Ab Initio and Density Functional Theory Study of the Ethylene Cycloaddition Reaction to 4*H*-Pyrazole

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The reactivities of the pyrazole tautomers as dienes for Diels–Alder cycloaddition reactions were studied by both *ab initio* and density functional theories (DFT). In all the studies, the 6-31G* basis sets were used. The structures of the reactants and transition states were optimized with the RHF and MP2 methods, while the MP4 energies were estimated on MP2 geometries. Two hybrid (B3LYP and B3P86) and nonlocal (BLYP and BP86) DFT methods were also used. The reactivity was determined on the basis of the frontier molecular orbital (FMO) energy gap between the pyrazole tautomers, and ethylene and by estimation of their activation energies. The activation energies for protonated 4*H*-pyrazole tautomers were estimated with these methods as examples of acid-catalyzed reactions. It was determined that, of all of the pyrazole tautomers, 4*H*-pyrazole is the most suitable as a diene for the Diels–Alder reaction. The reaction is LUMO diene-controlled if acid-catalyzed and is predicted to take place under mild conditions.

Introduction

Heterocyclic aromatic compounds are unique sources of building blocks in natural product synthesis.[1] Normally, if the heterocyclic compounds are the precursors in synthesis, then the chemical transformations are performed on the side chain.[2] Very rarely is the heterocyclic ring itself involved in the reaction.[3] One useful synthetic approach might be to use the heterocyclic compounds as dienes for the Diels–Alder reactions. This route can provide a wide variety of functionalized organic materials necessary for other synthetic paths. Unfortunately, because of the high stability of the aromatic ring, the activation energy of the corresponding cycloaddition reaction is too high and cannot be reached under normal conditions. Of course, there are some heterocyclic compounds that undergo cycloaddition reactions. Oxazole, in the Kondratova reaction,[5] and furan[6] in preparation of many natural products are exceptional examples.

Organic chemists have employed two special conditions in changing the reaction conditions to make other heterocyclic compounds more reactive as dienes for the Diels–Alder reactions: using high pressure or derivating the heterocyclics in such a way that the aromaticity is diminished. For example, in the case of thiophene, greater reactivity was obtained through thiophene oxidation to thiophenium oxide[7] or by thiophene S-methylation.[8] Here, present the results of both *ab initio* and density functional theory (DFT) studies for the pyrazole tautomers as dienes for the Diels–Alder reaction.

Computational Methodology

All calculations were performed with Gaussian 92[9] and implementation of density functional theory with the 6-31+G* basis set. The optimizations were performed without any geometric restrictions using the Fletcher–Powell[10] method and the default Gaussian convergence criteria. Gaussian 92 DFT methods (included local, nonlocal, and gradient-corrected) were used: restricted Hartree–Fock (RHF) self-consistent field; Slater exchange functional with Vosko, Wilk, and Nusair correlation functional (SVWN);[11] Becke's exchange with Lee, Yang and Parr correlation functional (BLYP);[12] Becke's exchange with Perdew's gradient-corrected functional (BP86);

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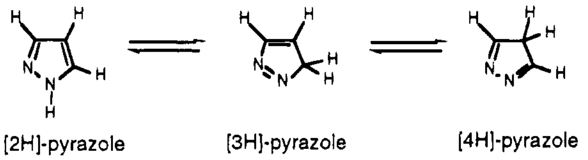
Becke's three-parameter[13] exchange with Lee, Yang, and Parr correlation functional (BECKE3LYP); and Becke's three-parameter exchange with Perdew;s gradient-corrected functional (BECKE3P86) and second order Møller–Plesset (MP2).[14] Each transition structure gives only one imaginary harmonic vibrational frequency, corresponding to the motion of the new C–C bonds for the concerted transition structures. The activation energies were estimated from those calculations and the MP4[15] calculations on the MP2-optimized geometries. In all the calculations, the 6-31+G* [16] basis set was used.

