# Some Observations on the Relative Reactivities of α-Enones of Oxanes and Cyclohexanes

*Summary:* Carbohydrate derived α,β-unsaturated ketones generally display higher reactivities than their carbocyclic counterparts toward a variety of reagents. Semiempirical calculations for prototypical structures show that the oxygen in the ring causes significant lowering of the LUMO energy. Attempts to correlate Diels–Alder reactivity with the calculated values are partially successful; however, it is observed that an exocyclic oxygen at the α′ position renders the system unreactive.

*Sir:* Stereoselectivity and reactivity are of central concern for efficient transformations of organic compounds. Extensive developments in the chemistry of carbohydrate derivatives over the past 10 years[2-4] have shown that certain carbon–carbon bond-forming reactions proceed with higher stereoselectivities in carbohydrates than in comparable carbocycles, and we have suggested a possible role for the ring oxygen in mediating these trends.[5,6] That similar contrasts are sometimes found in the *reactivities* of both classes of compounds is evident from the sampling of data in Table I for reactions of some α,β-unsaturated ketones. The effect of an oxygen, in the ring and/or pendant to it, on these trends in reactivity, is a point of interest, and in this paper we present some relevant theoretical and experimental observations.

The results in Table I[7-12] represent three different types of reactions of α,β-unsaturated ketones, and it is of interest to assess the importance of FMO considerations in determining these reactivity trends. Since the Diels-Alder reaction is the best understood of the three reaction types, we decided to focus our attention, initially, on the pertinent cases in Table I. Accordingly, we have carried out semiempirical MNDO molecular orbital calculations[13] on a series of oxygenated α-enones, to obtain the LUMO energies (Table II) which are seen to decrease from 1 to 7. The LUMO coefficients of all the enones in question are unaffected by changes in peripheral substituents; hence the Diels–Alder reactivities of these substrates should correlate directly with their LUMO energies.

We have, therefore, compared the Diels-Alder reactivities of α-enones **6a**, **7a**, and **4a** (Figure 1), and from the energies for the prototypical structures (6, 7, and 4, respectively) shown in Table II, the expected order of reactivity based on the calculated LUMO energies should be **7a** > **6a** > **4a**. However, the observed order in Figure 1 is **6a** > **7a** > **4a**.

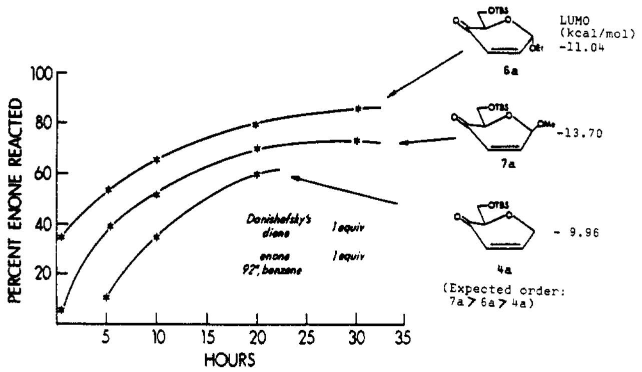

Figure 1. Reaction of α-enones with Danishefsky's diene.

A far more serious discrepancy involves enone **5a** which, although predicted to be more reactive than enone **4a**, actually fails to react with Danishefsky's diene[14] under similar experimental conditions (Table I).

The anomalies noted above arise from consideration of FMO interactions only and in order to assess the importance of other factors, we have examined model transition states for these Diels–Alder reactions, again using the MNDO protocol.[13] Our procedure, which is exemplified in Figure 2 for **6** involved placing the diene (1,3-dimethoxybutadiene was used in place of Danishefsky's diene[8]) and dienophile in parallel planes separated by 2.5 Å. The only constraint in the optimization of the geometric parameters of this system (i.e., all bond lengths, bond angles, and dihedral angles) was that the distance between the *centers of the reacting entities* remained fixed at 2.5 Å. Initially, the diene was oriented in an endo fashion directly above the olefin such that the midpoints of the olefin and the diene were located in the same *XY* plane. However, it is important to note that during the optimization procedure, the reacting centers were permitted free movement along the *X* and *Y* axes.

