ment at 110°. Organic solutions were dried with anhydrous granular K_2CO_3 and concentrated *in vacuo* with a Buchler rotary evaporator. Microanalyses were performed by PCR, Inc., Gainesville, Fla., and Micro-Tech Labs Inc., Skokie, Ill. Mass spectra were determined by Mr. J. W. Suggs and Mr. H. E. Ensley at Harvard University.

3-(2-Nitrophenyl)-1-(2-methyl-3-pyridyl)-2-propen-1-one (3).—To a solution of 12 g (0.079 mol) of 2-nitrobenzaldehyde (Aldrich), 3.0 g (0.075 mol) of NaOH, 30 ml of H_2O, 30 ml of EtOH, and 25 ml of Et_2O at 0–5° was added with stirring over 1 hr 10 g (0.074 mol) of 2-methyl-3-acetylpyridine.[4] A yellow precipitate formed during the addition, and near the end of the addition 25 ml of Et_2O was added. The mixture was stirred at 0–5° for 2 hr and then stored in a refrigerator at 5° for 24 hr. The solid was collected by filtration and dissolved in 300 ml of benzene. The benzene solution was washed with water and refluxed with 0.9 g of *p*-toluenesulfonic acid (Dean-Stark trap) for 4 hr. The solution was filtered, washed with aqueous $NaHCO_3$ and then H_2O, dried, and concentrated to give a dark solid. Chromatography over activity III basic alumina gave, with benzene elution, 3.4 g (17%) of **3** as a white solid, mp 133–135°. Recrystallization from MeOH–Et_2O gave colorless needles, mp 140–142°.

Pertinent spectral data for **3** are as follows: ir ($CHCl_3$) 2990, 1660, 1520, 1440, 1340, 1290, and 975 cm^{-1}; nmr ($CDCl_3$) δ 2.69 (s, 3), 7.7 (m, 8), and 8.6 ppm (m, 1).

Anal. Calcd for $C_{15}H_{12}N_2O_3$: C, 67.16; H, 4.51; N, 10.44. Found: C, 67.20; H, 4.60; N, 10.34.

2-[2-(2-Nitrophenyl)vinyl]-2-(2-methyl-3-pyridyl)-1,3-dioxolane (4).—A mixture of 6.85 g (0.0255 mol) of ketone **3**, 5.4 g (0.028 mol) of *p*-toluenesulfonic acid, 4.8 ml of ethylene glycol, and 120 ml of benzene was refluxed (Dean-Stark trap) with stirring. After 3 hr, more ethylene glycol (7 ml) and *p*-toluenesulfonic acid (1.7 g) were added and reflux was continued for 23 hr. The solution was allowed to cool and poured into water. The mixture was basified with 2 *N* NaOH and the benzene layer was separated. The aqueous layer was extracted with fresh benzene and the combined benzene extracts were washed with 1 *N* NaOH and then H_2O, dried, and concentrated to give 7.74 g (97%) of **4** as a yellow solid. Recrystallization from Et_2O–hexane gave large, colorless prisms, mp 91–93°.

Pertinent spectral data for **4** are as follows: ir ($CHCl_3$) 2980, 1520, 1440, 1340, 1050, and 969 cm^{-1}; nmr ($CDCl_3$) δ 2.70 (s, 3), 4.05 (m, 4), 6.67 (AB q, 2, J = 15 Hz), 7.4 (m, 4), 7.9 (m, 2), and 8.24 ppm (d of d, 1).

Anal. Calcd for $C_{17}H_{16}N_2O_4$: C, 65.38; H, 5.16; N, 8.97. Found: C, 65.48; H, 5.02; N, 8.89.

