Table I. Comparison of Experimentally Determined 9:8 Product Ratios with Those Predicted on the Basis of Several σ Constants

X	obsd[a]	pred-1[b]	pred-2[c]	pred-3[d]
NMe_2	1.8	2.1	1.9	1.8
OCH_3	2.4	2.5	2.5	2.6
F	3.3	3.1	3.1	3.2
Cl	3.6	3.3	3.4	3.4
CH_3	3.3	3.1	3.2	3.2
NO_2	2.9	4.5	4.3	4.0
CF_3	3.7	4.1	4.0	3.9
CN	2.3	4.4	4.2	4.0
H	3.5	3.4	3.4	3.5

[a] Average values derived from experiments performed at least in duplicate except for the chloro example (accuracy level = ±0.2). [b] Calculated from correlation using σ_R^0 values but omitting NO_2 and CN. [c] As in $a - \sigma_{R(BA)}$ values. [d] As in $a - \sigma_R^+$ values.

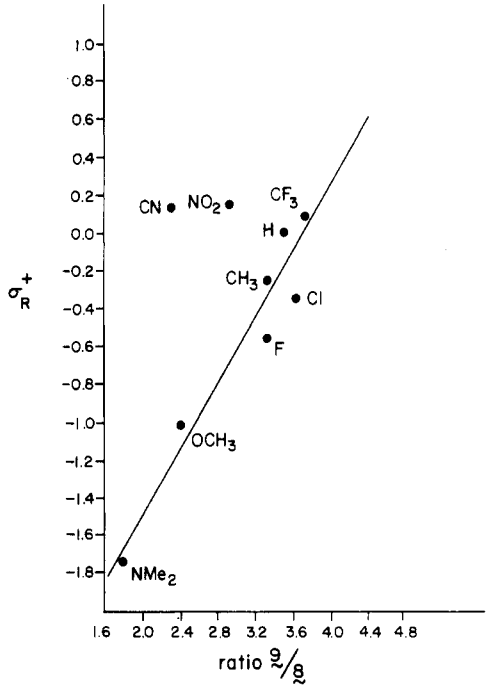

Figure 1. Plot of the σ_R^+ values of X versus the experimental 9:8 product ratios.

ratios to depend on σ_R^+ values, particularly if NO_2 and CN are omitted from the regression analysis.

Para-substituent effects on the chemical shifts of H_{cis} and H_α[11,22,25] in **3**, when analyzed by the DSP method, were also found to provide the best linear correlation when evaluated against σ_R^+ values. The somewhat exceptional nature of NO_2 and CN can be understood in conformational and π-polarization terms. Under normal circumstances, the phenyl ring in **3** is forced out of coplanarity with the fulvene ring for steric reasons.[11,22,23] Electron-releasing groups X increase the π overlap of the phenyl and fulvene part structures and significantly reduce the dihedral angle between the two rings. When X is characterized instead by an elevated σ_R^+ value, not only is the resonance effect strongly curtailed but π-electronic transmission is additionally attenuated because of the twist in existence about the bond interconnecting the two π networks.

At this point, it becomes intriguing to inquire what leads to the observed π-facial preferences. If one accepts the orbital tilting hypothesis[8] and sets 3-H as the standard, the heightened production of **8** when X is, for example, NMe_2 or OCH_3 signals that electron-releasing groups provide an influence synergistic to the norbornane contribution, much as in the isodicyclopentadienyl anion.[24] Electron release into the fulvene ring may thus cause the pπ lobes at the reaction sites to experience disrotatory tilting toward the methano bridge[8] and/or deformation along the longitudinal axis in the direction of the ethano bridge.[9] Tandem photoelectron spectroscopic/theoretical studies of **3** are expected to clarify which phenomenon is the more dominant. Nonetheless, the correlation observed here provides striking confirmation that remote electronic influences can indeed directly affect Diels–Alder stereoselection.

