actions are greater than the HOMO dienophile–LUMO diene interactions.[12] In this reaction the magnitudes of the two interactions are nearly the same; thus both interactions effect the regioselectivity. We found that the HOMO C-1 and C-4 coefficients of the diene predict a slight dominance of the meta product while the LUMO C-1 and C-4 coefficients favor the ortho product.[13] This dichotomy is resolved by the larger C-2 coefficients in both molecular orbitals which results in the ortho product dominating.

In conclusion, secondary orbital interactions do have a significant effect on the regioselectivity of the Diels–Alder reaction between unsymmetrically substituted dienes and dienophiles. In the cases where the C-1 and C-4 frontier coefficients of the dienes are of nearly equal magnitudes, they can be used to predict the preferred regioisomers.

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(12) In the cases of **1b** and **1c**, the HOMO dienophile–LUMO diene interactions will have a significant effect on the regioselectivity. These interactions favor the para isomer as does the HOMO diene–LUMO dienophile interactions.

(13) The C-3 positions in HOMO and LUMO of methyl acrylate and acrylic acid have greater coefficients than their corresponding C-1 and C-2 positions.

The Inductive Effect of Cyclopropane[1]

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As a result of studies of solvolyses of cyclopropane-substituted systems[3] we have been interested in determining the effect of nonconjugated cyclopropane[4] on the electronic environment at a reaction site involving electron-deficient carbon.

In surveying the literature it is readily apparent that the consensus is that cyclopropane is inductively electron withdrawing. This conclusion arises from consideration of dipole measurements[5] and measurements of infrared spectra and amine basicities,[6] the increased s character (hybridization) of the exocyclic cyclopropyl bonds,[7] the strain of the cyclopropyl group which should make it a negative pole and thus electron withdrawing[8] in the inductive sense, and from consideration of solvolysis data in which there is no conjugative interaction of the cyclopropyl group with the reactive site.[3a,9] Most striking is the recent finding that cyclopropane is a meta director in electrophilic substitution.[10] The general trend observed in most substituent effect studies is one of increasing electronegativity of a substituent with increasing s character, which is also paralleled by increases in σ^*[7b] values. Thus determination of the σ^* value for cyclopropane should give a good measure of the inductive effect of the cyclopropyl group, uncomplicated by other effects.

As one of the best correlations of inductive effects is that of the ionization constants with σ^* values ($\rho^* = +1.721 \pm 0.025$ in H_2O at 25°[11]) for aliphatic carboxylic acids, our goal became the synthesis of cyclopropaneacetic acid. Cyclopropaneacetic acid has been prepared by a variety of procedures, but each is either lengthy or gives a low yield. It was anticipated that the Willgerodt reaction of methyl cyclopropyl ketone using the Kindler modification[12] might be useful, although this had been tried previously[13] using the Carmack method.[14] Using the Kindler modification we achieved only an 8% yield of cyclopropaneacetic acid, but this was sufficient for our studies.

The ionization constants of acetic acid, isovaleric acid, vinylacetic acid, and cyclopropaneacetic acid were measured in water at 25° from pH titration curves. The measured pK_a values are listed and compared with some literature[15] values in Table I, along with the cor-

TABLE I

IONIZATION CONSTANTS OF ALIPHATIC ACIDS

$$RCH_2CO_2H + H_2O \underset{\substack{25°\\ H_2O}}{\overset{K}{\rightleftharpoons}} RCH_2CO_2^- + H_3O^+$$

R	p$K_a^{\text{lit.}}$	pK_a^{expt}	pK_a^{av}	$\sigma^*_{RCH_2}$[a]
H	4.76	4.75	4.76	0.000
		4.76		
		4.76		
CH_3CHCH_3	4.78	4.80	4.79	−0.125[b]
		4.78		
		4.74		
c-C_3H_5		4.73	4.74	+0.011
		4.75		
		4.74		
$CH_2{=}CH$	4.35	4.37	4.36	+0.226[b]
		4.36		
C_6H_5	4.31			+0.260[c]

[a] $\rho^* = +1.721 \pm 0.025$, ref 7b, p 606. [b] Calculated from measured and literature pK_a values. [c] Calculated from literature values.

