Merostabilization of Biradicaloid Intermediates as a Factor in Determining Rates and Regioselectivity in [4 + 2] Cycloaddition Reactions of Reissert Hydrofluoroborate Salts with Alkenes and Alkynes

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Reactions of 2-benzoyl-1,2-dihydroisoquinaldonitrile hydrofluoroborate with ethylene, acetylene, 1-hexyne, 1-phenylpropene, and *cis*-stilbene have been carried out. Also, reactions of 2-benzoyl-1-cyano-1,2-dihydrophthalazine and 2-benzoyl-1,2,3,4-tetrahydroisoquinaldonitrile hydrofluoroborates, respectively, with dimethyl acetylenedicarboxylate and with ethyl phenylpropiolate have been effected. The structures of most of the products have been established by unambiguous, independent syntheses. The kinetics of these reactions and of several additional ones reported previously have been measured. Arguments are presented that the rate and orientation data of these particular [4 + 2] cycloaddition reactions are better rationalized by invoking the concept of the formation of merostabilized biradicaloid intermediates than by invoking the concept of orbital symmetry allowed concerted ring closures.

The controversy between concerted and biradicaloid pathways for both Diels–Alder and 1,3-dipolar cycloaddition continues unabated on both the theoretical[2-8] and experimental fronts.[9-11] In our most recent previous paper,[12] we pointed out that, in the reactions of Reissert hydrofluoroborate salts with alkenes, we could rationalize and predict the more pronounced regiochemical results by consideration of relative stabilities of possible spin-paired diradicals formed in the initial Diels–Alder reaction, supplemented by consideration of obvious steric effects. In view of this and because Firestone[13] has spelled out possible experimental criteria to enable one to distinguish between the biradicaloid and synchronous mechanisms of [4 + 2] cycloaddition reactions, we have set out to examine thoroughly our own data, both old and new, in terms of Firestone's criteria.

New Reactions of Reissert Hydrofluoroborates with Alkenes

Evidence has been presented that solutions of the hydrofluoroborate salts of 2-acyl-1,2-dihydroisoquinaldonitriles (Reissert compounds) consist of equilibrium mixtures of **1**, **3**, and **4** (Chart I), the latter being the major component.[14-16] These salts are also presumed to be in equilibrium with the original Reissert compound, the 1,3-dipolar compound **2** (a mesoionic compound), and fluoroboric acid. Several studies of 1,3-dipolar addition reactions of hydrofluoroborate salts of Reissert compounds have been reported.[17-20] Numerous examples of complex, acid-catalyzed condensation–rearrangement reactions, which presumably involve an initial Diels–Alder type of cycloaddition of the olefin to the isomeric form **4** of the Reissert salt, together with detailed mechanisms of reaction have been provided.[12,17,21-26]

Chart I

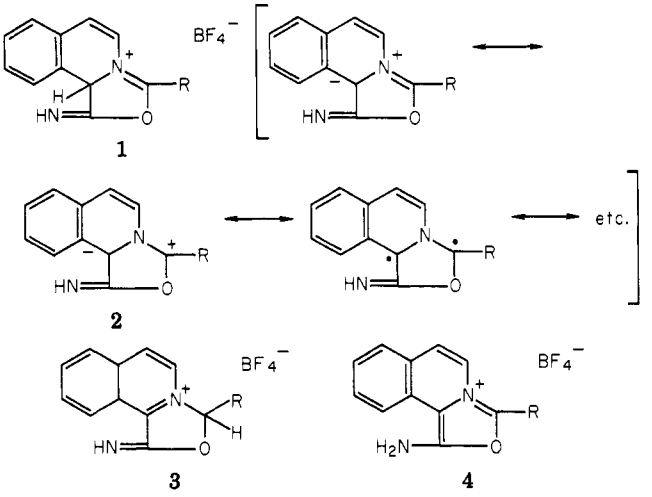

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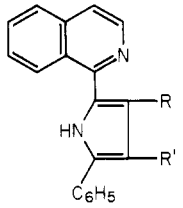
Table I. Rate Data for Reactions of Reissert Hydrofluoroborate Salts with Alkenes and Alkynes in DMF Solution