Table II. Statistical Analysis by the DSP Method According to the Four Established Scale Parameters

scale parameter	data utilized	ρ_I	ρ_R	λ	R^2
σ_R^-	all points	0.110	0.152	1.382	0.010
	omit CN	0.375	0.591	1.576	0.126
	omit NO_2, CN	1.471	2.264	1.539	0.604
σ_R^0	all points	−0.234	1.145	−4.893	0.167
	omit CN	0.143	1.703	11.909	0.431
	omit NO_2, CN	1.116	2.662	2.385	0.842
$\sigma_{R(BA)}$	all points	−0.349	1.074	−3.077	0.280
	omit CN	0.061	1.413	23.164	0.570
	omit NO_2, CN	0.961	1.897	1.974	0.923
σ_R^+	all points	−0.574	0.753	−1.312	0.430
	omit CN	−0.161	0.887	−5.509	0.717
	omit NO_2, CN	0.579	1.025	1.770	0.959

Acknowledgment. Financial support from the National Cancer Institute (Grant CA-12115) is gratefully acknowledged.

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(23) Sardella, D. J.; Keane, C. M.; Lemonias, P. *J. Am. Chem. Soc.* **1984**, *106*, 4962.
(24) Paquette, L. A.; Charumilind, P.; Kravetz, T. M.; Böhm, M. C.; Gleiter, R. *J. Am. Chem. Soc.* **1983**, *105*, 3126.

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Contrasting Behaviors in the Cleavage of Aryl Alkanoates by α- and β-Cyclodextrins in Basic Aqueous Solution

Summary: The kinetics of ester cleavage of 4-carboxy-2-nitrophenyl alkanoates (C2, C4, C6, C7, C8) in aqueous base containing α- or β-cyclodextrin (α- or β-CD) indicate that for the three longer esters there are processes involving *two* CD molecules which are quite distinct: with α-CD a 2:1 binding leads to *inhibition*; with β-CD a second-order process provides *catalysis*.

Sir: In aqueous base cyclodextrins (CDs)[1] cleave phenyl acetates via ester·CD complexes in which the aryloxy group is included in the hydrophobic cavity of the CD.[1-3] Longer

(1) (a) Bender, M.; Komiyama, M. *Cyclodextrin Chemistry*; Springer-Verlag: New York, 1978. (b) Saenger, W. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 344.
(2) (a) VanEtten, R. L.; Sebastian, J. F.; Clowes, G. A.; Bender, M. L. *J. Am. Chem. Soc.* **1967**, *89*, 3242. (b) Komiyama, M.; Bender, M. L. *J. Am. Chem. Soc.* **1978**, *100*, 4576. (c) Komiyama, M.; Bender, M. L. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1073. (d) Tee, O. S.; Takasaki, B. K. *Can. J. Chem.* **1985**, *63*, 3540.

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Table I. Constants for the Cleavage of 4-Carboxy-2-nitrophenyl Alkanoates 1 by α- and β-Cyclodextrins[a]

acyl	K_1, mM	K_2, mM	k_u, s^{-1}	k_c, s^{-1}	k_{c2}, M^{-1} s^{-1}	k_c/k_u	$k_2 = k_c/K_1$, M^{-1} s^{-1}
				(a) α-CD			
C2	8.9		0.096	0.17		1.8	19
C4	7.7	14	0.027	0.013		0.48	1.7
C6	1.4	29	0.027	0.038		1.4	27
C7	1.1	17	0.026	0.063		2.4	57
C8	0.50	26	0.022	0.074		3.4	150
				(b) β-CD			
C2	5.9		0.096	0.28		2.9	47
C4	1.5		0.029	0.0078		0.27	5.2
C6	0.38		0.024	0.0067	0.15	0.28	18
C7	0.27		0.026	0.014	0.24	0.54	52
C8	0.79		0.022	0.026	0.54	1.2	33

[a] At 25 °C, in a 0.4 M phosphate buffer of pH 11.6 containing 0.1% (v/v) MeOH. $[Ester]_0$ = 0.05 or 0.1 mM.

