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Diels–Alder Cycloadditions of Electron-Rich, Electron-Deficient, and Push–Pull Dienes with Cyclic Dienophiles: High-Pressure-Induced Reactions and Theoretical Calculations

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High-pressure-promoted (4 + 2) cycloadditions of cyclic dienophiles (mainly β-angelica lactone and cyclopentenone) with electron-rich and push–pull hetero-substituted dienes have been investigated. Only one regio- and stereoisomer was obtained in all cases. While these dienophiles reacted smoothly with alkoxy- and (silyloxy)butadiene derivatives, replacement of oxygen by sulfur resulted in a dramatic decrease in the reactivity of the dienes. On the other hand, push–pull dienes exhibited reactivity similar to that of the electron-rich dienes, in that the dienophilicity was not changed substantially by the influence of an electron-withdrawing group. Theoretical calculations of activation enthalpies have been carried out by the semiempirical AM1 method. These values and frontier orbital considerations have permitted us to interpret the experimental results and to establish a relative order of reactivity of the dienes and dienophiles herein studied.

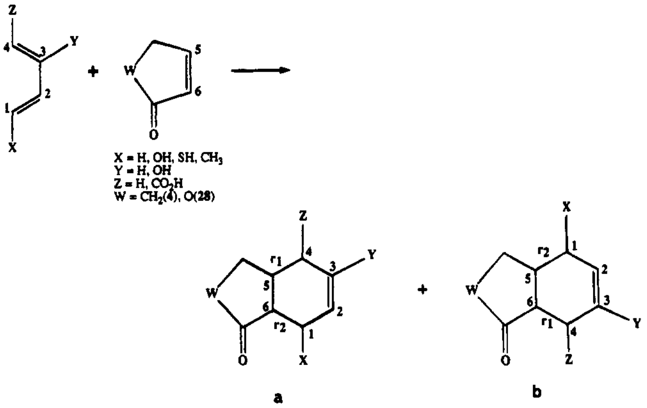
Introduction

The Diels–Alder cycloaddition is well-known to be one of the most powerful tools for organic chemists, and it has been the subject of numerous studies in order to rationalize its mechanism and to explore new synthetic applications.[1-3]

The use of *hetero-substituted dienes* has provided a useful means to achieve the regiocontrolled synthesis of a great variety of highly functionalized skeletons.[4] Alkyl- and silyloxy and alkyl- and arylthio groups are among the more common substituents in the electron-rich dienes, such as 1- and 2-[(trimethylsilyl)oxy]-1,3-butadiene (**1** and **7**), 1-(phenylthio)-1,3-butadiene (**6**),[5] and Danishefsky's diene (**10**)[6] (Table I). On the other hand, we have developed[7,8] a new kind of diene exhibiting 1,4-donor–acceptor substitution (push–pull dienes). They are 5-alkoxypentadienoates, **12** and **16**, that show an ambident reactivity, giving adducts with either acceptor (electron-deficient) or donor (electron-rich) dienophiles,[9] although with opposite regiochemistry.

It is worthy of note that *five-membered-ring dienophiles* such as β-angelica lactone (**2**) or cyclopentenone (**4**) have been scarcely used in (4 + 2) cycloadditions with C-substituted or hetero-substituted dienes, in spite of the interest of the resulting adducts as versatile synthetic building blocks.[9-12] In fact such cyclic compounds proved to be poor dienophiles that require high temperatures to afford adducts in good yields, and these conditions, as well as the use of strong Lewis acids as catalysts, are precluded if sensitive hetero-substituted dienes are used. In this respect, *high-pressure-induced cycloadditions* are reported to occur under milder conditions than thermally activated reactions, and often with improved selectivity.[13] For instance, this technique has been shown to be the best method to perform efficiently the cycloadditions of cycloalkenones and α,β-unsaturated lactones with electron-rich or push–pull dienes.[8,9,11,14,15]

Scheme I



In this paper we present a systematic study of the Diels–Alder reactions of cyclic (mainly five-membered-ring) dienophiles with a series of electronically varied dienes. Theoretical calculations were carried out to rationalize the observed reactivity and regioselectivity. A good agreement between experiments and theoretical predictions has been found in all cases. This has allowed us to establish general trends for the relative reactivity of the considered dienes and dienophiles, and for the regioselectivity of the corresponding cycloadditions.

Results and Discussion

Diels–Alder cycloadditions were performed under high-pressure conditions (see Experimental Section for further details). Electron-rich (**1**, **6**, **7** and **10**), push–pull (**12**, **16**, and **20**), and electron-deficient dienes (**23** and **26**) have been evaluated (Table I). β-Angelica lactone (**2**) and

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(1) (a) Sauer, J. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 211; (b) **1967**, *6*, 16.

(2) Sauer, J.; Sustmann, R. *Ibid.* **1980**, *19*, 779.

(3) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 876.

(4) Petrzilka, M.; Grayson, J. I. *Synthesis* **1981**, 753.

(5) Hopkins, P. B.; Fuchs, P. L. *J. Org. Chem.* **1978**, *43*, 1208.

(6) Danishefsky, S.; Kitahara, T.; Yan, C. F.; Morris, J. *J. Am. Chem. Soc.* **1979**, *101*, 6996.

(7) Maddaluno, J.; d'Angelo, J. *Tetrahedron Lett.* **1983**, *24*, 895.

(8) Guingant, A.; d'Angelo, J. *Tetrahedron Lett.* **1986**, *27*, 3729.

(9) Revial, G.; Blanchard, M.; d'Angelo, J. *Tetrahedron Lett.* **1983**, *24*, 899.

(10) Ichihara, A.; Kimura, R.; Moriyasu, K.; Sakamura, S. *Tetrahedron Lett.* **1977**, 4331.

(11) Ortuño, R. M.; Guingant, A.; d'Angelo, J. *Tetrahedron Lett.* **1988**, *29*, 6989.

