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Influence of Diene Substitution on Transition State Stabilization in Diels−Alder Reaction

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Abstract: A theoretical analysis of transition state stabilization in D−A reactions of substituted dienes according to the nature and position of the substituent has been carried on. Results revealed that substituents (de)stabilize TS through four effects (steric, mesomeric, inductive, and polarizability) acting principally by favoring the electronic transfer between the two partners. The correlations observed point out nevertheless that the reactivity of substituted dienes in [4 + 2] cycloadditions on ethylene may principally be predicted by the sole use of the $F + R$ electronic parameters.

The Diels−Alder (D−A) reaction is unquestionably the most widely investigated and used pericyclic reaction for carbon−carbon bond formation. Since its discovery in 1928[1] a tremendous amount of theoretical and experimental work has been devoted to the mechanism,[2] regioselectivity,[3] and stereoselectivity[3d,4−6] of the [4 + 2] cycloaddition. Although Sustmann,[2b,7] Houk,[8] and others[9−11] have studied the influence of the nature of the D−A partners on reactivity through reactant properties (frontier molecular orbitals[12]), there have been few theoretical investigations of D−A transition states involving substituents.[13−17] To our knowledge, no systematic theoretical work on the ability of substituents to (de)stabilize D−A transition states according to the nature of their effects has ever been conducted.

We recently examined the influence of the diene or dienophile substitution with a phosphonic group on D−A reaction.[18] This theoretical study showed the presence of substituent effects other than strictly inductive and mesomeric. Aiming to generalize this analysis and to possibly predict the reactivity behavior of substituted dienes in [4 + 2] cycloadditions, we have now examined the (de)stabilization of D−A transition states according to the diene substitution. Taking the cycloaddition of butadiene on ethylene as the reference, a selection of representative functional groups on 1- and 2-substituted dienes have been studied. Ab initio calculations[19] were performed at the DFT Becke3LYP[20] level with use of a 6-31G(d,p) basis set. A full optimization of each minimum and transition structure was always been performed and the various conformations of the substituents explored (only the most stable conformer being considered in this note). A check at the curvature and its eigenvector was systematically taken to guarantee the quality of the obtained results. 1,3-Butadiene derivatives exist in two minimum energy conformations, *s-trans* (torsion angle of 180°) and *s-gauche* (torsion angle around 35°).[21] If the *s-trans* conformation of the diene is known to be the most

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TABLE 1. Variation of Energy Barriers ($\Delta\Delta E^{\ddagger}$), LUMO Energy of Dienes, and Total NPA Charges of Ethylene Moiety at TS of [4 + 2] Cycloaddition with Diene Substitution

			$\Delta\Delta E^{\ddagger}$ (kcal mol^{-1})		LUMO energy (au)		NPA charge of ethylene at TS	
substituent	F	R	1-diene	2-diene	1-diene	2-diene	1-diene	2-diene
H	0.00	0.00	0.00	0.00	−0.0237	−0.0237	0.0003	0.0003
F	0.45	−0.39	−0.32	0.70	−0.0220	−0.0352	−0.0113	0.0031
Cl	0.42	−0.19	0.15	−0.39	−0.0368	−0.0386	0.0255	0.0190
Br	0.45	−0.22	−0.70	−0.59	−0.0382	−0.0398	0.0296	0.0208
Me	0.01	−0.18	1.27	1.23	−0.0162	−0.0161	−0.0095	−0.0071
CF_3	0.38	0.16	−0.89	−1.37	−0.0522	−0.0461	0.0401	0.0355
CCl_3	0.38	0.09	0.66	−1.13	−0.0631	−0.0537	0.0529	0.0471
CBr_3	0.28	0.01	−0.93	−1.92	−0.0694	−0.0701	0.0473	0.0522
*t*Bu	−0.02	−0.18	3.03	1.46	−0.0162	−0.0127	−0.0094	−0.0058
OMe	0.29	−0.56	2.19	2.96	−0.0091	−0.0167	−0.0344	−0.0151
OCF_3	0.39	0.04	1.18	−0.45	−0.0312	−0.0390	0.0065	0.0207
SMe	0.23	−0.23	1.64	0.67	−0.0293	−0.0236	−0.0015	0.0108
SCF_3	0.36	0.14	0.93	−2.46	−0.0483	−0.0473	0.0292	0.0332
SeMe	0.16	−0.16	0.07	−1.07	−0.0311	−0.0255	0.0057	0.0147
$SeCF_3$	0.43	0.02	−0.65	−2.21	−0.0499	−0.0478	0.0269	0.0323
CCH	0.22	0.01	0.51	−1.50	−0.0522	−0.0419	0.0327	0.0220
NC	0.47	0.02	−0.25	−1.66	−0.0638	−0.0585	0.0377	0.0337
CN	0.51	0.15	−0.64	−2.93	−0.0769	−0.0673	0.0639	0.0515
NH_2	0.08	−0.74	1.65	1.96	−0.0007	−0.0108	−0.0672	−0.0336
COOH	0.34	0.11	−0.55	−2.78	−0.0689	−0.0596	0.0474	0.0419
NO_2	0.65	0.13	−2.04	−4.07	−0.1008	−0.0945	0.0787	0.0721
SOMe	0.52	−0.03	0.85	−0.43	−0.0468	−0.0430	0.0328	0.0367
$PO(OH)_2$	0.34	0.08	−0.12	−1.73	−0.0563	−0.0429	0.0599	0.0444
SiH_3	0.06	0.04	1.29	−0.10	−0.0425	−0.0290	0.0219	0.0203