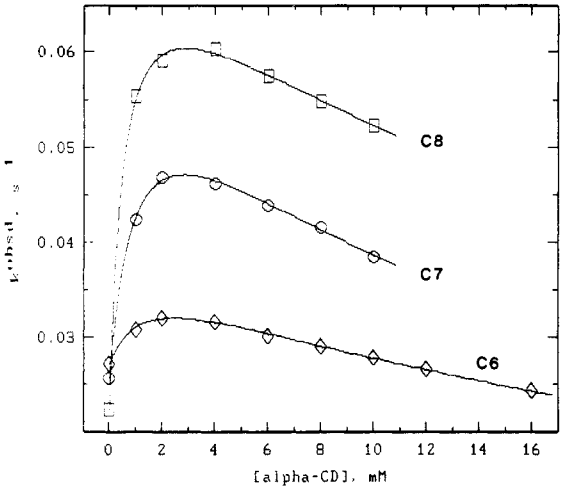


Figure 1. Plots of k^{obsd} vs [α-CD] for the cleavage of 4-carboxy-2-nitrophenyl hexanoate (C6), heptanoate (C7), and octanoate (C8) at pH 11.6. The curves conform to eq 4, consistent with a reactive 1:1 complex and an unreactive 2:1 (CD:ester) complex.

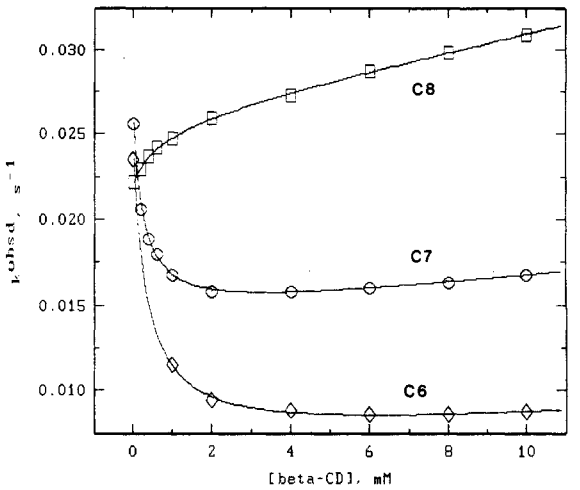
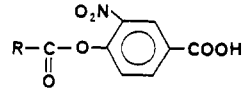


Figure 2. Plots of k^{obsd} vs [β-CD] for the cleavage of 4-carboxy-2-nitrophenyl hexanoate (C6), heptanoate (C7), and octanoate (C8) at pH 11.6. The curves conform to eq 6, consistent with a reactive 1:1 complex and a process involving a second molecule of CD.

chain *p*-nitrophenyl alkanoates appear to bind and undergo cleavage with their alkyl chains included in the cavity,[4] but it is not clear that ester cleavage always ensues from the principal ester·CD complex; another isomeric ester·CD complex might be the reactive form. To address such problems we are studying the behavior of various aryl alkanoate esters.[5]

We hereby report that the kinetics of the cleavage of 4-carboxy-2-nitrophenyl esters 1[6] by α- and β-CD vary markedly with the alkyl chain *and* with the CD. The



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acetate (C2), butanoate (C4), hexanoate (C6), heptanoate (C7), octanoate (C8)

shorter chain esters behave normally,[1-4] but contrasting behaviors are as seen with the three longer esters and the two CDs, as shown in plots of k^{obsd} vs [CD] (Figures 1 and 2).[7] This diversity can be explained by only three simple models.

With α-CD the C2 ester, like many other esters,[1-4] appears to exhibit saturation kinetics, consistent with eq 1 and 2.

$$\xleftarrow{k_u} S + CD \underset{K_1}{\rightleftharpoons} S{\cdot}CD \xrightarrow{k_c} \quad (1)$$

$$k^{obsd} = \frac{(k_u{\cdot}K_1 + k_c{\cdot}[CD])}{(K_1 + [CD])} \quad (2)$$

The C6, C7, and C8 esters show an additional, *inhibitory* process at high [CD] (Figure 1), and the results conform to a nonproductive 2:1 (CD:ester) binding:

$$S{\cdot}CD + CD \underset{K_2}{\rightleftharpoons} S{\cdot}CD_2 \quad (3)$$

This extra equilibrium requires that eq 2 be replaced by

$$k^{obsd} = \frac{(k_uK_1 + k_c[CD])K_2}{(K_1K_2 + K_2[CD] + [CD]^2)} \quad (4)$$

Equation 4 gives excellent fits to the data for the C4 (not shown), C6, C7, and C8 esters (Figure 1) with the constants presented in Table I (part a).

With β-CD the C2 and C4 esters obey eq 2, but the longer esters also have a *catalytic* process at high [CD]

(3) Matsui, Y.; Nishioka, T.; Fujita, T. *Top. Curr. Chem.* **1985**, *128*, 61.