First, let us focus on the reactivity between enones **6a** and **7a** (Figure 1). Examination of the model transition states for these two reactions reveal that in the case of **6a** in which the C-1 alkoxy substituent is pseudoaxial, the diene remains symmetrically oriented with respect to the olefin. However, in the corresponding model transition state involving the pseudoequatorial analogue **7a**, the diene is displaced significantly along the *Y* axis, away from the equatorial substituent. The net result is that the overlap between C-1′ of the diene and the α-position of the enone is decreased dramatically, which leads to a higher energy transition state. Interestingly, this displacement is even more pronounced in the case of **5a**, a completely unreactive substrate, with the diene being unable to achieve its preferred, "symmetrical" orientation about the double bond of the dienophile.

Based on the last analysis, it appeared that the unreactivity of **5a** vis-à-vis **6a** might be attributable to steric problems arising from the fact that the γ-substituent in **5a** is $CH_2OTr$ as compared with H in **6a**. Accordingly, the enones **5b** and **6b** (both of which have H in the γ-positions) were studied (Table I). The latter was found to react

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(1) Senior-year undergraduate research participant.

(2) Fraser-Reid, B.; Anderson, R. C. *Prog. Chem. Org. Nat. Prod.* **1980**, *39*, 1.

(3) Hanessian, S. *The Total Synthesis of Natural Products: The 'Chiron' Approach*; Pergamon: New York, 1983.

(4) Inch, T. D. *Tetrahedron* **1984**, *40*, 3161.

(5) Fraser-Reid, B.; Tsang, R.; Lowe, D. *Chemica Scripta* **1985**, *25*, 117.

(6) Fraser-Reid, B.; Tulshian, D. B.; Tsang, R.; Lowe, D.; Bow, V. G. S. *Tetrahedron Lett.* **1984**, *25*, 4579.

(7) Rahman, Md. A.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1985**, *107*, 5576.

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

(9) Ward, D. D.; Shafizadeh, F. *Carbohydr. Res.* **1981**, *95*, 155.

(10) Srivastava, R. M.; Carthy, B. J.; Fraser-Reid, B. *Tetrahedron Lett.* **1974**, 2175.

(11) Fraser-Reid, B.; Holder, N. L.; Hicks, D. R.; Walker, D. L. *Can. J. Chem.* **1977**, *55*, 3978.

(12) Fraser-Reid, B.; Anderson, R. C.; Hicks, D. R.; Walker, D. L. *Can. J. Chem.* **1977**, *55*, 3986.

(13) Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4899.

(14) Danishefsky, S.; Hirama, M.; Gombatz, K.; Harayama, T.; Berman, E.; Schuda, P. F. *J. Am. Chem. Soc.* **1979**, *101*, 7020. Danishefsky, S.; Zamboni, R.; Kahn, M.; Etheredge, S. J. *J. Am. Chem. Soc.* **1981**, *103*, 3460.

