hancement of acid strength for the carbon acids may occur due to the altered hybridization at the anionic carbon atom to an orbital with significantly enhanced s character.

Registry No. 1, 15194-58-8; 2, 25013-41-6; 3, 25012-80-0; 4, 65114-21-8; 5, 1724-45-4; 6, 60211-41-8; 7, 96666-81-8; 8, 89849-43-4; 9, 89849-42-3; 10, 96666-82-9; 11, 96688-77-6; 12, 96666-83-0.

Supplementary Material Available: Figure 3, showing the optimized geometries for all carbanions (5 pages). Ordering information is given on any current masthead page.

Theoretical Studies of the Regiospecificity of Diels–Alder Additions to Isoquinolinequinone

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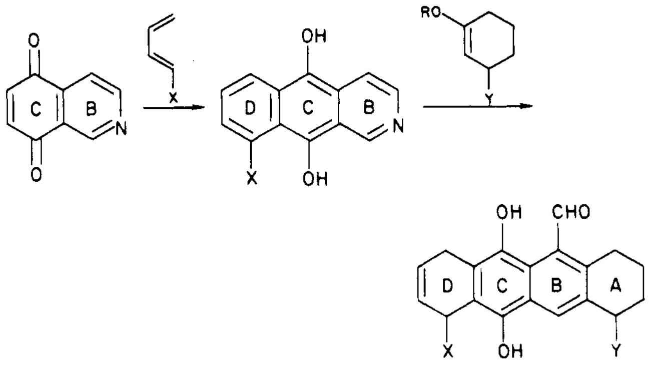
The MNDO approximation to molecular orbital theory is used to calculate the properties of isoquinolinequinone alone, as well as protonated or complexed with BF_3, at each oxygen or nitrogen. Frontier orbital theory is applied to the calculated species to illustrate how changes in regiospecificity of the Diels–Alder reaction might be anticipated as a function of the site of interaction and nature of the complexing acid. Another test of the regioselectivity was made by using the biradical model for the reaction mechanism. Radical localization energies were calculated by adding a hydrogen atom to each of the neutral and protonated species at each of the two reactive centers. Suggestions are made concerning experimental variables, particularly the choice of the diene and the acidity of the medium, that might be used to control regiospecificity in these reactions.

The Diels–Alder reaction is widely used in synthetic organic chemistry as a method of forming new rings. One of the most important reasons for its widespread use is the high regiospecificity that is often observed for these reactions. Control of this regiospecificity is a determining factor in designing successful synthetic procedure.

Several important theoretical studies of the Diels–Alder reaction have appeared in the literature[1–4]. The question of whether or not the reaction between ethylene and butadiene is synchronous or not has been studied by Dewar[2] and Salem[1] who reached different conclusions based upon potential surfaces calculated by using different MO methods. Theoretical studies of selectivity have more often been restricted to less expensive techniques, such as applications of perturbation theory to the MO's of the interacting molecules.[5,6,3] Frontier orbital theory,[7,8] one of the more sophisticated perturbation techniques, has been previously applied to several examples of the Diels–Alder reaction with success.[6,3,4]

Salts of isoquinolines have recently been shown to be useful synthetic intermediates because their heterocyclic rings serve as dienes in regiospecific Diels–Alder reactions that fuse new carbocyclic rings to the aromatic framework.[9–12] A synthetic plan could use the quinone portion of the subject isoquinolinequinone as a dienophile. Subsequently, the heterocyclic ring could be used as a diene. The outcome of these successive cycloadditions would be the fusion of the outermost A and D rings of naphthacene to the central B and C rings. It is important to control the regiospecificity of these reactions, if they are to be generally useful.