(4) Bonora, G. M.; Fornasier, R.; Scrimin, P.; Tonellato, U. *J. Chem. Soc., Perkin Trans. 2* **1985**, 367.

(5) Besides the esters discussed here, we are studying *m*- and *p*-nitrophenyl esters and some 4- and 5-chloroaspirin analogs (cf. ref 2d).

(6) The aryl group of 1 is more hydrophilic than *p*-nitrophenyl, and so binding of the alkyl chain is made more favorable. The esters also have the advantage of being more water soluble when ionized.

(7) Ester cleavage was monitored by the increase at 410 nm due to the release of the dianion of 4-carboxy-2-nitrophenol. Reaction conditions are given in the footnote of Table I.

(Figure 2) which is ascribed to the attack of a second molecule of CD on the ester·CD complex:

$$S{\cdot}CD + CD \xrightarrow{k_{c2}} \quad (5)$$

In this case eq 2 must be expanded to eq 6 which fits our data for the C6, C7, and C8 esters (Figure 2) with the constants given in Table I (part b).

$$k^{obsd} = \frac{(k_u K_1 + k_c[CD] + k_{c2}[CD]^2)}{(K_1 + [CD])} \quad (6)$$

For both α- and β-CD the variations of K_1 and k_c/k_u with chain length (Table I) are similar to those for other aryl esters.[4,5] Substrate binding becomes stronger whereas the "catalytic ratio" (k_c/k_u) and the "substrate specificity"[2a,d] ($k_2 = k_c/K_1$) decrease and then increase. Apparently, with a shorter, bound alkyl chain (C4 ester) the ester function sits too deeply in the CD cavity to be easily attacked by an ionized OH,[1,2] but with the longer esters it is held progressively higher and more accessible.

The unreactive 2:1 complexes of α-CD probably have the alkyl chain of 1 included in the first CD molecule (K_1) and the aryl group in the second (K_2) since the values of K_2 vary little with chain length. The additional catalysis seen with β-CD and the C6, C7, and C8 esters also involves two CD molecules, but, since the increases in k^{obsd} at high [CD] are linear (Figure 2), any 2:1 binding must be very weak. With increasing chain length the second-order process becomes more important (k_{c2} increases).

The different behaviors noted for the longer esters must relate to the cavity widths of α- and β-CD since their depths are the same.[1] Molecular (CPK) models suggest a fairly tight fit of alkyl chains in α-CD and a looser fit for β-CD. This seems to be the case with linear alcohols[3] and alkane sulfonate ions[8] (up to C8), but it is not clearly so with the present esters or with *p*-nitrophenyl alkanoates.[4] Nonetheless, the present results may mean that α-CD forms a 2:1 complex with the longer esters which is too tight to react whereas β-CD forms a weak, much looser 2:1 complex which can react.[9]

(8) Satake, I.; Ikenoue, T.; Takshita, T.; Hayakawa, K.; Meda, T. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2747. Satake, I.; Yoshida, S.; Hayakawa, K.; Meda, T.; Kusumoto, Y. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3991.

(9) This work was supported by an operating grant from the Natural Sciences and Engineering Research Council of Canada.

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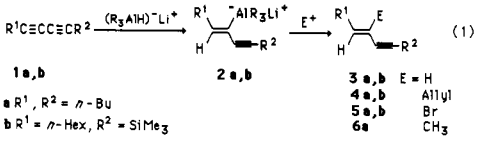
Configurational Instability of α-Alkenyl and α-Alkynyl Vinyllithiums. Syntheses of Stereodefined 2-Alkyl-1-en-3-ynes

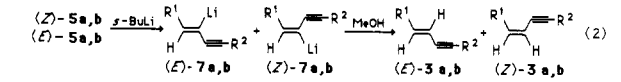
Summary: Metal–halogen exchange of either (*Z*)-enynyl bromides or (*Z*)-dienyl bromides by *sec*-BuLi produces vinyllithiums that are configurationally stable only at temperatures below −120 °C and −78 °C, respectively. Allylation of (*Z*)-enynylalanates with allyl bromide or methylation of (*Z*)-enynyl bromides with CH_3MgI and $Fe(acac)_3$ catalyst furnishes the corresponding 2-alkyl-1-en-3-ynes.