Results and Discussion

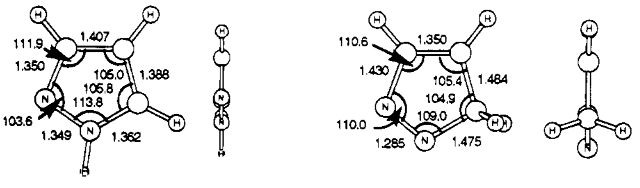
To the best of our knowledge, there is no experimental evidence supporting the employment of 2*H*-pyrazoles as dienes for the Diels–Alder reactions. The reports of their participation in the [4 + 2] cycloaddition has been shown to have been interpreted incorrectly.[17] There are three possible tautomers (Scheme 1). The common representation for the structure of pyrazole is actually 2*H*-pyrazole and is the most stable of all three tautomers. The N2 lone pairs are parallel with the π orbitals of the two double bonds, forming an aromatic heterocyclic system. The two other tautomers are not aromatic because conjugation of the π orbitals is disrupted by the methylene group in the ring and the lone pairs on the two nitrogens are perpendicular to the π orbitals of the two double bonds. Thus, one would undoubtedly select 4*H*-pyrazole as the most suitable diene for Diels–Alder (DA) reactions.

Scheme 1. The Structures of Three Possible Pyrazole Tautomers

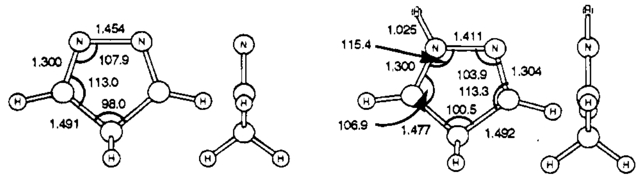


Judging the reactivity of different pyrazole tautomers can be approached by using frontier molecular orbital (FMO) theory, although some have disputed this approach for the study of reactivity and stereoselectivity.[18] The advantage of the FMO approach is that the results for reactivity can be obtained quickly. We have used the AM1 semiempirical MOPAC[19] method to optimize all three pyrazole tautomers and ethylene as a dienophile, while determining their reactivity on the basis of the FMO energy gap. According to the AM1 calculations, the pyrazole tautomer is 2*H*-pyrazole (0.0 kcal/mol), 4*H*-pyrazole (6.1 kcal/mol), and 3*H*-pyrazole (7.2 kcal/mol). If the Diels–Alder transition state structures have similar energies, then it can be assumed that 3*H*-pyrazole would be the most reactive pyrazole tautomer. The FMO energy gap with ethylene is calculated with the AM1 method, selecting 4*H*-pyrazole to be the most reactive pyrazole tautomer. The ethylene addition to 2*H*-pyrazole is HOMO diene-controlled (ΔE = 11.44 eV). While both 3*H*-pyrazole (ΔE = 10.25 eV) and 4*H*-pyrazole (ΔE = 10.17 eV) are LUMO diene-controlled, they are predicted to be more reactive than butadiene (ΔE = 10.77 eV). If protonated, 4*H*-pyrazole is predicted to be far more reactive as a diene for the Diels–Alder reaction (ΔE is merely 4.05 eV) . To confirm this order, the activation barriers for the ethylene addition to those dienes were estimated with the AM1 method. The calculated activation energies follow the FMO-predicted order of reactivity: 2*H*-pyrazole (51.0 kcal/mol), 3*H*-pyrazole (41.5 kcal/mol), 4*H*-pyrazole (26.0 kcal/mol), and protonated 4*H*-pyrazole (14.8 kcal/mol). The AM1 method predicts the activation energy of the ethylene addition to butadiene to be 23.8 kcal/mol, determining that only the cycloaddition reaction with protonated 4*H*-pyrazole might be experimentally achievable. This is not in agreement with the FMO energy gap calculations that selected both nonprotonated and protonated 4*H*-pyrazole to be experimentally suitable as dienes.