In this paper we present a theoretical study of the regiospecificity of the Diels–Alder reaction for the particular dienophile isoquinolinequinone, 1. This compound differs from 1,4-naphthoquinone only in the substitution of a nitrogen for a carbon at a position remote from the center of dienophilic activity. Compound 1 does not contain a plane of symmetry bisecting the dienophilic bond, but the effect of the nitrogen on this bond should be small. Thus, based purely on frontier orbital arguments, one would not expect a large Diels–Alder selectivity when 1 is used as a

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(4) (a) Gleiter, R.; Bohm, M. C. *Pure Appl. Chem.* **1983**, *55*, 237. (b) Zhixing, C. *Theor. Chim. Acta* **1983**, *62*, 293. (c) Alston, P. V.; Gordon, M. D.; Ottenbrite, R. M.; Cohen, T. *J. Org. Chem.* **1983**, *48*, 5051. (d) Blain, M.; Odiot, S.; Martin, G. J.; Gouesnard, J. P.; Chalvet, O. *Tetrahedron*, **1980**, *36*, 2775. (e) Oliva, A.; Fernandez-Alonso, J. I.; Bertran, J. *Tetrahedron* **1978**, *34*, 2029. (f) Eisenstein, O.; Lefour, J. M.; Anh, N. T.; Hudson, R. F. *Tetrahedron* **1978**, *34*, 523. (g) Feuer, J; Herndon, W. K.; Hall, L. H. *Tetrahedron*, **1968**, *24*, 2575.

(5) Salem, L. *J. Am. Chem. Soc.* **1968**, *90*, 553.

(6) Houk, K. N. *J. Am. Chem. Soc.* **1973**, *95*, 4092.

(7) Houk, K. N. *Acc. Chem. Res.* **1975**, *8*, 361.

(8) Fleming, I. "Frontier Orbitals and Organic Chemical Reactions"; Wiley: New York, 1976.

(9) Falck, J. R.; Manna, S.; Mioskowski C. *J. Am. Chem. Soc.* **1983**, *105*, 631.

(10) Manna, S.; Falck, J. R.; Mioskowski, C. *J. Org. Chem.* **1982**, *47*, 5021.

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(12) Franck, R. W.; Gupta, R. B. *Tetrahedron Lett.* **1985**, *24*, 293.

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Table I. Heats of Protonation

species	heat of formation	relative heat of protonation, kcal/mol
1	-14.77	
2a	153.34	0.00
2b	153.45	0.11
2c	158.17	4.83
3a	-268.20	0.00
3b	-266.72	1.48
3c	-265.80	2.40

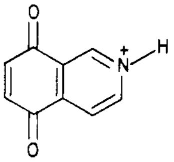
dienophile. A recent report confirms this expectation as the reaction of 1-methoxycyclohexadiene with 1 yields only a 2.8:1 mixture of the possible products.[13]

In principle, complexation of 1 with acid can occur at the nitrogen or either of the two oxygens. Any of these interactions will increase the polarization of the dienophilic bond. At the same time, these interactions should increase the dienophilic activity of 1 by lowering the LUMO (lowest unoccupied molecular orbital), thereby decreasing the energy difference between it and the HOMO (highest occupied molecular orbital) of the diene, which are the two interacting frontier orbitals.[14]

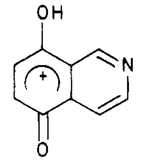
In this study we report the relative energies of interaction of 1 with protons and BF_3 at each of three basic sites, as well as, two different models for the regiospecificity of interaction of the protonated and neutral species with dissymmetric dienes.

Methods

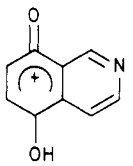
Molecular orbital calculations were performed by using the MNDO approximation of molecular orbital theory[15] on 1, its three possible conjugated Brønsted acids, **2a–c**, and its three possible complexes with BF_3, **3a–c**. The geometries were completely optimized for all species with following exceptions. The structure of 1 was constrained to be planar in all its complexes except for the proton or BF_3 that is attached. The BF_3 was, also, assumed to have local C_{3v} symmetry. Radical localization energies were calculated for the attachment of a hydrogen atom at C_1 and C_2 of 1 and **2a–c**. The resulting radicals were completely optimized (in up to 38 independent degrees of freedom) with the constraint that they be planar except for the CH_2 and the proton on N or O.