(12) Batllori, R.; Font, J.; Monsalvatje, M.; Ortuño, R. M.; Sánchez-Ferrando, F. *Tetrahedron* **1989**, *45*, 1833 and references cited therein.

(13) (a) Matsumoto, K.; Sera, A.; Uchida, T. *Synthesis* **1985**, 1. (b) Matsumoto, K.; Sera, A. *Ibid.* **1985**, 999.

(14) Laugraud, S.; Guingant, A.; d'Angelo, J. *Tetrahedron Lett.* **1989**, *30*, 83.

(15) Ferroud, C.; Revial, G.; d'Angelo, J. *Tetrahedron Lett.* **1985**, *26*, 3981.

0022-3263/91/1956-4135$02.50/0

Table I. High-Pressure-Induced Diels–Alder Cycloadditions of Electron-Rich (1, 6, 7, and 10), Push–Pull (12, 16, and 20), and Electron-Deficient Dienes (23 and 26) with Cyclic Dienophiles 2, 4, 8, 14, 18, and 21

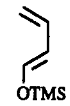
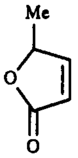
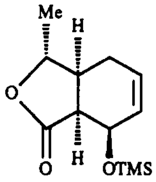
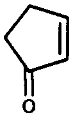
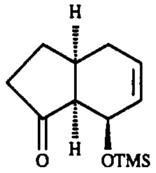
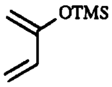
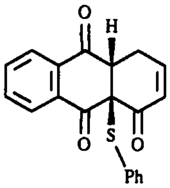
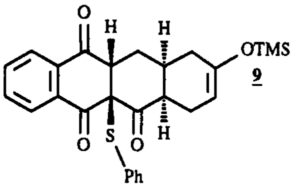
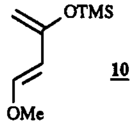
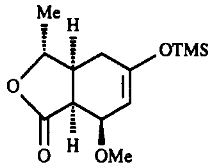
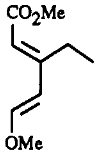
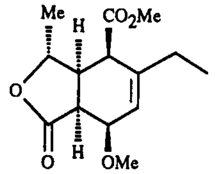
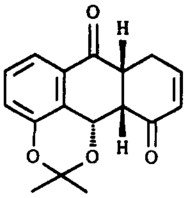
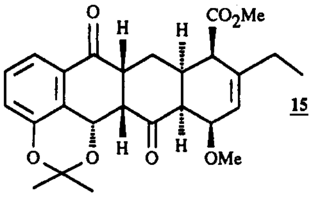
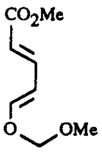
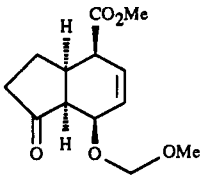
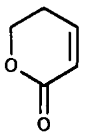
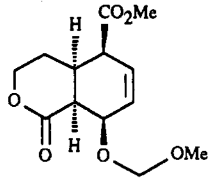
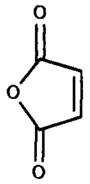
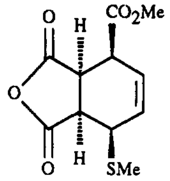
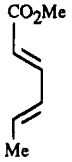
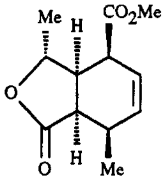
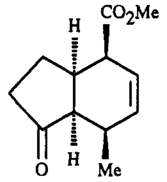
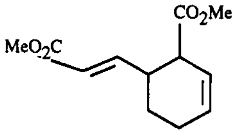
entry	diene structure	dienophile structure	conditns			cyclo adduct structure	yield, %
			pressure, kbar	temp, °C	time, h		
1	 1	 2	12	50	65	 3	85[a]
2	1	 4	12	50	65	 5	70
3	 6	2	15	55	40	None[b]	-
4	6	4	15	55	40	None[b]	-
5	 7	2	12	50	65	None[b]	-
6	7	 8	15	50	60	 9	75[c]
7	 10	2	10	40	48	 11	90[a]
8	 12	2	15	50	60	 13	65
9	12	 14	17	65	48	 15	75[d]
10	 16	4	15	20	96	 17	85[e]

Table I (Continued)

entry	diene structure	dienophile structure	conditns			cyclo adduct structure	yield, %
			pressure, kbar	temp, °C	time, h		
11	16	 18	17	50	48	 19	75[f]
12	 20	2	15	50	65	None[g]	-
13	20	4	15	50	65	None[g]	-
14	20	 21	15	20	70	 22	98
15	 23	2	15	50	66	 24	27[c]
16	23	4	14	70	48	 25	20[c]
17	 26	4	12	40	56	 27	8[h]

[a] See ref 11. [b] Diene polymerized, dienophile was recovered. [c] See ref 14. [d] See ref 8. [e] See ref 9. [f] See ref 15. [g] Starting materials were recovered. [h] Substantial amounts of dienophile were recovered.

cyclopentenone 4 were chosen as easily available and representative five-membered cyclic dienophiles to study the cycloadditions with these dienes. The reactions of alkyl cyclohexenones 8 and 14 and 2-penten-5-olide (18) with some dienes are also described to compare the behavior of five- and six-membered cyclic dienophiles (Table I).

