformity, while the protonated pyrrole is less aromatic than the lithiated pyrrole, it is actually more aromatic than pyrrole by itself (Table 1). We believe that for pyrrole (protonated), and *N*-formylpyrrole, due to the application of the Hammond rule, the CC bond distances are correct. Consequently, the reactivity is increased from the pyrrole through the mechanism, *N*-formylpyrrole to the protonated pyrrole.

Certainly, the best way to evaluate the reactivity of the "activated" pyrrole is through the computation of activation barriers. However, there are some secondary ways in which the reactivity of the pyrrole derivatives can be assessed. One of them is by using the principle of "uniformity" which we will now introduce. The highest degree of uniformity is "chaos", where everything is perfectly uniform (identical). This principle can be applied throughout science, as well as society in general. According to this principle, one system (pathway) will be selected from many if it leads to a more uniform system. Now, we can apply this principle to determine the reactivity of the activated pyrroles. Because pyrrole is an aromatic heterocyclic compound (unusually stable) it typically follows the ring bond order distribution. Therefore, the reaction that will produce the most uniform heterocycle ring's bond order in the transition state is the one with the lowest activation barrier energy. The sum of an average bond order deviation for pyrrole derivatives is presented in Table 1. Let us now evaluate the same property of the heterocyclic ring in its transition state (Table 3). Normally, the bond order average on the heterocycle of the transition state structure is diminished due to the formation of new CC bonds, but the equality of distribution of the bond order in the heterocyclic ring is essential in this evaluation. In the course of the reaction, all transition states show higher uniformity of the heterocycle bond orders except **TS3**. The largest increase in uniformity (CBOD) was observed for protonated pyrrole, and the least for the lithium-catalyzed cycloaddition (Table 3). Therefore, according to the uniformity principle, the order of reactivity with dienophile **DP1** is the protonated pyrrole, *N*-formylpyrrole, pyrrole, and lithiated pyrrole.

Let us now apply the same principle for evaluation of the stereochemical (*endo*–*exo*) outcomes of the cycloaddition reaction. Previously, we have used nonbonding interactions (secondary orbital interactions) in the cyclopropene addition to furan and butadiene as an explanation for *exo* over *endo* preference in the cycloaddition reaction.[20,21] The same principle can be used to explain the *exo* preference in the cycloaddition of pyrrole derivatives with dienophiles **DP1** and **DP2** as is demonstrated in Fig. 4. The SOI in **TS1** and **TS2** hydrogen bond with NH hydrogen and ether oxygen. For instance, the bond orders are 0.001 and 0.012, respectively. Of course these interactions

Table 3 Change in the heterocycle bond order uniformity (CBOU) in the transformation of the heterocycle in reaction with dienophile into the corresponding transition state structures. The bond orders are computed with the AM1 method

Transition state	BO_{12}	BO_{23}	BO_{34}	BO_{45}	BO_{51}	ABO	SBOD	CBOD
TS1	1.096	1.191	1.643	1.191	1.096	1.243	0.694	0.120
TS2	0.913	1.392	1.432	1.392	0.913	1.208	1.182	0.952
TS3	0.993	1.327	1.497	1.327	0.993	1.227	0.938	−0.176
TS4	1.045	1.205	1.624	1.206	1.043	1.225	0.761	0.499

BO_{nm} = bond order between the pyrrole ring atoms *n* and *m*; ABO = average ring bond order computed as sum of all ring's bond orders deviation by number of ring's atom (in our case it is five); SBOD = sum of ring's bond order deviation from an average bond order; CBOD = change of the heterocycle ring bond order deviation from the averaage bond order.

Table 4 The heterocycle ring bond order uniformity in the *endo* transition state and the *exo*–*endo* bond order difference

Heterocycle	BO_{12}	BO_{23}	BO_{34}	BO_{45}	BO_{51}	ABO	SBOD	BOD
Pyrrole	1.085	1.194	1.640	1.194	0.910	1.205	0.872	0.178
Pyrrole–H^+	0.905	1.382	1.434	1.382	0.905	1.202	1.186	0.004
Pyrrole–Li^+	0.987	1.294	1.525	1.294	0.987	1.217	0.922	−0.016

BO_{nm} = bond order between the pyrrole ring atoms *n* and *m*; ABO = average ring bond order computed as sum of all ring's bond orders deviation by number of ring's atom (in our case it is five); SBOD = sum of ring's bond order deviation from an average bond order; BOD = difference in deviation from average bond order in *endo* with regard to *exo* transition state.

are not present in the *endo* transition state structure. Thus, one can assume that the *exo* transition state should have a lower energy and the *exo* adduct should be the major product of the cycloaddition reaction.