2-(2-Indolyl)-2-(2-methyl-3-pyridyl)-1,3-dioxolane (5).—To a refluxing, stirred solution of 30 ml of triethyl phosphite (distilled and passed through activity I basic alumina prior to use) under N_2 was added a solution of 1.57 g (0.00503 mol) of **4** in 40 ml of triethyl phosphite over a period of 3.5 hr. After addition, the mixture was refluxed for 5 hr and then allowed to stand overnight at 25°. The mixture was concentrated to near dryness (vacuum pump) and the residue was dissolved in 100 ml of Et_2O. The solution was stirred and saturated with HCl gas at 0° until the formation of insoluble material was judged complete. The ether was decanted off, and the residue was washed with ether and then treated with $CHCl_3$ and 2 *N* NaOH (ice cooling). Further extraction with $CHCl_3$ gave, after washing, drying, and concentration, a dark oil. Chromatography over activity III basic alumina gave, with benzene elution, 0.73 g (52%) of **5** as oily crystals. Recrystallization from benzene and then $CHCl_3$–hexane gave pure **5** as colorless, fluffy needles, mp 182–183°. A larger run with 7.75 g of **4** gave **5** in 38% yield.

Pertinent spectral data for **5** are as follows: ir ($CHCl_3$) 3495, 2980, 1290, 1170, 1080, and 1430 cm^{-1}; nmr (CDC_3) δ 2.55 (s, 3) 3.85 (m, 4), 6.10 (broad s, 1), 7.1 (m, 5), 7.86 (d of d, 1), and 8.27 ppm (d of d, 1).

Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 73.01; H, 5.69; N, 10.11.

1,2-Dimethyl-3-[2-(2-indolyl)-1,3-dioxolan-2-yl]pyridinium Iodide (6).—A mixture of 1.37 g (0.00489 mol) of **5** and 10 ml of methyl iodide in 30 ml of benzene was stirred at 25° for 2 hr and then at 50° for 2 hr. After 3 days at 25°, the precipitate was collected and washed with benzene and then Et_2O to give 2.1 g (~100%) of **6** as a light yellow powder. Recrystallization from MeOH–Et_2O gave pure **6** as tiny, colorless needles, mp 214–216°.

Anal. Calcd for $C_{18}H_{19}N_2O_2I$: C, 51.20; H, 4.54; N, 6.63. Found: C, 51.02; H, 4.56; N, 6.48.

***cis*- and *trans*-1,2-Dimethyl-3-(2-indolylcarbonyl)piperidine (2 and 7).**—To a stirred solution of 0.5 g of $NaBH_4$ in 30 ml of 70% aqueous EtOH at 0–5° was added 0.56 g (0.0013 mol) of **6** over 1 min. After addition, more EtOH (5 ml) was added and the mixture was stirred at 0–5° for 1 hr and then at 25°. An additional 0.5 g of $NaBH_4$ and 15 ml of 50% EtOH were added after 4 hr at 25°. After stirring for 22 hr, the mixture was extracted with CH_2Cl_2. The extract was washed, dried, and concentrated to give 0.42 g of a yellow foam. The yellow foam was hydrogenated in 30 ml of EtOH with 0.15 g of 10% Pd/C at 25° (1 atm). Filtration and concentration gave 0.42 g of an amber oil. The amber oil was refluxed for 1 hr with 20 ml of 80% aqueous ethanol and 10 drops of concentrated HCl. The mixture was basified with 2 *N* NaOH, concentrated to near dryness, and extracted with CH_2Cl_2. The extract was washed, dried, and concentrated to give 0.30 g (88% crude from **6**) of a yellow-brown solid. Chromatography over activity III basic alumina gave, with benzene elution, 0.009 g (3%) of **2** as a yellow solid and 0.114 g (33%) of **7** as a white solid. Further elution with benzene and benzene–$CHCl_3$ gave 0.046 g of an amber gum which appeared to be a mixture of the alcohols derived from **2** and **7**.

Recrystallization from MeOH–Et_2O–hexane gave pure **2** as tiny prisms, mp 169–170° (lit.[2] mp 167–168°). This synthetic material was completely identical (tlc, infrared, mass spectrum) with a freshly recrystallized sample (mp 172–174°) of **2** as obtained[2] from **1**.