Sir: The hydroalumination of conjugated diynes **1**[2,3] with lithium trialkylaluminum hydrides is a highly stereo- and regioselective process, placing the aluminum at the internal position of the resultant double bond. With the silyl-substituted diynes **1b**,[3] the hydroalumination also occurs chemoselectively, with Al–H addition taking place exclusively at the non-silicon bearing triple bond. Protonolysis of the intermediate vinylalanates **2** cleanly affords the respective (*E*)-enynes **3**. In seeking to extend this methodology to carbon electrophiles to obtain stereodefined trisubstituted enynes, treatment of **2** with allyl bromide (2.0 equiv, 25 °C, 24 h) produced nearly quantitative yields of the isomerically pure (≥99%) allylated enynes (*E*)-**4a** (95%) and (*E*)-**4b** (94%) (eq 1). Unfortunately, however, the alkenylalanates **2** were unreactive toward other common alkylating agents, such as methyl iodide.[4]



(1)

In the course of our search for a general route for the alkylation of the vinylalanates **2**, we investigated their conversion into the more nucleophilic vinyllithiums. This was achieved by converting the vinylalanates **2** into the corresponding (*Z*)-enynyl bromides **5** and then via metal–halogen exchange to the vinyllithiums. Thus, treatment of **2** with 2 equiv of cyanogen bromide (−78 → 25 °C) furnished the enynyl bromides **5** (**a**, 91%; **b**, 92%) in high isomeric purity (≥98%). Lithiation of (*Z*)-**5a** by *sec*-BuLi (1.1 equiv, ether, −78 → 25 °C) occurred readily, yet produced the isomeric enynes (*E*)-**3a** (9%) and (*Z*)-**3a** (89%) upon protonolysis (eq 2). The formation of the *cis*-enyne



(2)

3a from the (*Z*)-enynyl bromide **5a** points to an isomerization of the initially formed vinyllithium (*E*)-**7a** to the respective *Z* isomer **7a**. Similar results were obtained from the lithiation of the silylated (*Z*)-enynyl bromide **5b**. The enynyllithium isomerization is an extremely facile process, taking place readily at −78 °C but is nearly entirely suppressed at −120 °C.[5] The equilibrium ratio of (*E*)-**7a**:(*Z*)-**7a** at room temperature must be in the range of 10:90 to 5:95, since nearly the same distribution of enynes (*E*)-**3a** and (*Z*)-**3a**, respectively, was obtained from the lithiation/methanolysis of either pure (*Z*)-enynyl bromide **5a** or from the corresponding *E* isomer **5a**.[7] The configura-

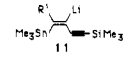
(1) Present address: Ethyl Corporation, Technical Center, P.O. Box 14799, Baton Rouge, LA 70898.

(2) Zweifel, G.; Lynd, R. A.; Murray, R. E. *Synthesis* **1977**, 52.

(3) Miller, J. A.; Zweifel, G. *J. Am. Chem. Soc.* **1983**, *105*, 1383.

(4) Alkenylalanates derived from simple 1-alkynes are known to react readily with typical alkylating agents such as methyl iodide: Baba, S.; Van Horn, D. E.; Negishi, E. *Tetrahedron Lett.* **1976**, 1927. Eisch, J. J.; Damasevitz, J. E. *J. Org. Chem.* **1976**, *41*, 2214. Uchida, K.; Utimoto, K.; Nozaki, H. *J. Org. Chem.* **1976**, *41*, 2215.

(5) It is interesting to contrast the configurational instability of (*E*)-**7a** and (*E*)-**7b** with the observed stereochemical stability of **11**.[6] The geometrical rigidity of **11** probably results from the additional stability gained through maximum separation of the two olefinic metal atoms.



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(6) Miller, J. A. Doctoral Dissertation, University of California, Davis, 1982. Zweifel, G.; Leong, W. *J. Am. Chem. Soc.* **1987**, *109*, 6409.

(7) The *E* bromide **5a** was synthesized from (*Z*)-**5a** by sequential treatment with *sec*-BuLi (−78 °C, 0.5 h) and BrCN. The resulting mixture (85% *E*:15% *Z*) was purified by preparative GLC (Carbowax-20M) to furnish 97% isomerically pure (*E*)-**5a**.

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