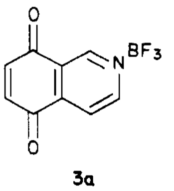
2a



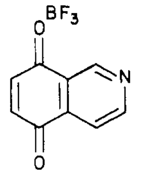
2b



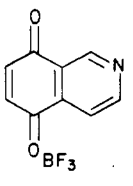
2c



3a



3b



3c

Results and Discussion

The heats of formation of the various closed shell species and their relative energies of complexation are presented in Table I, while the LUMO energies and coefficients for C_2 and C_3 are presented in Table II, and local charge density and dipole moments appear in Table III. Table IV gives the radical localization energies of 1 and **2a–c**. Figure 1 gives the numbering scheme for the structures.

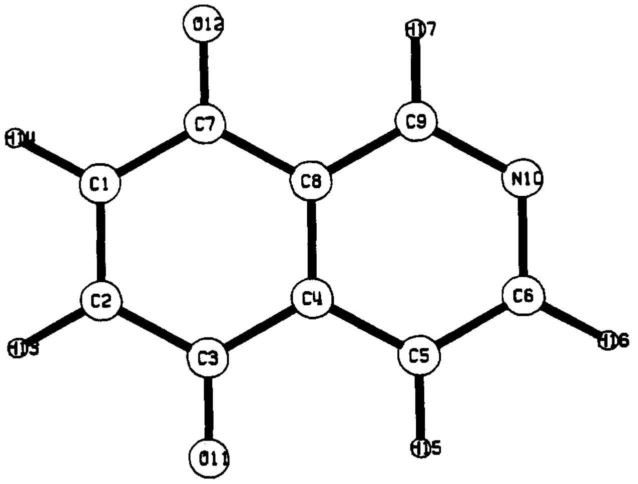


Figure 1. Numbering system for isoquinolinequinone used in the calculations.

Table II. LUMO Characteristics

species	LUMO energy, eV	LUMO at C_1, eV	LUMO at C_2, eV
1	-1.6316	0.3102	-0.3001
2a	-6.5118	0.0762	-0.0450
2b	-7.0310	0.1058	-0.4088
2c	-7.2256	-0.4500	0.0805
3a	-2.5065	0.2254	-0.2034
3b	-2.8408	-0.2471	0.3547
3c	-2.8580	-0.3754	0.2359

Table III. Charge Distributions

species	charge at C_1	charge at C_2	charge at C_4	charge at C_6	charge at N	P_z density at N
1	-0.080	-0.090	-0.050	0.076	-0.224	1.1441
2a	-0.065	-0.068	0.050	0.150	-0.137	1.4792
2b	-0.195	0.090	-0.013	0.196	-0.227	1.1591
2c	0.126	-0.219	-0.115	0.091	-0.154	1.0772
3a	-0.072	-0.088	-0.009	0.145	-0.192	1.2998
3b	-0.111	0.035	-0.035	0.111	-0.223	1.1488
3c	-0.018	-0.126	-0.081	0.080	-0.203	1.1243

Table IV. Hydrogen Localization Energies

species	radical site	protonated on	ΔH_f	ΔH of hydrogen localization	rel ΔH of hydrogen localization
1	C_1		-11.4	40.7	0.0
1	C_2		-11.2	40.9	0.2
2a	C_1	N	160.7	212.8	3.4
2a	C_2	N	157.3	209.4	0.0
2b	C_1	O_{12}	164.0	216.1	6.7
2b	C_2	O_{12}	159.5	211.6	2.2
2c	C_1	O_{11}	164.4	216.5	7.1
2c	C_2	O_{11}	170.9	223.0	13.6

As one would expect from the remoteness of the nitrogen causing the dissymmetry of 1 compared to 1,4-naphthoquinone, neither the orbital coefficients of the P_z orbitals of C_1 and C_2 in the LUMO of 1 (0.3102 and -0.3001, respectively) nor the local charge densities on these same carbons (-0.080 and -0.090) are very different in magnitude. The low selectivity of the Diels–Alder reaction[13] with 1 is not, therefore, surprising. Protonation of 1 at any of the three positions considered, however, has a considerable effect upon the polarization of both the LUMO and the charge distribution, as can be seen from Tables II and III.

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[13] Potts, K. T; Bhattacharjee, D.; Walsh, E. B. *J. Chem. Soc., Chem. Commun.* **1984**, 114.