reissert hydrofluoroborate	alkene or alkyne	temp, °C	10^5k, L mol^{-1} s^{-1}
4 (R = C_6H_5)	ethyl acrylate	−20.0	863 ± 2
4 (R = C_6H_5)	styrene	−20.0	150 ± 1
4 (R = C_6H_5)	diethyl maleate	50.0	280 ± 8
4 (R = C_6H_5)	1-hexene	30.0	14.7 ± 0.2
4 (R = C_6H_5)	1-phenylpropene	30.0	10.0 ± 0.2
4 (R = C_6H_5)	cyclohexene	50.0	3.00 ± 0.16
4 (R = C_6H_5)	*trans*-stilbene	90.0	33.5 ± 0.5
4 (R = C_6H_5)	phenylacetylene[a]	0.0	2.67 ± 0.33
4 (R = C_6H_5)	diphenylacetylene[a]	90.0	7.15 ± 0.02
4 (R = C_6H_5)	ethyl phenylpropiolate[b]	52.3	5.62 ± 0.12
11 (R = C_6H_5)	ethyl phenylpropiolate[b]	52.3	2.74 ± 0.12
14 (R = C_6H_5)	ethyl phenylpropiolate[b]	52.3	0.651 ± 0.030

[a] Nonequilibrium reaction.[18] [b] Equilibrium reaction.[18]

We have now carried out cycloaddition reactions of 2-benzoyl-1,2-dihydroisoquinaldonitrile hydrofluoroborate (4, R = C_6H_5) with ethyl acrylate, diethyl maleate, *cis*-stilbene, *trans*-stilbene, and ethylene. The most successful of these reactions was that with ethyl acrylate, ethyl 2-(1-isoquinolyl)-5-phenylpyrrole-3-carboxylate, **9a**, being



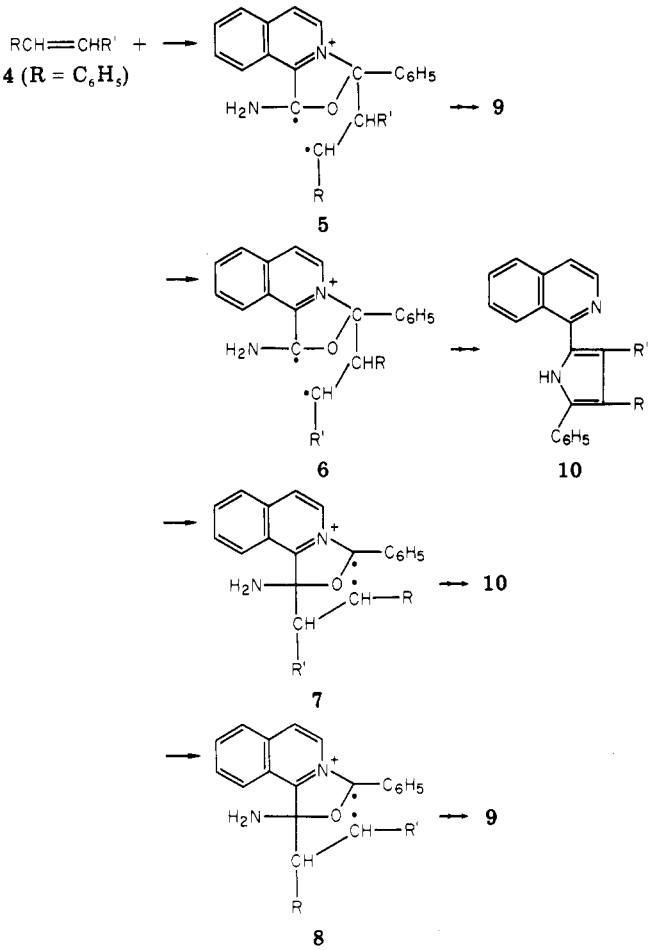
9a, R = CO_2Et; R′ = H
b, R = H; R′ = CO_2Et
c, R = R′ = CO_2Et
d, R = R′ = C_6H_5
e, R = R′ = H
f, R = C_6H_5; R′ = H
g, R = *n*-Bu; R′ = H
h, R = C_6H_5; R′ = CO_2Et

obtained in 71% yield at 60 °C with a 6-h reaction period and with 2 equiv of the alkene being employed. (Even at −20 °C, the yield of **9a** was 52%.) We could find no evidence for formation of the isomeric product, ethyl 2-(1-isoquinolyl)-5-phenylpyrrole-4-carboxylate (**9b**).