Adducts were always obtained in a highly regio- and stereoselective manner, though in variable yields. Table I shows the adducts produced along with the particular experimental conditions and yields for each reaction. The stereochemistry and regiochemistry of the adducts were assigned on the basis of a careful analysis of their high-resolution ^{1}H and ^{13}C NMR spectra and by comparing them with those of other known related compounds.[11,12]

Theoretical calculations were carried out by using the AM1 method.[16] Butenolide 28 and cyclopentenone 4 have been used as dienophiles, while butadienes substituted by hydroxyl, sulfhydryl, and carboxyl groups have been considered as simplified models of the dienes experimentally studied in this work (Scheme I). The theoretical results obtained for the reactions of 4 and 28 with several dienes are shown in Table II. All reactions studied can be represented by Scheme I, in which X, Y, and Z stand for the substituents on the diene, and W is an oxygen atom or a methylene group, depending on the dienophile. The formation of the two possible regioisomers **a** and **b** has been considered for each reaction. Moreover, since the cycloadditions may proceed via an endo or an exo approach, both of them have been calculated. Nevertheless, only the results corresponding to the most favorable case are collected in Table II. For this approach, the lengths of the two bonds forming, r_1 and r_2, the charge transfer between the diene and the dienophile, t, and the enthalpy of activation, $\Delta H^{\ddagger}$, are presented. Charge transfer between diene and dienophile fragments at the transition state has

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(16) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.

Table II. Results of the Theoretical Calculations on the Reactions of Several Dienes with 4 and 28, Respectively[a]

	substituents on the diene[b]									
entry	X	Y	Z	dienophile	regioisomer	predicted stereoisomer	r_1	r_2	t^c	ΔH^*
1	OH	H	H	28	a	endo	2.07	2.24	0.197	23.9
					b	endo	2.10	2.19	0.135	26.3
2	OH	H	H	4	a	exo	2.06	2.25	0.139	25.7
					b	endo	2.09	2.18	0.092	28.2
3	SH	H	H	28	a	exo	1.98	2.34	0.160	27.8
					b	exo	2.03	2.26	0.103	29.7
4	SH	H	H	4	a	exo	1.97	2.35	0.121	29.8
					b	exo	2.02	2.26	0.053	31.4
5	H	OH	H	28	a	exo	2.09	2.22	0.132	23.4
					b	exo	2.13	2.15	0.115	24.9
6	OH	OH	H	28	a	exo	2.05	2.31	0.196	21.6
					b	exo	2.06	2.23	0.148	27.0
7	OH	H	COOH	28	a	endo	2.11	2.17	0.105	25.9
					b	endo	2.12	2.14	0.080	31.2
8	OH	H	COOH	4	a	endo	2.11	2.17	0.059	27.1
					b	endo	2.12	2.13	0.032	32.7
9	SH	H	COOH	28	a	endo	2.01	2.28	0.106	32.1
					b	endo	2.04	2.21	0.053	35.3
10	SH	H	COOH	4	a	endo	2.02	2.26	0.054	33.9
					b	endo	2.05	2.20	−0.002	36.8
11	CH_3	H	COOH	28	a	exo	2.11	2.17	0.072	27.2
					b	exo	2.14	2.13	0.074	31.5
12	CH_3	H	COOH	4	a	exo	2.11	2.16	0.024	28.5
					b	exo	2.14	2.12	0.022	33.0
13	H	H	COOH	28	a	exo	2.19	2.10	0.043	25.5
					b	exo	2.21	2.07	0.064	28.9
14	H	H	COOH	4	a	exo	2.20	2.08	−0.007	26.2
					b	exo	2.22	2.06	0.020	30.0

[a] Transition-state lengths of the two bonds forming, r (Å), charge transfer between the diene and the dienophile, t (au), and enthalpies of activation, ΔH^* (kcal/mol), are presented in all entries for the two possible regioisomers. Only the most favorable endo/exo stereoisomer is taken into account in each case. [b] See Scheme I for the structure of the dienes. [c] Positive when transferred to the dienophile.

Table III. Frontier Orbital Energies (eV) and Coefficients on the Ethylenic Carbon Atoms of the Dienes Used in the Theoretical Calculations[a]

	substituents					coefficients			
diene	X	Y	Z	frontier orbital	energy	C_1	C_2	C_3	C_4
I	OH	H	H	HOMO	−8.868	−0.47	−0.52	0.34	0.52
				LUMO	0.416	−0.61	0.40	0.39	−0.53
II	SH	H	H	HOMO	−8.351	−0.33	−0.47	0.20	0.37
				LUMO	0.133	−0.59	0.46	0.35	−0.52
III	H	OH	H	HOMO	−9.218	−0.42	−0.29	0.42	0.67
				LUMO	0.324	−0.58	0.44	0.43	−0.52
IV	OH	OH	H	HOMO	−8.825	−0.38	−0.38	0.40	0.64
				LUMO	0.246	−0.65	0.46	0.33	−0.45
V	OH	H	COOH	HOMO	−9.223	−0.45	−0.54	0.29	0.53
				LUMO	−0.547	−0.53	0.27	0.51	−0.46
VI	SH	H	COOH	HOMO	−8.813	−0.30	−0.49	0.15	0.38
				LUMO	−0.821	−0.53	0.32	0.47	−0.46
VII	CH_3	H	COOH	HOMO	−9.608	−0.52	−0.48	0.32	0.54
				LUMO	−0.602	−0.49	0.28	0.52	−0.47
VIII	H	H	COOH	HOMO	−9.934	−0.54	−0.43	0.38	0.57
				LUMO	−0.623	−0.49	0.27	0.53	−0.48

[a] See Scheme I for the numeration of the carbon atoms.

been computed from the net atomic charges over each atom, obtained from the Mulliken population analysis. One should note that entropy terms have not been taken into account throughout this work. This simplication can be made reasonably, assuming that the effects of the pressure on the entropy parameters are very similar for all the reactions considered.[2,17b]

Nearly synchronous transition states for all the reactions studied can be predicted by observing the values of the lengths of the two bonds forming. Which bond is formed faster depends on the nature and position of the substituents on the diene. As a general rule, when only one of the terminal carbon atoms of the diene bears a substituent, the shortest C–C bond distance at the transition state always involves the unsubstituted end of the diene.

Table IV. Frontier Orbital Energies (eV) and Coefficients on the Ethylenic Carbon Atoms of 4 and 28[a]

				coefficients	
dienophile	W	frontier orbital	energy	C_5	C_6
28	O	HOMO	−10.883	0.49	0.57
		LUMO	−0.415	−0.66	0.54
4	CH_2	HOMO	−10.410	0.57	0.65
		LUMO	−0.041	−0.63	0.46

[a] See Scheme I for the numeration of the carbon atoms.