0022-3263/86/1951-2152$01.50/0

**Table I. Addition Reactions of α-Enones**

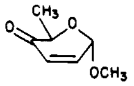
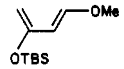
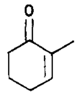
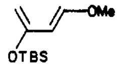
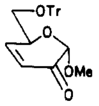
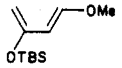
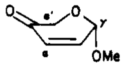
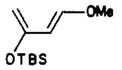
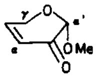
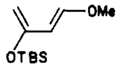
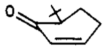
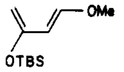
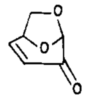
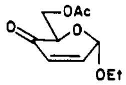
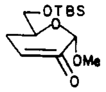
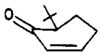
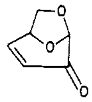
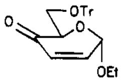
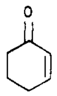
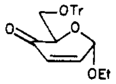
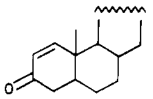
| substrate | LUMO, kcal | reagents | temp, °C (time, h) | yield, % | ref |
|---|---|---|---|---|---|
| | | Diels–Alder Reactions | | | |
|  6e | −11.04 |  | 110<br>(24) | 93 | 7 |
|  1a | −4.63 |  | 195<br>(50) | 53 | 8 |
|  5a | −10.56 |  | 110<br>(100) | no reaction | |
|  6b | −11.04 |  | 110<br>(12) | 85 | |
|  5b | −10.56 |  | 110<br>(13)<br>(90) | <br>~5<br>50 | |
|  1b | −4.63 |  | 110<br>(23) | <5 | |
|  3a | −9.95 |  | 168<br>(3) | 48 | 9 |
| | | 1,3-Dipolar Addition | | | |
|  6c | −11.04 | $CH_2N_2$ | 23<br>(0.16) | 69 | 10 |
|  5c | −10.56 | $CH_2N_2$ | 23<br>(12) | no reaction | |
|  1b | −4.63 | $CH_2N_2$ | 23<br>(12) | 55 | |
|  3a | −9.95 | $CH_2N_2$ | 23<br>(0.25) | 65 | |
| | | Conjugate Addition Photoalkylation | | | |
|  6d | −11.04 | $CH_3OH$, $Ph_2CO$, 350 nm | room temp<br>(8.5) | 75 | 11 |
|  1c | −4.63 | $CH_3OH$, $Ph_2CO$, 350 nm | room temp<br>(24, incomplete) | 33 | 11 |
|  6d | −11.04 | $CH_3CHO$, $Ph_2CO$, 350 nm | room temp<br>(5) | 67 | 12 |
|  1d | −4.63 | $CH_3CHO$, $Ph_2CO$, 350 nm | room temp<br>(12) | 42 | 12 |

**Table I** (Continued)

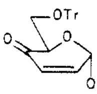
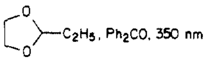
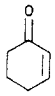
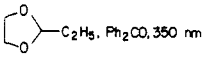
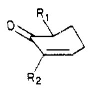
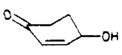
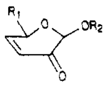
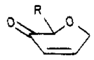
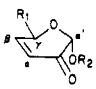
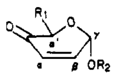
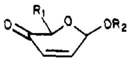
| substrate | LUMO, kcal | reagents | temp, °C (time, h) | yield, % | ref |
|---|---|---|---|---|---|
| <br>**6d** | −11.04 |  | room temp<br>(2) | 62 | 12 |
| <br>**1c** | −4.63 |  | room temp<br>(57) | 54 | 12 |

Table II. LUMO Energies (kcal/mol) from MNDO Calculations

| prototypes (R=R$_1$ = R$_2$ =H) |  | |  |  |  |  | |  | |  | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | | 2 | 3 | 4 | 5 | | 6 | | 7 | |
| kcal/mol | −4.63 | | −6.48 | −9.95 | −9.96 | −10.56 | | −11.04 | | −13.70 | |
| | R$_1$ | R$_2$ | | | | R$_1$ | R$_2$ | R$_1$ | R$_2$ | R$_1$ | R$_2$ |
| | a H | Me | | a, R$_1$R$_2$ = CH$_2$O | a, R = CH$_2$OTBS | a CH$_2$OTr | Me | a CH$_2$OTBS | Et | a CH$_2$OTBS | Me |
| | b *t*-Bu | H | | | | b H | Me | b H | Me | | |
| | c H | H | | | | c CH$_2$OTBS | Me | c CH$_2$OAc | Et | | |
| | d Δ′-cholestenone | | | | | | | d CH$_2$OTr | Et | | |
| | | | | | | | | e CH$_3$ | Me | | |