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The heats of protonation of **1** at the nitrogen and at O_{12} are predicted to be almost identical, while that at O_{11} is predicted to be almost 5 kcal/mol higher (see Table I). The explanation for this behavior is clear from the fact that protonation of either O_{11} or O_{12} leads to an extensively delocalized π cation. However, protonation at O_{11} leads to a cation which has one of its principal resonance structures containing the positive charge localized at the nitrogen while protonation at O_{12} does not. This same phenomenon is also reflected in the local charges (–0.154 and –0.227) and the P_z orbital densities (1.0772 and 1.1591) at nitrogen for protonation at O_{11} or O_{12}, respectively. Protonation at nitrogen leads to a σ-cation, with some π-stabilization (the P_z density at nitrogen is 1.4792), as in protonated pyridine.

Similar behavior is predicted for complexation with BF_3. The most significant differences are the greater selectivity for complexation at nitrogen for BF_3 relative to protons. This tendency is understandable as BF_3 complexation involves less positive charge transfer to the base than does protonation. The optimal ability of **2c** to delocalize the positive charge is what makes O_{12} competitive with the N as a basic site. The lower amount of charge delocalization in **3a–c** lessens the importance of this effect. Nevertheless, the enthalpies of **3a** and **3b** are similar enough for the arguments made for **2a–c** to be reasonably applicable here.

If the entropies of protonation and the free energies of solution be the same for all three positions, then one would expect the pK_a's for the three conjugate acids to be in the order **2c** > **2b** ≥**2a**. These conditions are unlikely to be met for several reasons. The charge is distributed somewhat differently for the three cations, as indicated by the dipole moments of Table III. Also the solvents used in a protonating medium will necessarily be different from those in which BF_3 is used as the acid. Therefore, solvation and entropic effects are likely to be the controlling factors for the relative basicities of **2a**,**b**, in particular.

Frontier orbital theory approximates the interaction of the diene and dienophile by using the techniques[8] of perturbation theory. In this model for reactivity, the stabilizing, second-order interaction between the diene and dienophile is proportional to the diene HOMO and the dienophile LUMO divided by the energy differences between these two orbitals. It is instructive to examine the orbital energy difference and overalp individually. Clearly, the lower the LUMO energy of the dienophile, the smaller will be the LUMO – HOMO energy difference with a given diene and the more reactive it should be. Thus, the protonated species, **2a–c**, should all be more reactive than the BF_3 complexes, **3a–c**, or isoquinolinequinone, itself, **1**. For both **2a–c** and **3a–c**, interaction of the acid at N leads to the species with the highest LUMO, while interaction at O_{11} leads to the lowest LUMO (although the difference in the LUMO's of **3b** and **3c** is not significnt). Thus, the LUMO energies favor the reactivities of the complexes in the reverse order of their stabilities.

The overlap of the diene and a given dienophile will be proportional to the LUMO coefficients at the reactive positions of the dienophile. These magnitudes also disfavor the reactivity of **2a** and **3a** at the C_1–C_2 double bond relative to its competitors.

If one imagines the dienophiles reacting with dienes of increasing reactivity, the relative change for $E_{\text{LUMO}} - E_{\text{HOMO}}$ will be greatest for the diene with the highest HOMO. Thus, frontier orbital theory would predict that more reactive dienes should have increased selectivity for the less stable conjugate acids in the Diels–Alder reaction. These factors should tend to increase the reactivity of **2c** relative to **2b**, and both **2b** and **3b** relative to **2a** and **3a** as the interacting diene becomes increasingly reactive.

The radical localization energies compiled in table IV suggest that attack on C_2 be more favorable for **2a** and **2b** but not for **2c**. The negligible difference in energy between **2a** and **2b** increases to 2.2 kcal/mol upon radical attack at C_2. The favored position of radical attack upon **2c** is seen to be at C_1, but attack upon **2c** is much less favorable than upon **2a** or **2b**. The dominating effect upon the relative energetics of these radical cations appears to be the avoidance of resonance structures that place the radical and (π) cationic sites, which clearly cannot easily stabilize each other, on adjacent positions in the ring. Protonation of the nitrogen leads to an increase of π-density on the N, favoring unpaired electron density on adjacent carbons.