A more reliable study of the pyrazole tautomer reactivity as a diene for the Diels–Alder reaction was further carried out by the MP2/6-31+G* theoretical model. The geometries of the pyrazole tautomers are presented in Figure 1. The predicted order of stability is the same as that from the AM1 calculation: 2*H*-pyrazole (0.0 kcal/mol), 4*H*-pyrazole (24.31 kcal/mol), and 3*H*-pyrazole (29.08 kcal/mol). The FMO order of reactivity calculated from the MP2/6-31+G* frontier orbital in the ethylene addition is the same as that from the AM1 calculation. The cycloaddition reaction should be LUMO diene-controlled. Because the 4*H*-pyrazole as a diene for the cycloaddition reaction has a higher energy than the 2H-tautomer, it may be necessary to introduce two substituents in the 4-position. The substituents should lock the structure of pyrazole in the 4*H*-tautomer form and by their electron-withdrawing capability decrease the pyrazole LUMO energy.



[2H]-pyrazole [3H]-pyrazole



[4H]-pyrazole protonated [4H]-pyrazole

Figure 1. Geometries of pyrazole tautomers calculated with MP2/6-31+G*.

The AM1 calculations predict the geometries of the reactants to be close to the experimental geometries and the geometries of the transition state structures. This is similar to the *ab initio* calculations, but an evaluation

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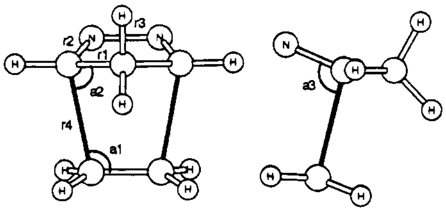
of the activation energies shows that the predicted calculations are very different.[20] They are too large in comparison to the results obtained experimentally and with the MP*n* *ab initio* methods. There has been considerable dispute concerning the mechanism of the Diels–Alder reactions,[21] but a recent theoretical study at the correlated level supports the concerted mechanism.[22] Here, we have considered only the concerted mechanism of the Diels–Alder reaction.

The most reactive pyrazole tautomer, 4*H*-pyrazole, in its nonprotonated and protonated forms has been further studied by both *ab initio* and DFT methods to estimate the activation energies and feasibility of the reactions. The calculated geometric parameters for the ethylene-4*H*-pyrazole transition state structure are presented in Table 1.

Table 1. Geometric Parameters of the Transition State Structure for the Ethylene Addition to 4*H*-Pyrazole Calculated with the 6-31+G* Basis Set



method	$r1$ (Å)	$r2$ (Å)	$r3$ (Å)	$r4$ (Å)	$a1$ (deg)	$a2$ (deg)	$a3$ (deg)
RHF	1.498	1.327	1.306	2.149	100.9	92.3	97.7
Becke3LYP	1.508	1.344	1.345	2.206	100.9	91.6	97.0
Becke3P86	1.495	1.333	1.345	2.238	100.8	90.9	96.3
BLYP	1.515	1.360	1.363	2.219	100.9	91.8	97.2
BP86	1.507	1.349	1.366	2.267	100.8	90.9	96.3
MP2	1.495	1.346	1.368	2.238	100.9	90.9	96.7

The transition state has a plane of symmetry that bisects both the dienophile and the diene. Thus, the structure represents synchronous formation of both C–C bonds. The RHF calculations are not suitable for the accepted geometry, and thus, methods with correlation should be considered. If we regard the MP2/6-31+G*-generated transition state structure to be the most accurate, then we find that there is considerable improvement in DFT methods over the RHF calculations. One nonlocal DFT method (BP86) generates a structure that is very close to the one calculated by the MP2 method (Table 2). Maximal disagreement (0.029 Å) is observed for the predicted C–C bond distance of the new forming bond ($r4$, Table 1).

As expected, the transition structure for ethylene addition to protonated 4*H*-pyrazole is not a synchronous concerted mechanism (Table 2). Considerable disagreement is found in the geometric parameters calculated by DFT and *ab initio* MP2 methods. In the case of the ethylene addition to 4*H*-pyrazole, excellent agreement is found with the BP86 and MP2 structures. In fact, all of the transition state structures generated with the DFT methods are closer to the MP2 calculations than to the RHF method calculations. In the case of ethylene addition to protonated 4*H*-pyrazole, the DFT-generated structures are somewhere between the one generated with RHF and MP2 *ab initio* methods. Nevertheless, all of the calculations predicted an asynchronous transition state. If we considered only the bond distance of two bonds in formation ($r7$ and $r8$, Table 2), then the predicted order of asynchronicity is MP2 (0.196), BECKE3P86 (0.470), BP86 (0.481), BECKE3LYP (0.528), BLYP (0.548), and RHF (0.762). Overall, the most compact structure is predicted by the MP2 calculation.