With the remaining alkenes, all of which are symmetrical, the problem of orientation did not arise. The reaction of 4 (R = C_6H_5) with diethyl maleate gave diethyl 2-(1-isoquinolyl)-5-phenylpyrrole-3,4-dicarboxylate (**9c**) in 40% yield under the same conditions as those described previously for the ethyl acrylate reaction, which we will henceforth refer to as the standard conditions. (At −20 °C, the yield dropped to 15%; at 60 °C during a 48-h reaction period, the yield increased slightly to 44%). The reaction of 4 (R = C_6H_5) with *trans*-stilbene under the standard conditions gave 2-(1-isoquinolyl)-3,4,5-triphenylpyrrole (**9d**) in 30% yield (39% at 90 °C). With *cis*-stilbene, the yield of **9d** under the standard conditions was but 4% (which could be raised to 23% by use of 30 equiv of *cis*-stilbene at 100 °C for 24 h).

The reaction of 4 (R = C_6H_5) with ethylene was carried out in Me_2SO solution at 25 °C, the gaseous alkene being bubbled through the solution for various periods of time. A 24-h reaction period afforded 2-(1-isoquinolyl)-5-phenylpyrrole (**9e**) in 24% yield. The use of DMF as solvent in place of Me_2SO had little effect on the yield.

Scheme I. Biradicaloid Intermediates in Reactions of 4 (R = C_6H_5) with Alkenes[a]



[a] See ref 12 for detailed equations.

We also measured the rates of reaction of some of the alkenes mentioned above, as well as several others discussed in a previous paper,[12] with 4 (R = C_6H_5). The results are summarized in Table I. The apparent order of decreasing reactivity of the alkenes in this reaction is ethyl acrylate > styrene > diethyl maleate > 1-hexene > 1-phenylpropene > cyclohexene, *trans*-stilbene.

The two major factors affecting this order might possibly be steric interactions in and the delocalization energy of the transition state leading to formation of each unstable biradicaloid intermediate. Where unsymmetrical alkenes are involved, four possible unstable biradicaloid intermediates must be taken into consideration, as shown in Scheme I. It is also assumed that the steric interactions

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and delocalization in each of the unstable biradicaloid intermediates 5–8 parallel the same features in the respective transition states leading to the biradicaloid intermediates. The use of these concepts permits us to rationalize both the rate data and orientation effects cited previously.

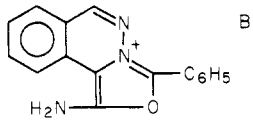
For example, for the most rapid (and either regiospecific or highly regioselective) reaction of the series, that with ethyl acrylate, let us set R = CO_2Et and R′ = H. Clearly, there will be much less delocalization energy for **6** than for **5** and less for **8** than for **7**.

It would not be difficult to decide that **5** is more stable than **7** on the basis of merostabilization theory (to be discussed later). Therefore, one would predict that the transition state leading to **5** would be of lowest energy, and general structure **9** (which is equivalent to **9a** in this illustration) would be formed preferentially, which is in accord with the facts. The analysis of the styrene reaction is similar and leads to the correct prediction that 2-(1-isoquinolyl)-3,5-diphenylpyrrole (**9f**) would be the major (or even exclusive) product.[12] Steric considerations will be discussed later.

Bhattacharjee and Popp[27] have reported the reactions of 1-cyano-2-benzoyl-1,2-dihydrophthalazine hydrofluoroborate (**11**) with several alkenes to produce the expected 2-(1-phthalazyl)pyrroles. For example, the reaction with styrene in DMF at 150 °C for 24 h gave 2-(1-phthalazyl)-3,5-diphenylpyrrole in 53% yield. As mentioned previously, we had obtained the analogous compound, 2-(1-isoquinolyl)-3,5-diphenylpyrrole (**9f**) in 48% yield by reaction of **4** (R = C_6H_5) with styrene in DMF at −20 °C for 6 h. There would seem to be no valid qualitative basis for differentiation between the relative energies of the possible phthalazyl–styrene biradicaloid adducts and **5–8** (R = C_6H_5; R′ = H), and roughly equivalent yields of the major product in the two reactions would be anticipated.