Regioselectivity. According to the values of the activation enthalpies shown in Table II, the theoretical calculations always predict the predominant formation of

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[17] (a) Tietze, L. F.; Hübsch, T.; Voss, E.; Buback, M.; Tost, W. *J. Am. Chem. Soc.* **1988**, *110*, 4065. (b) Isaacs, N. S. *Liquid Phase High Pressure Chemistry*; Wiley: Chichester, 1981. (c) Van Eldik, R.; Asano, T.; Le Noble, W. J. *Chem. Rev.* **1989**, *89*, 549.

regioisomer **a**, which corresponds to the sole compound experimentally produced in the reactions presented in Table I.

Regioselectivity in Diels–Alder reactions is usually interpreted in terms of interactions between frontier orbitals.[18] Tables III and IV present the energies and coefficients on the carbon atoms for the frontier orbitals of the studied dienes and dienophils at the fully optimized geometries, respectively.

All reactions can be classified as normal Diels–Alder cycloadditions,[2] and this implies that the most important interaction between the frontier orbitals is that involving the participation of the HOMO of the diene and the LUMO of the dienophile. The predominance of this interaction leads to a noticeable charge transfer from the diene to the dienophile at the transition states in the reactions with electron-rich dienes, as verified by the t values (entries 1–6 in Table II). On the other hand, both HOMO–LUMO energy differences are more similar in the reactions involving push–pull dienes (entries 7–14, Table II). Therefore, the charge transfer t is smaller in the latter cases, as expected.

From the coefficients presented in Tables III and IV, the preferential formation of regioisomer **a** is predicted in all cases, in good agreement with the calculated enthalpy barriers and with the high regioselectivity which is experimentally observed.

Stereoselectivity. With the butadiene derivatives bearing at least one substituent at the terminal carbon atoms, it has been found that all the adducts obtained correspond to an endo approach between the diene and dienophile. Regarding this stereoselectivity, the agreement between theory and experiment is not as satisfactory as it is for the regioselectivity. As a matter of fact, the calculations do not always give the same stereoadduct as the kinetically most favorable one (see Table II).

One factor that has been offered[19] in order to explain the discrepancies between theoretical and experimental results about the stereoselectivity is the fact that these reactions were carried out under high pressure in the laboratory, while theoretical calculations simulate the process in the gas phase at a very low pressure. Indeed, it is known that the formation of an endo adduct has a lower volume of activation at the transition state than that of the corresponding exo isomer. Consequently the former compound is favored under high-pressure conditions as established by the experimental findings.[17]

Reactivity of Dienophiles. From the results presented in Table I it is clear that β-angelica lactone (**2**) is slightly more reactive than cyclopentenone **4** toward all of the dienes tried. This fact agrees with the theoretical results collected in Table II, according to which butenolide **28** reacts with a lower enthalpy barrier than cyclopentenone **4**. This higher reactivity can be related to the lower LUMO energy, as shown in Table IV, thus favoring the interaction with the HOMO of the diene.

Reactivity of Electron-Rich Dienes. Table I shows that, in the case of the electron-rich dienes evaluated, 2-[(trimethylsilyl)oxy]-1,3-butadiene (**7**) did not react with β-angelica lactone (**2**), while the corresponding 1-substituted butadiene derivative (**1**) gave cycloadduct **3** in good yield (compare entries 1 and 5).[11] In contrast, diene **7** reacted with cyclohexenone **8**, giving the corresponding adduct in satisfactory yield,[14] although this cycloaddition required 15-kbar pressure (entry 6). The apparent low reactivity of **7** to give Diels–Alder adducts should be attributed to its easy polymerization under the reaction conditions, which competes with the cycloaddition process.

As expected, the most reactive diene is compound **10** (Danishefsky's diene), the increased reactivity of which is caused by the synergism of the two oxygen substituents. Accordingly, diene **10** gave the adduct **11** in 90% yield by reaction with the lactone **2**, at only 10-kbar pressure[11] (entry 7, Table I).

From a theoretical point of view, the calculations for the OH-substituted butadienes predict the 1,3-disubstituted derivative to be the most reactive (entry 7, Table II), in good agreement with the experimental results. However, the reactivity of 2-hydroxybutadiene with **28** is predicted to be of the same order as that of 1-hydroxybutadienes (entries 5 and 1, respectively, Table II). This result cannot be confirmed by our experimental results, as mentioned above.

In general, *oxygen-substituted dienes have been shown to be much more reactive than the analogous sulfur derivatives* (see Table I). Thus, while lactone **2** and cyclopentenone **4** reacted with diene **1** at 12-kbar pressure giving the respective adducts in good yields (entries 1 and 2), diene **6** showed a total lack of reactivity toward these dienophiles, even at 15-kbar pressure (entries 3 and 4). This was not expected a priori, since several authors have pointed out the predominant role of sulfur over oxygen in the activation and orientation of the diene.[20] Nevertheless, theoretical calculations are in accordance with our experimental results. The computed activation enthalpies are about 4 kcal/mol higher for the reactions with 1-mercaptobutadiene than those for reactions with 1-hydroxybutadiene.[21]

Reactivity of Push–Pull Dienes. Surprisingly, the presence of the ester group in the push–pull dienes **12** and **16** does not diminish notably their reactivity with respect to the parent 1-[(trimethylsilyl)oxy]-1,3-butadiene (**1**). Thus, these dienes added to lactones **2** and **18**[15] and ketones **4**[9] and **14**,[8] although a little more drastic reaction conditions were required than with diene **1** (entries 8–11, Table I). Once again, replacement of oxygen by sulfur in dienes **12** and **16** produces a dramatic diminution of reactivity: all attempts to effect cycloaddition of alkylthio-substituted push–pull diene **20** with dienophiles **2** and **4** were fruitless (entries 12 and 13, Table I). Nevertheless, **20** gave the expected adduct **22** almost quantitatively, by reaction with the much more reactive dienophile maleic anhydride (**21**) (entry 14, Table I). Replacement of sulfur by carbon, namely, the use of methyl sorbate (**23**) as diene, had a surprising effect: this diene reacted with dienophiles **2** and **4**, giving adducts **24** and **25**, respectively, albeit in modest yields (entries 15 and 16, Table I). Finally, an attempt to accomplish cycloaddition of **4** with methyl 1,3-pentadienonate (**26**) gave adduct **27**, resulting from the

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[18] (A) Houk, K. N. *J. Am. Chem. Soc.* **1973**, *95*, 4092. (b) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley: London, 1976.