The best method for determining reactivity is calculating the activation barriers. We have used both DFT and *ab initio* methods for estimating the reactivity of 4*H*-pyrazole and protonated 4*H*-pyrazole in the cycloaddition reaction with ethylene. The reactivity of these two dienes is also compared with that of 1,3-butadiene. The total energies are presented in Table 3 and the activation energies in Table 4. In all the calculations, it is predicted that 4*H*-pyrazole and protonated 4*H*-pyrazole are more reactive as dienes for the DA reactions than 1,3-butadiene. Because the experimental activation barriers for ethylene addition to pyrazoles are not available, both DFT and *ab initio* methods were calibrated using the example of ethylene addition to butadiene. The experimental value for this cycloaddition reaction is 25.1 kcal/mol. From our previous results of DFT calculations with the 6-31G** basis set, the best results for this addition were obtained with the B3LYP DFT hybrid method,[23] with an activation energy difference of only 0.2 kcal/mol from the experimental value (Table 4). We have also investigated this system with the MP4/6-31+G*//MP2/6-31+G* *ab initio* method with the purpose of calibrating these methods. The activation energy calculated with the MP2/6-31+G* theoretical model for the ethylene–butadiene cycloaddition reaction is 18.5 kcal/mol which is 6.6 kcal/mol lower than the experimental value. It is well-known in computational chemistry that the MP2 *ab initio* method overestimates the correlation interaction, producing energies lower than the experimental values. The MP4 method produced activation energies that are 1–2 kcal/mol away from the experimental values. The Becke3LYP calculations on the ethylene–butadiene system were not performed with the same basis set, but we consider the *ab initio* MP4/6-31+G*//MP2/6-31+G* method to be the most reliable for energy evaluation.

All of the applied theoretical models agree that 4*H*-pyrazole and protonated 4*H*-pyrazole are much better dienes for Diels–Alder reactions than is butadiene. A similar observation was obtained by comparison of the FMO energy gaps. The activation energy calculated with the DFT methods for the ethylene addition to 4*H*-pyrazole is between 13.4 and 20.6 kcal/mol and should be achievable under normal reaction conditions. The MP4/6-31+G*//MP2/6-31+G* theory model also predicts a moderate activation energy of 16.1 kcal/mol, which suggests facile reaction conditions. In the case of protonated 4*H*-pyrazole, the predicted activation energy is below 10 kcal/mol. On the basis of the MP4 calibration, we believe that this activation energy should be around 5 kcal/mol, allowing this reaction to be performed even at low temperature.

On the basis of the results presented here, we can conclude that hybrid DFT methods such as Becke3LYP and BP86 are suitable for obtaining reliable results for

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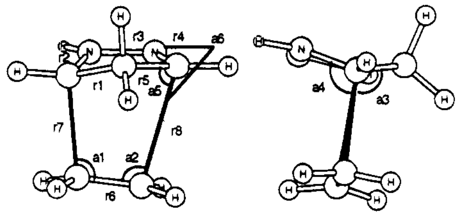
Table 2. Geometric Parameters of Transition State Structure for Ethylene Addition to Protonated 4*H*-Pyrazole Calculated by Using the 6-31+G* Basis Set



	*r*1 (Å) *a*1 (deg)	*r*2 (Å) *a*2 (deg)	*r*3 (Å) *a*3 (deg)	*r*4 (Å) *a*4 (deg)	*r*5 (Å) *a*5 (deg)	*r*6 (Å) *a*6 (deg)	*r*7 (Å)	*r*8 (Å)
				RHF				
r	1.511	1.363	1.344	1.281	1.506	1.391	1.864	2.626
a	104.6	94.9	104.6	107.2	82.8	83.2		
				Becke3LYP				
r	1.508	1.360	1.352	1.316	1.505	1.389	2.019	2.547
a	104.0	96.9	99.8	103.7	84.8	87.8		
				Becke3P86				
r	1.495	1.343	1.350	1.309	1.496	1.375	2.105	2.575
a	102.6	97.9	98.0	102.6	84.3	87.7		
				BLYP				
r	1.520	1.378	1.368	1.332	1.515	1.403	2.021	2.569
a	104.7	96.3	100.0	103.8	84.9	88.3		
				BP86				
r	1.507	1.358	1.367	1.326	1.507	1.388	2.132	2.613
a	103.2	97.3	98.0	102.4	84.4	88.0		
				MP2				
r	1.492	1.340	1.355	1.335	1.494	1.379	2.227	2.423
a	101.2	100.2	93.9	99.2	88.2	91.7		