This problem can also be explored through the heterocycle bond order uniformity. More uniform isomeric transition state structures should have lower activation barriers and consequently should be responsible for the formation of the major reaction product. The heterocycle ring bond order uniformities for an *exo* transition state structure with dienophile **DP1** are presented in Table 3 while their comparison with the *exo* isomeric transition state structures is presented in Table 4. Clearly in the case of pyrrole we have a preference for *exo* product formation. The preference for an *exo* isomer in cycloaddition with protonated pyrrole is very small due to the fact that a strong hydrogen bond was formed with the dienophile moiety, and therefore a decrease in the ring bond order uniformity is seen. This can also be true for cycloaddition reaction with lithiated pyrrole. Similar results are obtained for reaction with **DP2** (Fig. 3) as dienophile.

In the case of addition of dienophiles **DP1** and **DP2** to pyrrole and protonated pyrrole the first step is that the hydrogen bonding reactant complexes should be formed. The AM1 computed structure of the hydrogen bonding complex with dienophile **DP1** is presented in Fig. 5. These complexes actually bring the reactants together. This does not necessarily mean that the reactants are already oriented in such a way that the reactions might occur. Actually, additional energy is necessary for orienting them in such a way that reaction may occur. Considering the nature of the two hydrogen bonding complexes presented in Fig. 5, it is very easy to see that twisting through keeping a hydrogen bond is necessary to achieve an *exo* transition state structure, while for an *endo* transition state structure the hydrogen bond must be broken. Considering the fact that the hydrogen bond stabilizes both reactant complexes to a smaller degree in *exo* transition states, one can conclude that the cycloadduct product obtained through the *exo* transition state should be dominant. This clearly demonstrates reorganization of the reactants in the hydrogen complex, that favors one transition state (cycloaddition product) over the other.

To confirm our observation on the basis of bond order uniformity and hydrogen bonding stabilization, we have computed hydrogen bonding (lithium complexation) stabilization energies and activation barriers for *exo* and *endo* **DP1** and **DP2** addition to pyrrole, protonated pyrrole, and lithiated pyrrole. Total energies for the reactants, complexes and transition state structures are presented in Table 5 with reaction energies in Table 6. Hydrogen complexation energy between the dienophile **DP1** and the pyrrole is estimated to be 6.5 kcal mol^{-1}. Due to the fact that the dienophile **DP2** is actually vinyl ether and it basically should be smaller, the computed hydrogen bonding complexation with this dienophile should be smaller than in the case of dienophile **DP1**. Therefore, the estimated complexation energy for pyrrole and **DP2**, 4.7 kcal mol^{-1}, is what one would expect. Considering the fact that protonated pyrrole is a much stronger acid than pyrrole, it is expected that its hydrogen bonding complexes would also be stronger. This is demonstrated by computing the B3LYP/6-31G(d,p) stabilization energy (Table 6).

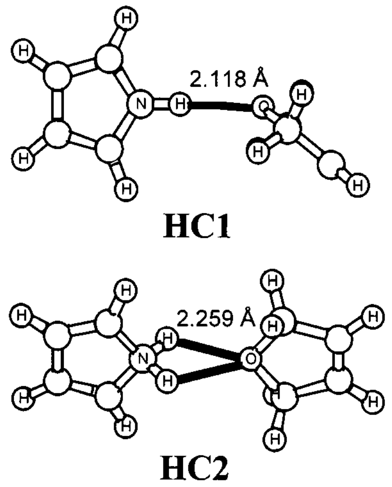

Fig. 5 The AM1 computed hydrogen bonding complexes between dienophile **DP1** and pyrrole (**HC1**) and protonated pyrrole (**HC2**).

Previously, we have estimated that the activation barrier for ethylene addition to pyrrole is 30.5 kcal mol^{-1} (Table 2). In the case of ethylene addition to pyrrole, there is no formation of hydrogen bonding complexation that is part of the reaction pathway with both dienophiles **DP1** and **DP2**. Therefore, it is not surprising that the computed activation barrier for addition of these two dienophiles is around 10 kcal mol^{-1} higher. Because stabilization hydrogen bonding in the *exo* transition state structure between pyrrole and **DP1** (**TS1**, Fig. 4) is relatively strong, and stronger than SOI in the *endo* isomeric transition state, the formation of *exo* isomer is preferred. This is not any truer for the transition state structures with dienophile **DP2**. The hydrogen bond formed with two ether oxygens in the

Table 5 Total energies (a.u.) for reactants, complexes, and transition state structures computed with B3LYP/6-31G(d,p) on AM1 geometries