New Reactions of Reissert Hydrofluoroborates with Alkynes

In new work on 1,3-dipolar addition reactions of Reissert hydrofluoroborate salts with alkynes, we have found that acetylene undergoes reaction with **4** (R = C_6H_5) in either DMF or Me_2SO to give 3-phenylpyrrolo[2,1-*a*]isoquinoline (**12**, R = R′ = H), a known compound.[19] The yield of the



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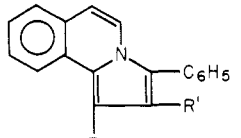

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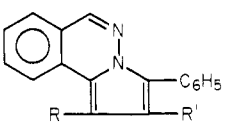
product was but 10% when acetylene was bubbled through a solution of **4** in DMF for 80 h at 25 °C. The use of Me_2SO in place of DMF provided a 19% yield of **12** (R = R′ = H) under the same conditions.

The reaction of **4** (R = C_6H_5) with 1-hexyne gave 1-*n*-butyl-3-phenylpyrrolo[2,1-*a*]isoquinoline (**12**, R = *n*-Bu; R′ = H) in 26% yield when a ninefold excess of the alkyne was used in DMF at 55 °C for 48 h. In a competing reaction involving an initial Diels–Alder cycloaddition, 2-(1-isoquinolyl)-3-*n*-butyl-5-phenylpyrrole (**9g**), a known compound,[12] was also obtained in 3% yield. An explanation for the occurrence of such competing reactions has been offered previously.[21] Under the conditions previously employed for the reaction of **4** (R = C_6H_5) with styrene, no apparent reaction occurred with either 1-phenylpropyne or 2-hexyne.

Although Bhattacharjee and Popp[27] have correctly reported the results of the reaction of 1-cyano-2-benzoyl-1,2-dihydrophthalazine hydrofluoroborate (**11**) with dimethyl acetylenedicarboxylate and with ethyl phenylpropiolate, they neither proved the structures of the products in an unambiguous manner nor did they investigate the kinetics of these reactions. Such work had previously been carried out by Wang.[28] Therefore, we are providing a summary of Wang's data here.

The reaction of **11**[14] with dimethyl acetylenedicarboxylate in DMF at 80 °C for 24 h gave dimethyl 3-phenylpyrrolo[2,1-*a*]phthalazine-1,2-dicarboxylate (**13**, R = R′ = CO_2Me) in 75% yield. (Bhattacharjee and Popp[27] reported that they obtained the same compound in 83% yield.) Saponification of the ester by the action of alcoholic potassium hydroxide gave 3-phenylpyrrolo[2,1-*a*]-phthalazine-1,2-dicarboxylic acid (**13**, R = R′ = CO_2H) in 87% yield. Decarboxylation of the diacid in quinoline containing copper chromite afforded 3-phenylpyrrolo-[2,1-*a*]phthalazine (**13**, R = R′ = H) in 94% yield. An independent synthesis of **13** (R = R′ = H) was achieved in 47% yield by phosphoric acid catalyzed hydrolysis and decarboxylation of 3-phenylpyrrolo[2,1-*a*]phthalazine-2-carboxamide (**13**, R = H; R′ = $CONH_2$), the latter compound having been prepared in 52% yield by base-catalyzed condensation of 1-cyano-2-benzoyl-1,2-dihydrophthalazine with acrylonitrile.

The reaction of **11** with ethyl phenylpropiolate in methylene chloride–DMA solution under reflux for 15 h gave ethyl 1,3-diphenylpyrrolo[2,1-*a*]phthalazine-2-carboxylate (**13**, R = C_6H_5; R′ = CO_2Et) in 73% yield.