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Table II

Substituent Constants for Cyclopropane

σ_i	Value	% $\mathcal{R}$[a]
σ^*	$+0.017$[b]	5
$\sigma_{CH_2X}{}^*$	$+0.011$[c]	5
σ_I	$+0.01$,[d] -0.08[e]	0
$\sigma_m{}^+$	-0.04,[f] -0.06[g]	33
σ_m	-0.07,[h] -0.102,[i] -0.14[j]	22
$\sigma_R{}^\circ$	-0.13[e]	84
σ°	-0.21[k]	41
σ_p	-0.19,[l] -0.21,[h] -0.23,[j] -0.24[l]	53
$\sigma_p{}^+$	-0.410,[m] -0.439,[n] -0.45,[f] -0.462[g]	66

[a] Defined in ref 17. [b] T. L. Brown, J. M. Sandri, and H. A. Hart, *J. Phys. Chem.*, **61,** 698 (1951). [c] This work. [d] Reference 9a. [e] R. G. Pews, *J. Amer. Chem. Soc.*, **89,** 5605 (1967). [f] R. C. Hahn, T. F. Corbin, and H. Shechter, *ibid.*, **90,** 3404 (1968). [g] D. H. Man and J. B. Stothers, *Can. J. Chem.*, **45,** 225 (1967). [h] J. Smejkal, J. Jones, and J. Farkas, *Collect. Czech. Chem. Commun.*, **29,** 2950 (1964). [i] J. A. Landgrebe and W. Becker, *J. Amer. Chem. Soc.*, **90,** 395 (1968). [j] T. F. Corbin, Ph.D. Dissertation, Ohio State University, 1956. [k] R. G. Pews and N. D. Ojha, *J. Amer. Chem. Soc.*, **91,** 5769 (1969), [l] R. Levina, P. A. Gimbitskii, L. P. Guseva, and P. K. Agasyan, *Zh. Obshch. Khim.*, **34,** 146 (1964); *Chem Abstr.*, **60,** 10519*a* (1964). [m] L. B. Jones and V. K. Jones, *Tetrahedron Lett.*, 1493 (1966). [n] L. B. Jones and S. S. Eng, *ibid.*, 1431 (1968).

responding derived $\sigma^*_{CH_2}$ values. The substituent constant thus found for nonconjugated cyclopropane, $\sigma^*_{CH_2} = +0.011$, is little different from that for hydrogen, indicating a very weak electron withdrawal by cyclopropane as compared with vinyl or phenyl, as has also been reported recently by Martin and Ree for a conjugated but nonbisected geometry of a cyclopropylcarbinyl system.[9a] This indicates that hybridization (sp^2 for cyclopropane, vinyl and phenyl σ bonding orbitals) is *not* the dominant factor in determining the electronegativity and the inductive effect of the cyclopropyl group. Recent arguments[16] indicate that the low reactivity of the 1-nortricyclyl system is caused by angle strain deformations in the carbonium ion and not by an inductive withdrawal by cyclopropane. The experimental finding of a small, weak electron-withdrawing effect, as opposed to the larger effects observed for vinyl and phenyl, tends to support that argument.

The known substituent constants which have been determined for cyclopropane in various types of reaction environments are listed in Table II with the corresponding values of % $\mathcal{R}$,[17] a measure of the sensitivity of resonance effects of particular substituent constants. The changes of the substituent constant values for cyclopropane in different reaction types is seen to be proportional to the corresponding changes in % $\mathcal{R}$. This clearly demonstrates the response of electron donation by cyclopropane toward increasingly more electron-deficient centers, superimposed on a small, weak electron-withdrawing effect of the cyclopropyl group.