Although the Diels–Alder reaction is usually thought to be concerted, there is probably a considerable amount of biradical character in the transition state, particularly for reaction of unsymmetrical dienes and/or dienophiles. It has been suggested that this reaction might even have a biradical intermediate.[16] The regiospecificity can often be predicted by examining the relative energies of the possible biradical intermediates that could be hypothetically formed. When this model for the transition state is used and isoquinolinequinone is the dienophile, there is no predicted regiospecificity, as the radical localization energies for **1** are virtually identical. Here the frontier orbital approach and radical localization model lead to similar predictions. When protonated isoquinolinequinone is the dienophile, the situation becomes more complicated. The two most favorable protonated transition states suggest that the preferred intial attack should be at C_2. On the other hand, frontier orbital theory predicts selectivity for attack at C_2 with a poor diene, selectivity for attack at C_1 with a reactive diene (assuming that **2b** not **2a** is the more important intermediate for reaction with a poor diene).

The apparent differences in the predictions of the regioselectivity of the reaction can be understood upon consideration of the thermodynamics of the reaction; therefore, upon the choice of the diene. An active diene, that undergoes a highly exoergonic Diels–Alder reaction, should react via an early transition state. In such a case, little bond forming can be expected to take place, the transition state resembles the reactants, and frontier orbital theory should be effective. For the case of a relatively inactive diene, which underoges Diels–Alder reactions with some difficulty and is only mildly exoergonic, the transition state should be later along the reaction path. In such a transition state, a significant amount of bond forming can be expected, making the radical localization model more useful for predicting the regiospecificity. The radical localization model makes the same prediction as the frontier orbital model with a poor diene. As reaction of a poor diene will proceed via a late transition state, the frontier orbital and radical localization models are seen to agree.

The extreme fecundity of synthetic organic chemistry finds its origin in the diversity of possible reactions available to many reactants and in the increasing mastery of the control of these reactions. The present example typifies a situation where, in principle, either of the two possible regioselectivities ought to be obtainable by proper control of the acidifying medium and the activity of the diene. Thus, all possible products ought to be attainable through judicious choice of reagents. The present level

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[16] Firestone, R. A. *J. Org. Chem.* **1972**, *37*, 2181.

of MO theory clearly cannot make quantitiative predictions for reactions that will undoubtably involve differential solvation of the various species studied. Nevertheless, MO theory can be quite useful for identifying those instances where competing reaction paths might be of similar energies and suggesting what changes in reaction design might be successful in changing the relative importance of the different pathways.

Acknowledgment. This work was supported in part by grants from the City University of New York PSC-CUNY Research Award Program CA-37359 from the National Cancer Institute, DHHS, and CH-272 from the American Cancer Society.

Registry No. 1, 50-46-4; **2a**, 96649-31-9; **2b**, 96649-32-0; **2c**, 96649-33-1; **3a**, 96666-24-9; **3b**, 96666-25-0; **3c**, 96666-26-1.

Regiospecific A,B Capping onto β-Cyclodextrin. Characteristic Remote Substituent Effect on ^{13}C NMR Chemical Shift and Specific Taka-amylase Hydrolysis

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Received December 31, 1984

A,B-regiospecific (97% A,B and 3% A,C) capping of β-cyclodextrin was first achieved by the use of *m*-benzenedisulfonyl chloride. The A,B regiochemistry is ascertained by a remarkable effect of a remote substituent of ring A on the high-field ^{13}C NMR chemical shift of ring B. Further support for the A,B structure is obtained by its specific hydrolysis to disubstituted fragmental sugars catalyzed by Taka-amylase. The novel cap was converted to a series of A,B-disubstituted β-cyclodextrins—diiodo, dideoxy, bis(butylsulfenyl), bis(phenylsulfenyl), and bis((*p-tert*-butylphenyl)sulfenyl). Characteristic remote chemical shifts in 100-MHz ^{13}C NMR were observed for these A,B derivatives, the C_6, C_4, and C_1 shifts of which were extremely useful for the differentiation of an A,B regioisomer from other regioisomers. Noteworthy is the remarkable chemical shift difference thus produced between C_6, C_4, and C_1 on the A ring and C_6, C_4, and C_1 on the B ring, providing an interesting possibility of spectroscopic determination of clockwise and counterclockwise A,B structure.