Table 3. Total Energies (a.u.) Calculated by Using the 6-31+G* Basis Set

compd or structure[a]	RHF	Becke3LYP	Becke3P86	BLYP	BP86	MP2	MP3/MP2	MP4/MP2
A	−78.035 82	−78.593 25	−78.877 73	−78.544 18	−78.584 51	−78.291 18	−78.311 72	−78.325 90
B	−154.926 25					−155.433 85	−155.466 04	−155.495 51
C	−224.771 28	−226.174 62	−226.818 08	−226.099 33	−226.178 99	−225.480 97	−225.497 91	−225.543 37
D	−225.129 74	−226.525 50	−227.171 10	−226.447 46	−226.528 77	−225.824 35	−225.846 90	−225.888 72
E	−232.887 21					−233.695 58	−233.733 77	−233.784 66
F	−302.742 00	−304.734 96	−305.672 90	−304.611 61	−304.742 11	−303.755 12	−303.774 42	−303.843 64
G	−303.127 15	−305.107 72	−306.046 26	−304.981 63	−305.111 98	−304.116 13	−304.145 34	−304.208 50

[a] A, ethene; B, butadiene; C, 4*H*-pyrazole; D, protonated 4*H*-pyrazole; E, transition state structure of ethene + butadiene; F, transition state structure of ethene + 4*H*-pyrazole; G, transition state structure of ethene + protonated 4*H*-pyrazole.

Table 4. Activation Energies (kcal/mol) Calculated by Using the 6-31+G* Basis Set

process[a]	RHF	Becke3LYP	Becke3P86	BLYP	BP86	MP2	MP3/MP2	MP4/MP2
E	46.97	24.92[b]		23.09[b]		18.48	27.60	23.06
F	40.85	20.65	14.38	20.02	13.42	10.67	22.09	16.08
G	24.10	6.92	1.61	6.28	0.81	0.37	8.33	3.84

[a] E, ethene addition to butadiene; F, ethene addition to 4*H*-pyrazole; G, ethene addition to protonated 4*H*-pyrazole. [b] Calculated with the 6-31G** basis set.

these and similar cycloaddition systems. The MP4 single point energy on the MP2 geometry will produce energies that are very close to the experimental results. The dominant pyrazole 2*H*-tautomer structures are unlikely to undergo a Diels−Alder cycloaddition reaction because of their high stability. Of the two remaining tautomers, 4*H*-pyrazole is the most reactive one. The reaction is LUMO diene-controlled, so that electron-withdrawing substituents in the 3- and 5-position will facilitate the reaction. Using acid increases the diene electron acceptor ability, also catalyzing the cycloaddition reaction. In this case, the reaction may proceed under very mild conditions.

There is an abundance of experimental data that support this theoretical study. The cycloaddition reaction of 3,5-diaryl-4,4-dimethyl-4*H*-pyrazole with cyclopentadiene forms 1,4-diaryl-8,8-dimethyl-2,3-diazabicyclo[2.2.1]hept-2-ene.[24] *p*-Nitrophenyl substituents in the 3 and 5-positions greatly enhance the reactivity of the 4*H*-pyrazole, thereby confirming the inverse electron-demanding (LUMO) diene-controlled reaction. A Hammett correlation ($\rho = 3.24$) demonstrated the pronounced sensitivity of this acid-catalyzed reaction. The reaction is over in 5 min in $CHCl_2$/CF3COOH at 0 °C,[25] demonstrating a very low reaction barrier.

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