Experimental Section

Cyclopropaneacetic Acid.—Cyclopropaneacetic acid was prepared by the Willgerodt reaction.[12] Cyclopropyl methyl ketone (8.4 g, 0.10 mol), piperidine (13.0 g, 0.15 mol), and sulfur (4.8 g, 0.15 mol) were heated at reflux for 2.4 hr and the resulting black reaction mixture was poured onto ice. The solution was extracted with ether and washed with ice-cold 10% hydrochloric acid followed by saturated aqueous sodium bicarbonate solution and then by water. The solution was dried over anhydrous sodium sulfate, filtered, and concentrated. The residual product could not be crystallized and was hydrolyzed with 1.2 equiv of 10% aqueous potassium hydroxide without further purification. The alkaline solution was acidified, extracted with ether, dried over sodium sulfate, concentrated, and distilled, giving 0.8 g (8%) of cyclopropaneacetic acid, bp 89-94° (14 mm), $n^{25}D$ 1.440 [lit.[18] bp 90° (15 mm), $n^{25}D$ 1.4320). The infrared and nmr spectra were consistent with the assigned structure.

Acidity Determination.—Samples of the acids, generally in the range of 5–10 mg, were weighed to 0.1-mg accuracy into 50-ml beakers to which 25 ml of water (redistilled from sodium hydroxide to remove carbon dioxide) was added. The pH of the solution was measured with a Beckman glass electrode (40498) and a Beckman calomel electrode (39970), both immersed in the solution to a depth sufficient to cover the bulb of the glass electrode. The electrodes were connected to a Sargent Model DR pH meter with which a relative accuracy of ±0.005 pH could be obtained. The pH meter was standardized using a buffer of pH 4.64 (M/10 NaOAc/HOAc). Increments ranging from 0.02 to 0.2 ml of sodium hydroxide (carbonate-free, 0.1176 *N*, standardized against potassium biphthalate) were added from a microburet (5.00 ml) graduated in 0.002 ml. After each addition the solution was stirred mechanically for 1 min and the pH was measured. The determination of the end point was made by the rate of change in the slope of the titration curve. At the conclusion of the titration, the electrode was checked against the standard buffer and was always found to be within 0.01 pH unit of the nominal value. The pH values at 25, 50, and 75% neutralization were read off the titration curves and from each a value of pK_a was calculated using eq 1, in which the concentrations of the

$$pK_a = pH - \log \frac{[RCOO^-]}{[RCOOH]} \qquad (1)$$

anion ($RCOO^-$) and undissociated acid (RCOOH) have been calculated taking into account the change in concentration of the acid and the anion due to dissociation of the acid. Sample data from one titration curve and calculations are shown in Table III for cyclopropaneacetic acid in water solution at 25°.

Table III[a]

Neutralization, %	NaOH, ml (0.1176 *N*)	NaOH × 10^{-5}, mol	pH	H^{+b} × 10^{-5}, mol	$RCOO^{-c}$ × 10^{-5}, mol	$RCOOH^d$ × 10^{-5}, mol	$pK_a{}'^e$
25	0.3412	4.01	4.26	0.139	3.72	12.33	4.738
50	0.6825	8.02	4.74	0.046	8.06	7.98	4.737
75	1.0237	12.04	5.22	0.157	12.06	4.00	4.741

[a] Titration end point 1.365 ml, original volume of solution 25.0 ml. [b] H^+, $RCOO^-$, and RCOOH refer to moles of hydrogen ion, cyclopropaneacetate ion, and undissociated acid present in the titration vessel. H^+ is derived from the observed pH and the total volume of solution. [c] $RCOO^-$ = moles of NaOH added plus moles of H^+. [d] RCOOH = moles of acid used (16.05×10^{-5}) minus $RCOO^-$. [e] From eq 1.

Registry No.—Cyclopropane, 75-19-4; cyclopropylacetic acid, 5239-82-7; cyclopropyl methyl ketone, 765-43-5.

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