stable, numerous studies indicate that cycloaddition should occur from the *s-gauche* conformer, which presents the more favorable geometry for cycloaddition.[2a,b,4c] The aim of this study is to analyze the influence of substituents on the energy, rising specifically at transition states, and to differentiate it from interactions induced by substituents on conformational equilibrium of ground states. The activation energies $\Delta E^{\ddagger}$ were thus calculated by summing the energies of the isolated reactants considering the dienes in a *s-gauche* conformation (eq 1). The influence of substitution on activation energies ($\Delta E^{\ddagger}$) was analyzed through the variation of the latter ($\Delta\Delta E^{\ddagger}$; eq 2) by taking the cycloaddition of butadiene with ethylene as the reference.

$$\Delta E^{\ddagger} = E_{(\mathrm{TS})} - E_{(\text{reactants with diene in } s\text{-}gauche \text{ conformation})} \quad (1)$$

$$\Delta\Delta E^{\ddagger} = \Delta E^{\ddagger}_{(\mathrm{ref})} - \Delta E^{\ddagger}_{(\text{with substituent})} \quad (2)$$

Quantitative information on the inductive and/or mesomeric nature of substituents is provided respectively by the *F* and *R* constants[22] published by Hansch.[23] Table 1 reports all results obtained on the studied compounds.

A first analysis reveals a linear correlation[24] between the variation of activation energy ($\Delta\Delta E^{\ddagger}$) and a global electronic effect estimated by $F + R$ (Figures 1 and 2). The poorer correlation observed for 1-substituted dienes is at first interpreted by the steric interactions rising between ethylene and the substituent at the transition state, such interactions being negligible in the case of 2-substituted dienes. This is well-illustrated by the $\Delta\Delta E^{\ddagger}$ values obtained with Me versus *t*Bu substituents, both having similar electronic but very different steric effects (Table 1). Despite such steric perturbations, a growing

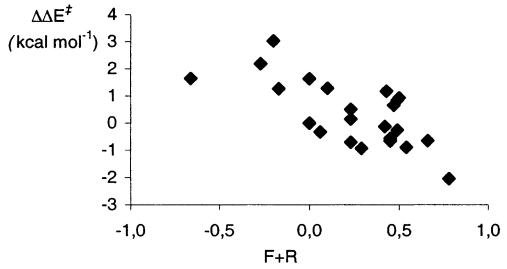

FIGURE 1. Plot of $\Delta\Delta E^{\ddagger}$ (kcal mol^{-1}) versus $F + R$ values for 1-substituted dienes: $r = 0.676$.

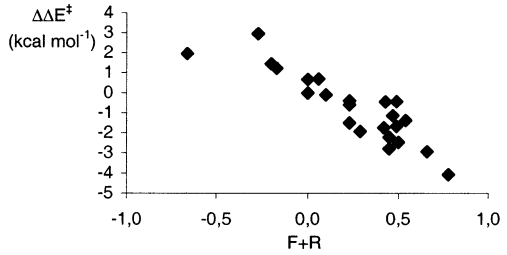

FIGURE 2. Plot of $\Delta\Delta E^{\ddagger}$ (kcal mol^{-1}) versus $F + R$ values for 2-substituted dienes: $r = 0.876$.