[19] Sodupe, M.; Oliva, A.; Bertrán, J.; Dannenberg, J. J. *J. Org. Chem.* **1989**, *54*, 2488.

[20] See, for instance: (a) Evans, D. A.; Bryan, C. A.; Sims, C. L. *J. Am. Chem. Soc.* **1972**, *94*, 2891. (b) Cohen, T.; Mura, A. J., Jr.; Shull, D. W.; Fogel, E. R.; Ruffner, R. J.; Falck, J. R. *J. Org. Chem.* **1976**, *41*, 3218. (c) Trost, B. M.; Vladuchick, W. C.; Bridges, A. J. *J. Am. Chem. Soc.* **1980**, *102*, 3548, 3554. (d) Cohen, T.; Kosarych, Z. *J. Org. Chem.* **1982**, *47*, 4005. (e) Trost, B. M.; Caldwell, C. G.; Murayama, E.; Heissler, D. *Ibid.* **1983**, *48*, 3252. (f) Proteau, P. J.; Hopkins, P. B. *Ibid.* **1985**, *50*, 141. (g) Kahn, S. D.; Pau, C. F.; Overman, L. E.; Hehre, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 7381.

[21] Theoretical calculations have also been carried out for the reactions of cyclopentenone **4** with the dienes **1** and **6**. The computed enthalpy barriers, 26.5 and 30.1 kcal mol^{-1}, respectively, are very similar to those corresponding to the reactions of **4** with the model dienes (entries 2 and 4 in Table II).

self-condensation of the diene, in poor yield (8%), along with polymeric materials (entry 17, Table I).

This order of reactivity of push–pull dienes is reproduced by theoretical calculations, as deduced from the activation enthalpies presented in Table II (entries 7–14). Furthermore, the theoretical results confirm that the reactivity of dienes does not drastically change with the introduction of an electron-withdrawing group. Thus, reactions of cyclopentenone **4** and lactone **28** with 1-hydroxy-1,3-butadiene and 4-hydroxy-1,3-pentadienoic acid, respectively, gave differences between the activation enthalpies of about 1.5–2.0 kcal/mol (compare entries 2 and 8 for **4** and entries 1 and 7 for **28** in Table II). These differences are much lower than those observed between the reactions of both O-substituted electron-rich and push–pull dienes, and the related S-substituted dienes, as discussed above.

Conclusions

This investigation presents a general interpretation and rationalization for the behavior of unsaturated γ-lactones and cycloalkenones as dienophiles in Diels–Alder cycloadditions involving several kinds of hetero-substituted dienes.

On the basis of the preceding findings, three main points emerge: (a) butenolides are slightly more reactive than cyclopentenone; (b) the reactivity of alkoxy-substituted push–pull dienes is similar to that of the monoalkoxy-1,3-butadienes; (c) sulfur-substituted dienes are much less reactive than their oxygen and carbon counterparts.

Experimental Section

Melting points were determined on a hot stage and are corrected. Distillation of small amounts was effected in a bulb-to-bulb distillation apparatus; only the oil bath temperatures are given. Electron-impact mass spectra were recorded at 70 eV.

General Procedure for Theoretical Calculations. The AM1[16] method was used in the energy calculations. Total geometry optimization was performed throughout. Transition states were directly located through minimization of the root mean square gradient and have been characterized through the computation of the force constant matrix.[22] For a transition state this matrix must have only one negative eigenvalue. All calculations were carried out with the AMPAC program.[23]

General Experimental Procedures. The particular experimental conditions for each reaction are given in Table I. The dienophile (2–4 mmol) and 1.5 equiv. of the diene (1 M solution of diene in CH_2Cl_2) were introduced, by means of a syringe, into a 1-, 3-, or 4-mL Pyrex glass cell (1.5-mm wall thickness) fitted with a 1 mm inner diameter capillary orifice. All reactions were performed in a piston-cylinder high-pressure apparatus for pressures up to 20 kbar.[24] For reactions performed at temperatures higher than 20 °C, an external heating jacket was used. Cells were immersed in hexane, which was used as piezotransmitter liquid and was contained in the high-pressure apparatus, this being closed on the bottom side with a steel stopper. Then the mobile piston was inserted, and the whole assembly was placed between the pistons of a hydraulic press. The pressure was raised to an extent depending on the reaction conditions used in each case. After stabilization of the pressure, the heater was switched on, whereupon the temperature was raised to the values given in Table I for each reaction (40–70 °C). The reaction mixture was kept under these conditions for a convenient time and then cooled to room temperature. After decompression the solvent was removed, and the residue was purified by flash column chromatography on silica gel (mixtures of hexane–ethyl acetate as eluents) followed by distillation or recrystallization.

Cycloadditions **3**,[11] **9**,[14] **11**,[11] **15**,[9] and **17**,[15] are known compounds prepared for the first time in our laboratories, under the reaction conditions described in Table I, and reported previously to this work. Details on yield and physical and spectroscopic (IR, MS, ^1H NMR, and ^{13}C NMR) data are given in the references cited.