Recrystallization from MeOH–Et_2O–hexane gave pure **7** as tiny cubes of fluffy needles, mp 184–185°. This material was distinguishable from **2** in the fingerprint region of the infrared spectrum, and **7** exhibited a higher R_f (0.73) and a lighter brown-colored spot on tlc than did **2** (R_f 0.69). **7** showed nearly the same mass spectrum as **2**.

Pertinent spectral data for **7** are as follows: ir ($CHCl_3$) 3520, 3370, 2970, 1650, 1520, 1340, 1130, and 1110 cm^{-1}; nmr ($CDCl_3$) δ 0.88 (d, 3, J = 6 Hz), 2.38 (s, 3), 7.3 ppm (m, 5). A mixture nmr spectrum of **2** and **7** clearly showed separate methyl resonances for the two epimers.

Anal. (**7**) Calcd for $C_{16}H_{20}N_2O$: C, 74.97; H, 7.86; N, 10.93. Found: C, 74.93; H, 7.92; N, 10.97.

Conversion of 7 into 2.—A mixture of 15 mg of a mixture of **2** and **7** (~50:50 by tlc) was refluxed under N_2 with 1.2 ml of 10% aqueous NaOH and 1.5 ml of 50% aqueous EtOH for 5 hr. Extraction with CH_2Cl_2 gave, after the usual work-up, 15 mg of a yellow solid showing only **2** by tlc, mp 167–169°. Recrystallization from MeOH–Et_2O–hexane gave pure **2** (tlc, infrared). A similar reaction with 44 mg of pure **7** gave 37 mg (84%) of **2**. The epimerization appears to be complete in 30 min by tlc and no **7** can be detected by tlc or nmr.

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Registry No.—**2**, 42031-20-9; **3**, 42031-21-0; **4**, 42031-22-1; **5**, 42031-23-2; **6**, 42031-24-3; **7**, 42031-25-4; *o*-nitrobenzaldehyde, 552-89-6; 2-methyl-3-acetylpyridine, 1721-12-6.

Secondary Orbital Interactions Determining Regioselectivity in the Diels–Alder Reaction

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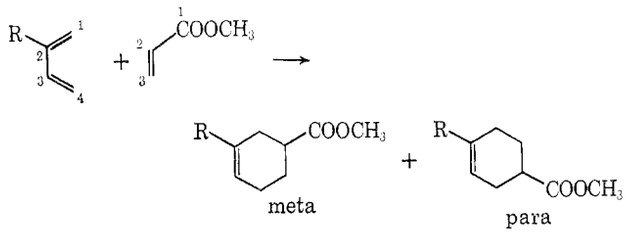
Recently, there has been considerable interest in the prediction of the preferred regioisomers of the Diels–

Alder reaction between unsymmetrically substituted dienes and dienophiles from molecular orbital calculations.[1,2] Houk[2] has proposed two generalizations for predicting the preferred regioisomers from terminal frontier coefficient magnitudes and frontier orbital energies. We have also examined these reactions using the frontier coefficient magnitudes and frontier orbital energies from INDO[3] calculations to determine the effect of secondary orbital interactions on the regioselectivity of these reactions.

The conformations[4] used in these calculations were the cisoid planar for the dienes and the transoid planar for the dienophiles. We found that the interpretations from the INDO calculated eigenvectors and eigenvalues were independent of small changes[6] in bond angles, bond distances, and rotational conformations. Thus, there was no justification of the use of computer time for an extensive optimization of the structures of these dienes; so standard bond angles and bond lengths[7,8] were used.