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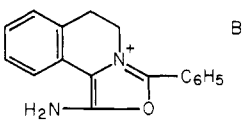
(Bhattacharjee and Popp[27] obtained the same compound in 72% yield.) Saponification of the ester afforded 1,3-diphenyl[2,1-*a*]phthalazine-2-carboxylic acid (**13**, R = C_6H_5; R′ = CO_2H) in 92% yield, and decarboxylation of the acid provided 1,3-diphenylpyrrolo[2,1-*a*]phthalazine (**13**, R = C_6H_5; R′ = H) in 93% yield. An independent synthesis of **13** (R = C_6H_5, R′ = H) was achieved in 27% yield by phosphoric acid catalyzed hydrolysis and decarboxylation of 1,3-diphenylpyrrolo[2,1-*a*]phthalazine-2-carboxamide (**13**, R = C_6H_5; R′ = $CONH_2$) which had been prepared in 21% yield by base-catalyzed condensation of 1-cyano-2-benzoyl-1,2-dihydrophthalazine with cinnamonitrile.

2-Benzoyl-1,2,3,4-tetrahydroisoquinaldonitrile hydrofluoroborate[14] (**14**) was treated with dimethyl acetylenedicarboxylate to give dimethyl 4,5-dihydro-3-phenylpyrrolo[2,1-*a*]isoquinoline-1,2-dicarboxylate (**15**, R = R′ = CO_2Me) in 66% yield. The reaction of **14** with ethyl



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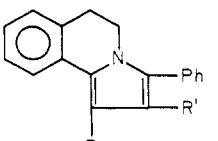

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Table II. pK_a Values for Reissert Hydrofluoroborate Salts in Methanol at 27.5 °C

Reissert hydrofluoroborate	pK_a
4 (R = methyl)[21]	4.80 ± 0.10
4 (R = benzyl)[53]	4.85 ± 0.05
4 (R = cyclopropyl)[21]	5.00 ± 0.10
4 (R = *m*-ClC_6H_4)[18]	5.60 ± 0.10
4 (R = phenyl)[19]	5.80 ± 0.10
4 (R = *p*-$MeOC_6H_4$)[18]	6.15 ± 0.05
11 (R = phenyl)[14]	6.15 ± 0.05
11 (R = *p*-$MeOC_6H_4$)[14]	6.30 ± 0.05
4 (R = 1-naphthyl)[21]	6.55 ± 0.15
4 (R = styryl)[54]	6.80 ± 0.20
14 (R = phenyl)[14]	6.90 ± 0.10

phenylpropiolate afforded ethyl 4,5-dihydro-1,3-diphenylpyrrolo[2,1-*a*]isoquinoline-2-carboxylate (**15**, R = C_6H_5; R′ = CO_2Et) in 51% yield. The structures of these compounds were based on analyses, typical reactions (such as saponification and decarboxylation of the resulting carboxylic acids), NMR and IR spectral data, and analogy.

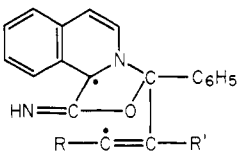
Interpretation of the Data on the 1,3-Dipolar Addition Reactions

In 1,3-dipolar addition reactions of Reissert hydrofluoroborates with alkynes, the key 1,3-dipolar compound is **2**. Since both **2** and the original Reissert compound are conjugate bases of the cation **4**, the rate of each 1,3-dipolar addition reaction will have some dependence on the acidity of **4**. Consequently, we decided to measure the pK_a values of a number of hydrofluoroborate salts, and these data are presented in Table II. Of course, these pK_a values refer to the dissociation reaction which leads to the parent Reissert compound, inasmuch as the parent is recovered in quantitative yield when each Reissert hydrofluoroborate salt is neutralized with base. However, one would anticipate that the order of relative acidities of **4** with reference to formation of the parent Reissert compound would parallel that with reference to the formation of **2**. Thus, since the concentration of **2** would affect the rate of a given 1,3-dipolar addition reaction, increasing acidity of **4** should contribute to an increased rate of 1,3-dipolar addition with a given dipolarophile.

The pK_a values of **4** (R = C_6H_5, *p*-$MeOC_6H_4$, and *m*-ClC_6H_4), **11**, and **14** are among those given in Table II. Rate data for the reactions of **4** (R = C_6H_5) with phenylacetylene, diphenylacetylene, and ethyl phenylpropiolate are provided in Table I. Also, rate data for the reaction of **11** and **14** with ethyl phenylpropiolate are given in Table I.