Methyl (*E*,*E*)- and (*E*,*Z*)-5-(methylthio)penta-2,4-dienoate (20): entries 12 and 13, Table I. To a stirred solution of [(methylthio)methyl]triphenylphosphonium chloride[25] (4.1 g, 11.4 mmol) in 35 mL of THF, 16 mL of ether, and 4 mL of hexamethylphosphoric triamide at 0 °C, was added under N_2 a 2.5 M solution of *n*-BuLi in hexane (4.6 mL, 11.5 mmol). The resulting mixture was warmed to room temperature and stirred for an additional 1 h. To this solution, cooled at 0 °C, was added methyl (*E*)-4-oxo-2-butenoate[26] (1.3 g, 11.4 mmol). After stirring overnight at 20 °C, water (5 mL) was added and the aqueous phase was extracted with ether (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$), and the solvents were removed under reduced pressure. The residue was taken up into hexane, and triphenylphosphine oxide was filtered off. Solvent was removed, and the crude product was flash chromatographed on silica gel (4:1 hexane–ethyl acetate) to give 1.16 g (64%) of a 9:1 mixture of (*E*,*E*)-**20** and (*E*,*Z*)-**20**, as a colorless solid, mp 41.5 °C after sublimation. The major stereoisomer is characterized by the following data: IR (KBr) 1715, 1625 cm^{-1}; 90-MHz ^1H NMR ($CDCl_3$) δ 2.33 (3 H, s), 3.72 (3 H, s), 5.70 (1 H, d, $J = 15.3$ Hz), 6.06 (1 H, dd, $J = 14.7$ Hz, $J' = 10.8$ Hz), 6.80 (1 H, d, $J = 14.7$ Hz), 7.26 (1 H, dd, $J = 15.3$ Hz, $J' = 10.8$ Hz); 63-MHz ^{13}C NMR ($CDCl_3$) δ 14.54, 51.23, 116.50, 122.16, 139.81, 143.40, 167.68. Anal. Calcd for $C_7H_{10}O_2S$: C, 53.16; H, 6.33; S, 20.25. Found: C, 53.02; H, 6.39; S, 20.08.

(1*R,2*S**,6*R**)-2-[(Trimethylsilyl)oxy]bicyclo[4.3.0]non-3-en-9-one (5):** entry 2, Table I; yield, 334 mg (70%); bath temperature 30 °C (0.01 Torr); IR (film) 1745, 1655 cm^{-1}; MS, *m/e* (relative intensity) 224 (M, 9.4), 209 (60.8), 142 (62.7), 127 (79.2), 73 (100.0); 250-MHz ^1H NMR (C_6D_6) δ 0.1 (9 H, s), 1.47–2.23 (8 H, complex absorption), 4.30 (H_2, ddd, $J_{1,2} = 5.0$ Hz, $J_{2,3} = 4.5$ Hz, $J_{2,4} = 1.0$ Hz), 5.55 (H_4, ddt, $J_{3,4} = 10.0$ Hz, $J_{4,5} = 4.0$ Hz, $J_{2,4} = 1.0$ Hz), 5.67 (H_3, ddt, $J_{3,4} = 10.0$ Hz, $J_{2,3} = 4.5$ Hz, $J_{3,5} = 2.0$ Hz); 20-MHz ^{13}C NMR ($CDCl_3$) δ 0.07, 26.21, 28.44, 32.45, 39.03, 50.35, 62.38, 127.19, 127.90, 219.89. Anal. Calcd for $C_{12}H_{20}O_2Si$: C, 64.26; H, 8.99. Found: C, 64.00; H, 9.03.

Methyl (1*R,2*S**,5*S**,6*R**,9*S**)-3-ethyl-5-methoxy-9-methyl-7-oxo-8-oxabicyclo[4.3.0]non-3-ene-2-carboxylate (13):** entry 8, Table I; yield, 200 mg (65%); bath temperature 120 °C (0.05 Torr); IR (film) 1780, 1735 cm^{-1}; MS, *m/e* (relative intensity) 268 (M, 13), 196 (100), 139 (65), 105 (95), 91 (76); 250-MHz ^1H NMR ($CDCl_3$) δ 1.03 (3 H, t, $J = 7.4$ Hz), 1.30 (3 H, d, $J = 6.0$ Hz), 2.05 (2 H, m), 2.67 (H_1, dd, $J_{1,9} = 9.4$ Hz, $J_{1,2} = J_{1,6} = 8.7$ Hz), 2.83 (H_6, dd, $J_{1,6} = 9.0$ Hz, $J_{5,6} = 5.5$ Hz), 3.36 (3 H, s), 3.46 (H_2, dd, $J_{1,2} = 8.7$ Hz, $J_{2,4} = 1.5$ Hz), 3.71 (3 H, s), 4.04 (H_5, dd, $J_{5,6} = J_{4,5} = 5.5$ Hz), 4.70 (H_9, dq, $J_{1,9} = 9.4$ Hz, $J_{9,Me} = 6.0$ Hz), 5.97 (H_4, dd, $J_{4,5} = 5.5$ Hz, $J_{2,4} = 1.5$ Hz); 20-MHz ^{13}C NMR ($CDCl_3$) δ 11.8, 20.5, 28.1, 41.8, 43.6, 45.2, 52.1, 57.2, 70.6, 78.9, 121.0, 140.8, 171.8, 175.1. Anal. Calcd for $C_{14}H_{20}O_5$: C, 62.92; H, 7.11. Found: C, 62.77; H, 7.33.