Employing Houk's generalizations and terminal coefficient magnitudes and orbital energies from the INDO calculations, the experimentally preferred regioisomers[5,9] were predicted for the cases **1a–1e** in which



1a, R = CH_3
b, R = Cl
c, R = CN
d, R = C_6H_5
e, R = OCH_3

there were considerable differences between the magnitudes (Table I) of the C-1 and C-4 HOMO coefficients of the dienes. However, it was found that the terminal carbons of the 1-substituted 1,3-butadienes studied have almost equal HOMO coefficients (Table II) implying, a 1:1 ratio of ortho and meta isomers

TABLE I

ISOMER RATIOS AND P_z COEFFICIENTS OF HOMO FOR 2-SUBSTITUTED 1,3-BUTADIENES

Substituent[a]	Ratio of para:meta	P_z coefficients[b] C-1	C-2	C-3	C-4
CH_3	2.3:1[c]	0.614	0.420	0.348	0.506
OCH_3	*d*	0.650	0.345	0.223	0.369
C_6H_5	4.0:1[c]	0.572	0.341	0.214	0.335
Cl	6.7:1[c]	0.546	0.346	0.266	0.397
CN	5.3:1[c]	0.595	0.405	0.342	0.490

[a] Registry numbers are, respectively, 78-79-5, 3588-30-5, 2288-18-8, 126-99-8, 5167-62-4. [b] These are absolute values. The other atomic orbital coefficients are zero for HOMO. [c] Reference 9. [d] Para isomer was the only product isolated for 1-ethoxy-1,3-butadiene.[5]

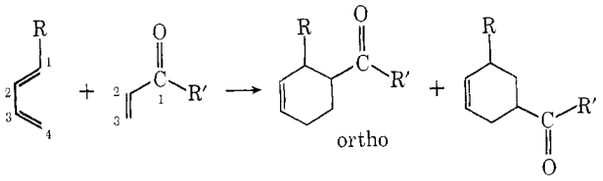
TABLE II

ISOMER RATIOS AND P_z COEFFICIENTS OF HOMO FOR 1-SUBSTITUTED 1,3-BUTADIENES

Substituent[a]	Ratio of ortho:meta	P_z coefficients[b] C-1	C-2	C-3	C-4
CH_3	9:1[c]	0.531	0.456	0.350	0.534
COOH	8.8:1[d]	0.483	0.384	0.314	0.460
C_6H_5	39:1[d]	0.408	0.443	0.230	0.416
p-$NO_2C_6H_4$	*e*	0.424	0.426	0.247	0.419

[a] Registry numbers are, respectively, 504-60-9, 626-99-3, 1515-78-2, 20264-89-5. [b] These are absolute values. The other atomic orbital coefficients are zero. [c] Reference 9. [d] Reference 5. [e] The ortho isomer was the only product isolated (71%).[10]

which is contrary to experimental evidence. In these cases (**2a–d**) it is well known[5,9,10] that the ortho isomer



2a, R = CH_3; R′ = OCH_3
b, R = C_6H_5; R′ = OCH_3
c, R = COOH; R′ = OH
d, R = *p*-$NO_2C_6H_4$; R′ = OH

dominates. We have found that the preferred regioisomers can still be predicted by considering the secondary orbital interactions between the C-2 and C-3 positions of the diene and the position C-1 of the dienophile in the endo transition state.[11] In these cases the C-2 HOMO coefficients are significantly larger than their corresponding C-3 coefficients (Table II). Thus, the stabilization of the endo transition is greater when C-1 of the dienophile is near the secondary position C-2 of the diene, yielding the ortho isomer.

By similar analysis, the secondary orbital interactions in the endo transition state of the 2-substituted 1,3-butadienes favor the meta isomer instead of the experimentally preferred para isomer. This indicates the greater importance of the terminal orbital interactions in determining regioselectivity.

Consideration was also given to the substituent effect on the HOMO–LUMO splitting on the diene. For all cases but the reaction of 1-carboxy-1,3-butadiene with acrylic acid, the HOMO diene–LUMO dienophile inter-

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(6) Small changes in bond angles and bond distances effect the magnitudes of the coefficients and orbital energies only in the third decimal place.

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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

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

R	$pK_a^{lit.}$	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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