Reactants	Separated reac.	Complex	*exo*-TS	*endo*-TS
Pyrrole + **DP1**	−441.3957009	−441.4060199	−441.3425068	−441.3378425
Pyrrole + **DP2**	−477.2868127	−477.2942595	−477.2331383	−477.2330577
H–pyrrole + **DP1**	−441.7175063	−441.7433646	−441.7016708	−441.6901344
H–pyrrole + **DP2**	−477.6059666	−477.6248000	−477.5875714	−477.5898234
Li–pyrrole + **DP1**	−448.7358375	−448.7836767	−448.6995853	−448.6749499
Li–pyrrole + **DP2**	−484.6269493	−484.6493192	−484.5719021	−484.5675700

Table 6 Energy of complexation and activation barriers[a] (kcal mol^{-1}) computed with B3LYP/6-31G(d,p)//AM1 theory model

Reaction	ΔE_{I}	ΔE_{II}	ΔE_{III}	$\Delta\Delta E$
Pyrrole + **DP1**	6.5	39.9	42.8	2.9
Pyrrole + **DP2**	4.7	38.4	38.4	0.0
H–pyrrole + **DP1**	16.2	26.2	33.4	7.2
H–pyrrole + **DP2**	11.8	23.4	21.9	−1.5
Li–pyrrole + **DP1**	30.0	52.8	68.2	15.4
Li–pyrrole + **DP2**	14.0	48.6	51.3	2.7

[a] Reaction barriers are computed as the energy difference between the transition state and the reactant complex. ΔE_{I} = complexation energy; ΔE_{II} = activation barrier for an *exo* cycloaddition reaction; ΔE_{III} = activation barrier for an *endo* cycloaddition reaction; $\Delta\Delta E$ = *exo* energy preference.

exo transition state (**TS5**, Fig. 4) is very long, and the methylene hydrogens are relatively acid and can form strong SOI with the pyrrole double bond in the *endo* transition state. In fact the B3LYP/6-31G(d,p) computes identical activation barriers for both transition state structures.

The addition of dienophiles **DP1** and **DP2** to protonated pyrrole is an excellent example of control which secondary orbital interactions have on the reaction outcome. As we have already pointed out, dienophile **DP1** has a relatively basic ether oxygen atom while dienophile **DP2** has a relatively acidic methylene group. Furthermore, protonated pyrrole has two distinctive characteristics that will govern its cycloaddition reaction outcome with dienophiles **DP1** and **DP2**: highly acidic N–H hydrogen and fully located double bonds (BO$_{23}$ and BO$_{45}$, Table 1). In the *exo* transition state the higher p density is between C3–C4 (BO$_{34}$, Table 4) the exact position that can make significant SOI with methylene hydrogens similar to that we have previously observed in cyclopropene addition to butadiene.[20] Computed activation barriers (Table 6) fully agree with our qualitative observation. The activation barriers for cycloaddition reaction with protonated pyrrole are substantially lower than with pyrrole and therefore the reaction should be experimentally feasible. Furthermore, strong hydrogen bonding interaction in the *exo* transition state for dienophile **DP1** to protonated pyrrole means the *exo* transition state is preferred. At the same time hydrogen bonding in the reaction with dienophile **DP2** is not dominant, the SOI in the *endo* transition state is preferred and consequently the *endo* transition state has the lower activation barrier (Table 6).

As we have demonstrated earlier, lithiated pyrrole is an aromatic system that is not eager to react, activation barriers should be very high. Furthermore, the lithium cation forms a strong complex with ether that will ensure the preference of *exo* cycloaddition reaction. The B3LYP computed activation barriers fully agree with this observation.

Conclusion

We have demonstrated that the ring bond order uniformity might be a very powerful approach to determine the reactivity of heterocyclic dienophiles such as pyrrole. The reaction will go reluctantly with bond order uniformity in chemical systems, but on the other hand the reaction that goes through a more bond order uniform system is preferred. The hydrogen bonding and secondary orbital interactions are ones that govern the cycloaddition reaction outcome. For instance, if the diene and dienophile are strong hydrogen donors and hydrogen acceptors, respectively, then the transition state structure that enables hydrogen bonding is preferred over the other. The same is the case with secondary orbital interactions between p electrons of one system and hydrogen atoms of the other system; the transition state that increases this interaction is the one that is preferred, as it was in the case of **DP2** addition to protonated pyrrole.

In general, using metal ions helps to organize reactants that are capable of performing the target reaction. In the case of using lithium in the addition of dienophiles **DP1** and **DP2** to pyrrole this is also the case, but the activation barriers are exceptionally high. The major reason for this pyrrole behavior is that pyrrole nitrogen has an exceptionally low metal complexation ability, and therefore the cyclopentadiene type complexation is preferred. In this way, the bond order uniformity of the pyrrole ring is increased and its willingness to react as a diene in the cycloaddition reaction decreases.

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