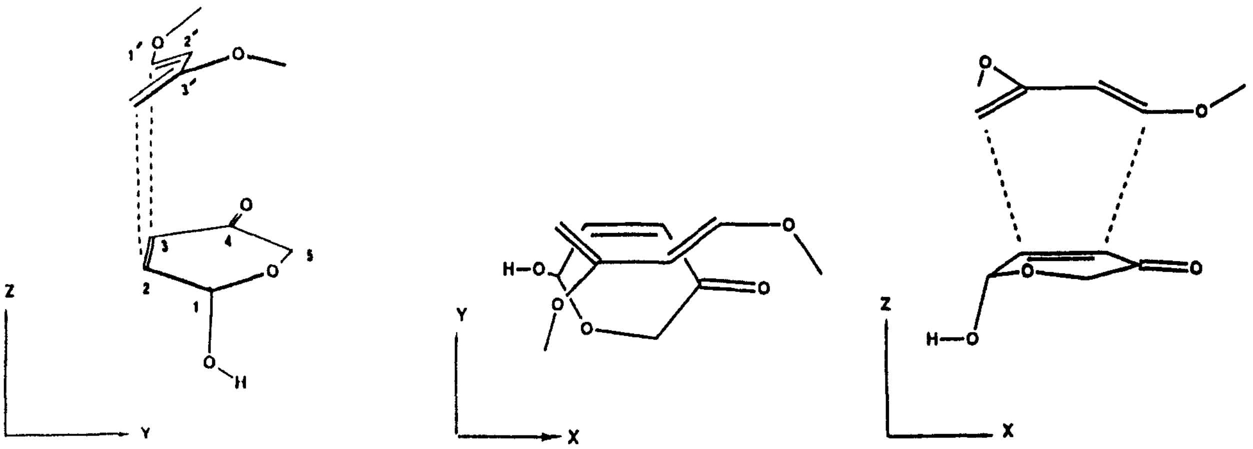


**Figure 2.** MNDO transition-state model for reaction of **6** with 1,3-dimethoxybutadiene.

substantially at room temperature while the former gave little sign of an adduct after 13 h at 110 °C—*even though their LUMO energies are of the same order of magnitude. Furthermore, the carbocycle* **1a** *reacts appreciably even though it has a much higher LUMO energy than* **5a**/**5b**.

That the disparity in reactivities is not confined to the Diels–Alder reaction can be seen from the data for reactions with the 1,3-dipolarophile diazomethane. Indeed, the contrast between **6c** and **5c** is dramatized even further.

Finally, we would like to comment on the relative reactivity of carbohydrates vs. carbocycles in Diels–Alder reactions. Firstly, from the results in Figure 1, it appears that the exocyclic oxygen at the γ-position (i.e., the glycosidic oxygen of **6a** and **7a**) does not have a dramatic effect on Diels–Alder reactivities. However, the data in Table I show that the carbocycles (**1a**/**1b**) are *generally* less reactive than the heterocycles. Thus, it appears that the ring oxygen is the decisive factor in determining the reactivity trends.

We believe that the enhancement of reactivity is electronic in origin, owing to the stabilization of proximate π-orbital by the ring oxygen. Since in the heterocyclic substrates the ring oxygen has a two-point association with the enone chromophore, the inductive stabilization of the enone π-orbitals afforded by the ring oxygen is approximately double that of a pendant oxygen substituent (compare values for **1**, **2**, and **4** in Table II). This tends to greatly facilitate LUMO-controlled processes.

However, comparison of the results for **5a**, **5b**, **5c**, and **3a** show that an exocyclic oxygen at the α′-position has a profound effect on the reactivity of the chromophore. Our present models do not provide a rationalization for these surprising results. However, further studies are under way and will be reported in due course.

**Acknowledgment.** This work was supported by grants to B.F.R. from the National Science Foundation (CHE-8304283), the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Institutes of Health (AI 20117) and to D.L. from the National Institutes of Health (GM 26908). We are grateful to Professors Pat Mariano (University of Maryland) and Ken Houk (University of Pittsburgh) for helpful discussion.