The specific rate constants for the reactions of **4** (R = various aryl groups) with ethyl phenylpropiolate[18] do not parallel the pK_a values given in Table II. Therefore, for these reactions, other effects must be of greater importance than the relative concentrations of **2**. It should be mentioned that the acidities of **4** did not vary greatly, the value of ρ for a plot of pK_a of **4** (R = meta- and para-substituted phenyl) vs. σ being only 0.98. Thus, no large effects based on the relative acidities of **4** would have been anticipated in any event.

As in the case of the initial Diels–Alder cycloaddition of Reissert hydrofluoroborate salts with alkenes, the concept of the initial formation of unstable biradicaloid intermediates in the reactions of the 1,3-dipolar compound **2** with alkynes enables one, in many instances, to predict which of two possible regeoisomeric products will predominate. Again, a primary qualitative evaluation of the relative energies of the possible unstable biradicaloid intermediates which can be formed and a secondary evaluation of steric effects are involved in such predictions. For example, let us consider the four possible unstable biradicaloid intermediates **16–19**, which can be formed by reaction of **2** (R = C_6H_5) with an alkyne, RC≡CR′. If we let R = C_6H_5 and R′ = H [in the reaction of **2** (R = C_6H_5) with phenylacetylene], the unstable biradicaloid intermediate **16**, having "captodative" substituents at one radicaloid site (to be discussed later) and an α-phenylvinyl radical at the other radical site, should have the largest delocalization energy of the four possibilities and should therefore be formed in the highest concentration, leading to preferential production of the adduct **20**.[21] Loss of HNCO from **20** will then give 1,3-diphenylpyrrolo[2,1-*a*]isoquinoline (**12**, R = C_6H_5; R′ = H), which was proved to be the exclusive product.[21]



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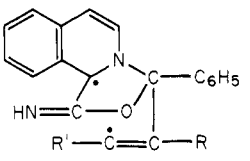

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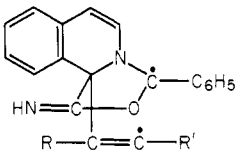

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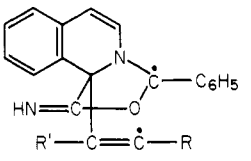

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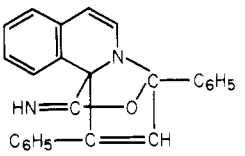

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We have previously reported that reaction of **4** (R = C_6H_5) with ethyl cinnamate gives mainly ethyl 2-(1-isoquinolyl)-3,5-diphenylpyrrole-4-carboxylate (**9h**, R = C_6H_5; R′ = CO_2Et). If an unstable biradicaloid intermediate, **5** (R = C_6H_5; R′ = CO_2Et), is involved, this result implies that a phenyl group is more effective in delocalizing an α-alkyl radical than is a carbethoxy group. There is much evidence to support this concept, particularly in the examination of the extensive literature on the relative reactivities of monomers with polymer radicals.[29]

We have also previously reported[18] that the reaction of **2** with ethyl phenylpropiolate gives ethyl 1,3-diphenylpyrrolo[2,1-*a*]isoquinoline-2-carboxylate (**12**, R = C_6H_5; R′ = CO_2Et). Thus, to be consistent with our previous argument with regard to 1,3-dipolar addition reactions of **2**, **16** (R = C_6H_5; R′ = CO_2Et) must have a greater delocalization energy than **17**, the same situation as when **4** undergoes a Diels–Alder reaction with ethyl cinnamate. In other words, a vinyl radical is more stabilized by an α-phenyl group than by an α-carbethoxyl group, the same as in the case of an alkyl radical. The results are in accord with this statement. Firestone[30] has provided a thorough review of the subject of orientation in 1,3-dipolar cycloadditions according to the spin-paired diradical mechanism.

The fact that phenylacetylene is distinctly more reactive than diphenylacetylene toward **2** (Table I) is consistent

(29) Walling, C. "Free Radicals in Solution"; Wiley: New York, 1957; pp 118–120.
(30) Firestone, R. A. *J. Org. Chem.* **1972**, *37*, 2181–2191.
(31) Doak, K. W. *J. Am. Chem. Soc.* **1950**, *72*, 4681–4686.

with the concept of the formation of an unstable biradicaloid intermediate in these 1,3-dipolar cycloaddition reactions. Doak[31] has reported that diphenylacetylene is 0.011 and 0.019 times as reactive as phenylacetylene toward the polymeric acrylonitrile and methyl acrylate radicals, respectively. Also, consistent with our kinetics data (Table I), Doak has shown that phenylacetylene is less than one third as reactive as styrene toward the polymer radicals cited above.