A basic principle showing how enzyme activity develops may be given by eq 1. For preparation of an artificial

$$\text{(enzyme activity)} = \text{(guest recognition)}^1 + \text{(multifunctional catalysis)} + \text{(local environment)} \quad (1)$$

multifunctional catalyst having certain specific enzymic activity, specific three-dimensional arrangement of two (or more) functional groupings is necessary and important. The geometrical arrangement may be classified into the limiting conformations, *E*, *R*, and *Z*, shown in Figure 1.

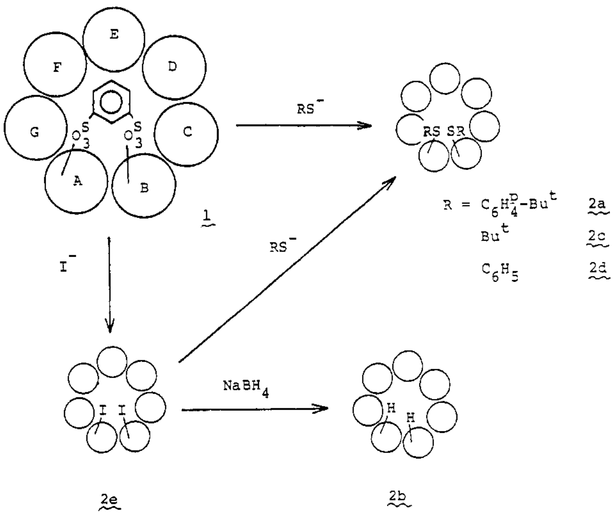
Disubstituted β-cyclodextrins have been used successfully as artificial enzymes.[2] The cyclodextrin cavity provides an effective recognition site as well as an appropriate local environment and the functional groups provide an effective catalytic site. Disubstituted β-cyclodextrins were conveniently prepared through regiospecific bifunctionalization at A,C[3a,c] or A,D[3] positions (see Scheme I), which are close to the *R* and *E* regiochemistry, respectively.

We now report that regiospecific A,B bifunctionalization is achieved in good preparative yield by use of *m*-benzenedisulfonyl chloride as the capping reagent. The A,B cap should be a good starting material for the preparation of a variety of artificial enzymes each of which has functional groups on the primary rim in the *Z* regiochemistry.

Results and Discussions

The A,B cap, 1, was prepared from *m*-benzenedisulfonyl chloride and dry β-CD in dry pyridine. Practically pure 1 was obtained in 40% preparative yield. Precaution must be taken not to use too much (≫30 mol %) of the A,B capping reagent, which easily leads to the formation of double caps and a triple cap in a nearly statistical ratio. When an appropriate amount of the capping reagent is used, the A,B capping is found to be a convenient and efficient procedure.

Scheme I. A,B Regiospecific Functionalization of β-Cyclodextrin



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† Responsible for Taka-amylase-catalyzed hydrolysis.

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(2) (a) Breslow, R.; Doherty, J. B.; Guillot, G.; Lipey, C. *J. Am. Chem. Soc.* **1978**, *100*, 3227. (b) Breslow, R.; Bovy, P.; Hersh, C. L. *Ibid.* **1980**, *102*, 2115. (c) Tabushi, I; Kuroda, Y.; Mochizuki, A. *Ibid.* **1980**, *102*, 1152. (d) Tabushi, I.; Kuroda, Y. *Ibid.* **1984**, *106*, 4580.

(3) (a) Tabushi, I.; Kuroda, Y.; Yokota, K.; Yuan, L. C. *J. Am. Chem. Soc.* **1981**, *103*, 711. (b) Tabushi, I.; Yuan, L. C. *Ibid.* **1981**, *103*, 3574. (c) Tabushi, I.; Yamamura, K.; Nabeshima, T. *Ibid.* **1984**, *106*, 5267.