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(22) F and R are the constants evaluating, in the Hammett theory, respectively field/inductive and resonance effect of substituents as described by Swain and Lupton (see ref 23). Those constants are calculated from the equations $\sigma_p = F + R$ and $F = 1.297\sigma_m - 0.385\sigma_p + 0.033$ and are available for more than 500 substituents.

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(24) The relationship between $\Delta\Delta E^{\ddagger}$ and $F + R$ values is approximated by a linear correlation even if the region of strong electronic releasing groups, such as NH_2, suggests a bending of the curve.

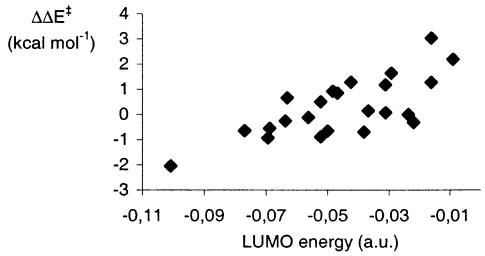

FIGURE 3. Plot of $\Delta\Delta E^{\ddagger}$ (kcal mol^{-1}) versus LUMO energies (au) of 1-substituted dienes: $r = 0.734$.

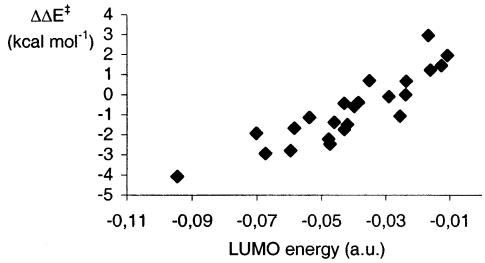

FIGURE 4. Plot of $\Delta\Delta E^{\ddagger}$ (kcal mol^{-1}) versus LUMO energies (au) of 2-substituted dienes: $r = 0.887$.

stabilization of transition states with diene substitution follows clearly the electronic withdrawing power of the substituent in both positions.

The energies of frontier molecular orbitals (FMO) of dienes are also directly influenced by substituent effects.[25] Correlations between $\Delta\Delta E^{\ddagger}$ and the energy of the calculated HOMO ($r = 0.679$ and 0.719 for 1- and 2-substituted dienes, respectively) and LUMO ($r = 0.734$ and 0.887 for 1- and 2-substituted dienes, respectively; Figures 3 and 4) energies of the substituted dienes can be observed. Those correlations confirm that stabilization of transition states in the D−A reaction can be largely (but not totally) forecast by the energy of the frontier molecular orbitals of reactants as predicted by Fukui.[12] According to FMO theory, the lower quality of the correlation of $\Delta\Delta E^{\ddagger}$ values against HOMO energies than LUMO energies, as the increase of transition state stabilization with the decrease of those, would indicate (as our observations above) that $HOMO_{dienophile}$-$LUMO_{diene}$ is the "dominant"' interaction in the considered D−A reactions, which mean that dienes would react as electrophiles and ethylene as nucleophile.

All these results would mean that either the Alder's rule[2a] is not as good as its inverse (this is opposite to the Anh[9] and Fujimoto[26] deductions) or that unsubstituted ethylene prefers to react as a nucleophile rather than an electrophile in D−A reactions (such assertion is also supported by orbital analysis by Spino[11]).

The analysis of electronic transfer between dienes and dienophiles at the transition state was realized by using the total Natural Population Analysis (NPA)[27] charges of the ethylene moiety (Table 1). These values present also a good linear correlation with the total electronic

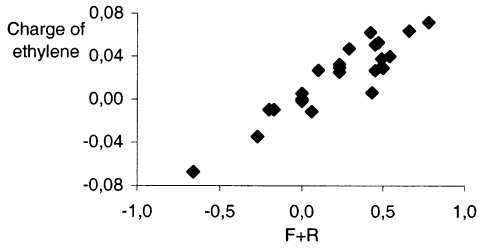

FIGURE 5. Plot of total NPA charges of ethylene moiety at TS versus $F + R$ values for 1-substituted dienes: $r = 0.912$.