**Registry No.** **4a**, 101712-13-4; **5a**, 101833-54-9; **5b**, 67834-49-5; **6a**, 101833-53-8; **6b**, 60249-17-4; **7a**, 101712-12-3.

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# *Additions and Corrections*

## Vol. 48, 1983

**Jean Toullec,* Mohiedine El-Alaoui, and Pascal Kleffert.** Ring Substituent Effects on Acetophenone Dimethyl Acetal Formation. 1. Dual-Parameter Treatment of Equilibrium Data in Methanol, Water, and Dodecane.

Page 4809. Due to errors in the application of eq 12, Table II should be corrected as follows:

**Table II. Cumulative Data for Substituent Effects on the Ketone to Acetal Equilibrium Constant in the Acetophenone Series (25 °C)**

| X in $XC_6H_5$-$COCH_3$ | $10^4K_X$ methanol[a] | dodecane[b] | water[b] |
|---|---|---|---|
| 4-$OCH_3$ | 0.882 ± 0.039 | 17.4 | 0.614 |
| 4-$CH_3$ | 2.42 ± 0.17 | 45.8 | 1.47 |
| H | 6.32 ± 0.11 | 109 | 3.43 |
| 4-F | 6.91 ± 0.37 | 115 | 2.08 |
| 4-Cl | 13.4 ± 0.6 | 236 | 4.46 |
| 3-Cl | 28.3 ± 0.4 | 465 | 6.11 |
| 3-$CF_3$ | 43.8 ± 1.5 | | |
| 3-$NO_2$ | 99.7 ± 5.6 | 2020 | 15.0 |
| 4-$NO_2$ | 147 ± 13 | 1860 | 18.0 |

[a] Measured by the water concentration jump method. Figures are standard deviations. [b] Calculated by eq 12 with data on equilibrium constants in methanol and data on Gibbs free energy of transfer (cf. Table III).

Page 4812. Consequently, eq 21 should read:

$$\log (K_X)_d = (1.69 \pm 0.18)\sigma^n + (0.91 \pm 0.28)(\sigma^+ - \sigma^n) - (1.96 \pm 0.08)$$

$$(\mathcal{R} = 0.997;\ s = 0.07;\ F = 397;\ pF = 43;\ n = 8)^{24,25,32}$$

and the intercept term of eq 22 should be (3.53 ± 0.10) instead of (4.42 ± 0.10). Footnote (32): Figures after the sign ± are twice the standard deviations of the regression coefficients instead of the standard deviations.

Further small changes would also be required in Table V (page 4813) for regression parameters from data in dodecane, but all the conclusions are valid.

## Vol. 49, 1984

**Balram Dhawan* and Derek Redmore.** *O*-Hydroxyaryl Diphosphonic Acids.

Page 4019, column 2: add 57.0 ($OCH_3$) to $^{13}C$ spectral data of **5d**.

Page 4020, column 1: add 57.13 ($OCH_3$) to $^{13}C$ spectral data of **7d**.

Page 4020, column 2: In the $^1H$ NMR spectral data of **10a**, 4.16 (q, $J$ = 7 Hz, 8 H, $CH_2$) should be corrected as 4.16 (dq, $J_{H-H} \approx J_{P-H} \approx$ 7 Hz, 8 H, $CH_2$).

## Vol. 50, 1985

**Hashime Kanazawa, Misuzu Ichiba, Nobuyuki Shimizu, Zenzo Tamura, and Keitaro Senga*.** Further Studies on the Ring Transformation of Pyrimido[5,4-*e*]-*as*-triazine 4-Oxides to Pyrrolo[3,2-*d*]pyrimidines Involving 1,3-Dipolar Cycloaddition Reactions.

Page 2414. The footnote in Chart II: $Me_2SO$-$d_6$ should read $CF_3COOH$.