(1*R,2*S**,3*S**,6*R**)-3-(Methoxycarbonyl)-6-(methylthio)-4-cyclohexene-1,2-dicarboxylic acid anhydride (22):** entry 14, Table I; yield, 143 mg (98%); mp 164 °C (from ether); IR (KBr) 1855, 1785, 1750, 1670 cm^{-1}; 200-MHz ^1H NMR ($CDCl_3$) δ 2.25 (3 H, s), 3.35 (H_3, ddd, $J_{2,3} = 10.0$ Hz, $J_{3,4} = 4.0$ Hz, $J_{3,5} = 2.5$ Hz), 3.49 (H_6, ddd, $J_{1,6} = 10.0$ Hz, $J_{5,6} = 4.0$ Hz, $J_{4,6} = 2.4$ Hz), 3.76 (H_1, dd, $J_{1,6} = 10.0$ Hz, $J_{1,2} = 7.6$ Hz), 3.82 (3 H, s), 3.98 (H_2, dd, $J_{2,3} = 10.0$ Hz, $J_{1,2} = 7.6$ Hz), 6.08 (H_5, ddd, $J_{4,5} = 9.6$ Hz, $J_{5,6} = 4.0$ Hz, $J_{3,5} = 2.5$ Hz), 6.40 (H_4, ddd, $J_{4,5} = 9.6$ Hz, $J_{3,4} = 4.0$ Hz, $J_{4,6} = 2.4$ Hz); 63-MHz ^{13}C NMR ($CDCl_3$) δ 16.55, 39.22, 40.67, 43.14, 44.36, 52.70, 127.04, 131.51, 168.80, 169.65, 170.62; HRMS calcd for $C_{11}H_{12}O_5S$ *m/e* 256.0405, found 256.0407. The proton and the ^{13}C NMR spectra are available as supplementary material for this work.

(1*R,2*R**,5*S**,6*S**,9*S**)-2-(Methoxycarbonyl)-5,9-dimethyl-8-oxabicyclo[4.3.0]non-3-en-7-one (24):** entry 15, Table I; yield, 200 mg (27%); mp 108 °C (from diisopropyl ether); IR

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(22) McIver, J. W.; Komornicki, A. *J. Am. Chem. Soc.* **1972**, *94*, 2625.

(23) Dewar, M. J. S.; Stewart, J. J. P. *QCPE* **1986**, *6*, 24, QCPE Program 506.

(24) Jurczak, J.; Chmielewski, M.; Filipek, S. *Synthesis* **1979**, 41.

(25) Wittig, G.; Schlosser, M. *Chem. Ber.* **1961**, *94*, 1373.

(26) Stotter, P. L.; Eppner, J. B. *Tetrahedron Lett.* **1973**, 2417.

(CHCl$_3$) 1760, 1730, 1650, cm^{-1}; MS, *m/e* (relative intensity) 224 (M, 3.9), 152 (43.7), 121 (43.8), 93 (100.0); 250-MHz ^{1}H NMR (CDCl$_3$) δ 1.24 (3 H, d, $J = 6.3$ Hz), 1.36 (3 H, d, $J = 7.4$ Hz), 2.29 (H$_5$, m), 2.98 (H$_1$, H$_6$, m), 3.01 (H$_2$, m), 3.72 (3 H, s), 4.07 (H$_9$, m), 5.84 (H$_4$, ddd, $J_{3,4} = 9.3$ Hz, $J' = 3.4$ Hz, $J'' = 3.0$ Hz), 6.14 (H$_3$, ddd, $J_{3,4} = 9.3$ Hz, $J' = 3.3$ Hz, $J'' = 2.6$ Hz); 63-MHz ^{13}C NMR (CDCl$_3$) δ 16.3, 22.1, 30.5, 41.6, 44.0, 44.9, 51.7, 78.0, 125.6, 136.1, 172.2, 176.2. Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.26; H, 7.19. Found: C, 64.24; H, 7.25.

Methyl (1*R,2*S**,5*R**,6*R**)-5-methyl-7-oxobicyclo[4.3.0]non-3-ene-2-carboxylate (25)**: entry 16, Table I; yield, 273 mg (20%); bath temperature 100 °C (0.01 Torr); IR (film) 1730 (br), 1660 cm^{-1}; MS *m/e* (relative intensity) 208 (M, 22.3), 148 (37.9), 106 (37.8), 105 (100.0), 93 (85.2); the structure of adduct **25** has been unambiguously established by using ^{1}H–^{1}H and ^{1}H–^{13}C 2D NMR spectroscopy; 250-MHz ^{1}H NMR (CDCl$_3$) δ 0.96 (3 H, d, $J = 7.5$ Hz), 1.50 (H$_9$, m), 1.73 (H$_{9'}$, m), 2.00 (H$_8$, H$_{8'}$, m), 2.29 (H$_5$, m), 2.44 (H$_6$, dd, $J_{1,6} = J_{5,6} = 8.0$ Hz), 2.80 (H$_1$, dddd, $J_{1,9} = 9.6$ Hz, $J_{1,6} = J_{1,9'} = 8.0$ Hz, $J_{1,2} = 6.6$ Hz), 3.20 (H$_2$, ddd, $J_{1,2} = 6.6$ Hz, $J_{2,3} = 3.2$ Hz, $J_{2,4} = 2.5$ Hz), 3.61 (3 H, s), 5.63 (H$_3$, ddd, $J_{3,4} = 10.0$ Hz, $J_{2,3} = 3.2$ Hz, $J_{3,5} = 3.1$ Hz), 5.84 (H$_4$, ddd, $J_{3,4} = 10.0$ Hz, $J_{2,4} = J_{4,5} = 2.5$ Hz); 63-MHz ^{13}C NMR (CDCl$_3$) δ 18.1, 23.8, 28.1, 36.8, 38.5, 41.4, 48.7, 51.5, 122.9, 133.5, 172.9, 219.3; HRMS calcd for $C_{12}H_{16}O_3$ *m/e* 208.1099, found 208.1087. This compound is accompanied by ca. 15% of an unidentified isomer (^{1}H and ^{13}C NMR). The proton and ^{13}C NMR spectra are available as supplementary material for this work.