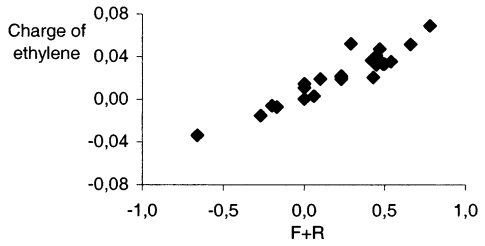

FIGURE 6. Plot of total NPA charges of ethylene moiety at TS versus $F + R$ values for 2-substituted dienes: $r = 0.938$.

effect $F + R$ of the substituent (Figures 5 and 6): diene substitution with a globally withdrawing group promotes the electronic transfer from ethylene to the diene, while substitution with a donor group induces the opposite electronic transfer. The NPA charges are less sensible to steric interactions and furnish a good correlation in both cases. A similar relationship is observed between $\Delta\Delta E^{\ddagger}$ and global NPA charges on ethylene ($r = 0.682$ and 0.912 for 1- and 2-substituted dienes, respectively). This indicates that substituents influence mainly the reactivity of dienes in D−A reactions by favoring the electronic transfer between the two partners at the transition state.

An additional reason for the systematic lower quality of correlations in the cycloaddition of 1-substitued dienes could be due to the fact that the magnitude of inductive and mesomeric effects differs for dienes substituted at position 1 or 2. Indeed, the variation of electronic transfer at TS, and consequently its stabilization, versus the nature of the electronic effects (inductive or mesomeric) of substituents reveals similar influences for an inductive group at position 1 or 2 (cf. NO_2, SOMe, NC, and $SeCF_3$), but mesomeric effects appear to dominate in 1-substituted butadienes (cf. OMe, NH_2, and *t*Bu). The experimental higher reactivity of 1-(electron-donor-conjugating)-substituted 1,3-butadienes compared to the corresponding 2-substituted dienes has been reported already by Sauer,[2a] Sustmann,[7a] and Schubert,[7b] and supports the present theoretical analysis.

The correlations in the case of 2-substituted dienes are systematically better, as we observed and discussed above. Those residues computed for those correlations are still significant, however, and show a lack in the "explanation" of the phenomenon. A careful analysis of $\Delta\Delta E^{\ddagger}$ values according to $F + R$ values or FMO energies suggests an additional factor completing the steric,

(25) The expected decrease of the energy of FMO with the electronic withdrawing power of the substituents (evaluated by $F + R$) can be observed with the reasonable coefficient of correlation ($r = 0.840$ and 0.828 for HOMO and LUMO, respectively).

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(27) (a) Foster, J. P.; Weinhold, F. *J. Am. Chem. Soc.* **1980**, *102*, 7211. (b) Reed, A. E.; Weinhold, F. *J. Chem. Phys.* **1983**, *78*, 4066. (c) Reed, A. E.; Weinstock, R. B.; Weinhold, F. *J. Chem. Phys.* **1985**, *83*, 735.

inductive, and mesomeric effects. The series F → Cl → Br, Me → CF_3 → CCl_3→ CBr_3, OMe → SMe → SeMe, and OCF_3 → SCF_3 → $SeCF_3$ show indeed a supplementary increase of stabilization evolving in the indicated order.[28] The presence of elements from the 3rd and 4th periods seems to favor the TS stabilization. This should most probably result from the high polarizability of such elements.[29]

All this analysis indicates that substituents influence the dienes reactivity in D−A reactions by acting on the transition state through electronic delocalization (via inductive and mesomeric effects), steric interactions (for 1-substituted dienes), and finally polarization effects. The correlations observed point out nevertheless that the reactivity of substituted dienes in [4 + 2] cycloadditions on ethylene may principally be predicted through the calculated LUMO's energies or by the sole use of the $F + R$ values which are available for all the usual substituents in organic synthesis. Our investigations have indeed shown that the electronic delocalization is the most important and that it operates by favoring the electronic transfer between the two D−A partners. Having identified the different factors, a more detailed analysis of the relationships presented here is now carried out aiming to develop a quantitative treatment predicting the evolution of transition state stabilization and subsequently the reactivity of substituted dienes.

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Supporting Information Available: Cartesian coordinates, total energies at the B3LYP 6-31G(d,p) level, and number of imaginary frequencies of the considered dienes and transition states. This material is available free of charge via the Internet at http://pubs.acs.org.

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(28) Deletion of substituents containing elements from the 3rd and 4th period enhances significantly the correlation coefficient of $\Delta\Delta E^{\ddagger}$ versus $F + R$ (r becomes respectively 0.791 and 0.912 for 1- and 2-substituted dienes).

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