Methyl 3-[(1*R,2*R**)- and -(1*S**,2*R**)-2-(methoxycarbonyl)cyclohex-3-en-1-yl]-(*E*)-propenoate (27)**: entry 17, Table I; yield, 34 mg, (8%); IR (film) 1740 (sh), 1730, 1660, 1655 (sh) cm^{-1}; 250-MHz ^{1}H NMR (CDCl$_3$) δ 1.9 (1 H, m), 1.96 (1 H, m), 2.11 (2 H, m), 2.83 (1 H, m), 3.30 (1 H, m), 3.64 (3 H, s), 3.70 (3 H, s), 5.86 (3 H, m), 7.00 (1 H, dd, $J = 15.75$ Hz, $J' = 8.0$ Hz); 63-MHz ^{13}C NMR (CDCl$_3$) δ 16.7, 20.7, 33.8, 40.4, 47.0, 47.3, 117.3, 118.7, 125.5, 144.7, 162.5, 168.2. This compound has been previously described by House.[27]

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Supplementary Material Available: Copy of HRMS for **25** and copies of ^{13}C and ^{1}H NMR spectra for **22** and **25** (5 pages). Ordering information is given on any current masthead page.

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(27) House, H. O.; Rasmusson, G. H. *J. Org. Chem.* **1963**, *28*, 27.

Stereochemical Control in Reactions of Nucleophiles with Oxocarbenium Ions Formed by Intramolecular Opening of Activated Epoxides by Neighboring Carbonyl Groups

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Tandem cyclization/reduction and cyclization/alkylation processes for the stereoselective synthesis of 2,5-disubstituted tetrahydrofurans, 2,6-disubstituted tetrahydropyrans, and 2,7-disubstituted oxepanes are described. In the presence of Lewis acids or TMSOTf, γ,δ-, δ,ϵ- and ϵ,ζ-epoxy ketones and esters undergo cyclization to the corresponding oxocarbenium ions, which react in situ with a variety of organosilanes and organoaluminum reagents to give the substituted oxacyclic products. For the synthesis of substituted tetrahydrofurans, the stereochemical control of the addition process was much higher with TMSOTf than $BF_3 \cdot OEt_2$.

Introduction

The synthesis of functionalized tetrahydrofuran and tetrahydropyran rings has received considerable attention because of the many biologically active compounds that contain these ring systems.[1] The polyether antibiotics, which perhaps best exemplify this group, contain an array of tetrahydrofuran and tetrahydropyran rings interconnected at the carbons adjacent to the oxacyclic ring oxygens.[2] The synthesis of these ionophores has spawned the development of many methods for the synthesis of 2,5-disubstituted tetrahydrofurans and 2,6-disubstituted tetrahydropyrans.[3] For instance, the synthesis of one tetrahydrofuran ring of lasalocid A relies on the acid-induced ring closure of an epoxy alcohol[14] prepared by hydroxyl-directed epoxidation of the corresponding bishomoallylic alcohol (eq 1). In this case the ratio of the tetrahydrofuran diastereomers is determined in the epoxidation step, which requires good long-range acyclic stereochemical control. An alternative strategy that avoids this requirement makes use of C-glycosylation techniques (eq 2)[3i,k,l] to join one

---

(1) *Polyether Antibiotics*; Westley, J. W., Ed.; Marcel Dekker: New York, 1982. *Chemical Structures of Interest to the Division of Cancer Treatment*, Vol. VI, Compounds in Development-Drugs with Clinical Activity, Lomax, N. R.; Narayanan, V. L.; National Cancer Institute, Washington, D. C., 1988. For a review on macrolide antibiotic synthesis see: Masamune, S.; McCarthy, P. A. In *Macrolide Antibiotics*; Omura, S., Ed.; Academic Press: Orlando, 1984; pp 127–198.

(2) Wierenga, W. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; John Wiley and Sons: New York, 1981; pp 287–351. Westly, J. W. In *Antibiotics, Chemotherapeutics, and Antibacterial Agents for Disease Control*; Grayson, M., Ed.; John Wiley and Sons: New York, 1982; pp 301–318.

(3) For a general review, see: (a) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309. Semple, J. E.; Joullie, M. M. *Heterocycles* **1980**, *14*, 1825. For recent examples of cyclization techniques see: (b) Tamooka, K.; Matsuzawa, K.; Suzuki, K.; Tsuchihashi, G. *Tetrahedron Lett.* **1987**, *28*, 6339. (c) Labelle, M.; Guindon, Y. *J. Am. Chem. Soc.* **1989**, *111*, 2204. (d) Nicolaou, K. C.; Hwang, C. K.; Nugiel, D. A. *J. Am. Chem. Soc.* **1989**, *111*, 4136. (e) Semmelhack, M. F.; Zhang, N. *J. Org. Chem.* **1989**, *54*, 4483. (f) McCormick, M.; Monahan, R. III; Soria, J.; Goldsmith, D.; Liotta, D. *J. Org. Chem.* **1989**, *54*, 4485. (g) Bartlett, P. A.; Chapuis, C. *J. Org. Chem.* **1986**, *51*, 2799. (h) Bartlett, P. A.; Ting, P. C. *J. Am. Chem. Soc.* **1984**, *106*, 2668. For recent examples of noncyclization techniques see: (i) Martin, O. R.; Rao, S. P.; Kurz, K. G.; El-Shenawy, H. A. *J. Am. Chem. Soc.* **1988**, *110*, 8698. (j) Panek, J. S.; Sparks, M. A. *J. Org. Chem.* **1989**, *54*, 2034. (k) Nicolaou, K. C.; Dolle, R. E.; Chucholowski, A.; Randall, J. L. *J. Chem. Soc. Chem. Comm.* **1984**, 1153 and 1155. (l) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976.

(4) Nakata, T.; Schmid, G.; Vranesic, B.; Okigawa, M.; Smith-Palmer, T.; Kishi, Y. *J. Am. Chem. Soc.* **1978**, *100*, 2933.

0022-3263/91/1956-4141$02.50/0