Examination of Firestone's Criteria

As mentioned previously, Firestone[13] has suggested some experimental criteria which, in his opinion, allow one to distinguish between biradicaloid and synchronous mechanisms of [4 + 2] cycloaddition reactions. Let us now examine the pertinent criteria as applied to our systems.

Firestone has presented arguments that, for a concerted [4 + 2] cycloaddition reaction, the order of reactivity of substituted alkenes toward a given diene (or 1,3-dipolar compound) should be XCH=CHX $\gg$ CH_2=CHX. For comparable reactions (Table I and ref 12) with 4 (R = C_6H_5), we have found the following rate ratios: k_2 (for styrene)/k_2 (for *trans*-stilbene) $\simeq$ 33 333;[32] k_2 (for ethyl acrylate)/k_2 (for diethyl maleate) $\simeq$ 1700; k_2 (for 1-hexene)/k_2 (for cyclohexene) $\simeq$ 23; k_2 (ethyl acrylate)/k_2 (ethyl cinnamate) $\simeq$ 5800[32,33]. In all of these examples, the monosubstituted alkene reacts with 4 (R = C_6H_5) at a faster rate than the 1,2-disubstituted alkene.

Firestone also contends that, for a concerted [4 + 2] cycloaddition, an alkyne should react with a given dienophile (or dipolarophile) at a faster rate than a related alkene. For the biradicaloid mechanism, the relative rates should be of roughly the same magnitude. For comparable reactions with 4 (R = C_6H_5), we have found the following rate ratios: k_2 (for styrene)/k_2 (for phenylacetylene) $\simeq$ 400;[32] k_2 (*trans*-stilbene)/k_2 (diphenylacetylene) $\simeq$ 4.7. In neither of these comparisons is the alkyne more reactive than the alkene.

Finally, Firestone states that, for appropriate concerted [4 + 2] cycloaddition reactions, the Hammett equation should be applicable. For the biradicaloid mechanism, the presence of both electron-donating and electron-withdrawing substituents on appropriately situated phenyl rings should cause acceleration of the reaction, and a V-shaped Hammett plot would result. Superficially, our results would appear to support the concerted mechanism. In the reactions of 4 (R = C_6H_5) with para-substituted styrenes, the kinetics data could be correlated by the Hammett equation, the value of ρ being 0.74.[12] In like manner, the kinetics data for the reactions of 4 with para-substituted ethyl cinnamates could be correlated by the Hammett equation, this time with ρ = 1.24.[12] However, the fact that merostabilization (see below) of the biradicaloid intermediate at one end of the molecule outweighs benzylic stabilization at the other end (particularly if the aryl group is somewhat twisted out of the plane of the radical by steric interaction with the isoquinoline ring) decreases the importance of the observed Hammett relationships.

Merostabilization Considerations

Although most of the data for reactions of Reissert hydrofluoroborate salts with alkenes and alkynes can be rationalized nicely in terms of the formation of unstable biradicaloid intermediates, we do not wish to generalize that all [4 + 2] cycloaddition reactions occur by this mechanism. Huisgen[9,10,34] has presented far too much data to the contrary to warrant such a broad generalization. Rather, because the key biradicaoloid intermediates formed in the Reissert salt reactions, **5** and **16**, respectively, have a special stabilizing feature, the preferential formation of these biradicaloids represents a driving force for the biradicaloid mechanism in our systems.

The unstable biradicaloid intermediates of types **5** and **16** are readily formed because one of the radical centers in each case is stabilized by concomitant substitution with a donor ($\ddot{N}H_2$ and :O: in the case of **5** and $\ddot{N}$ in the case of **16**) and an acceptor (>C=N^+< in the case of **5** and >C=NH in the case of **16**) group. Stella, Janousek, Merényi, and Viehe[35] refer to this phenomenon as "captodative substitution", Baldock, Hudson, Katritzky, and Soti[36] as "merostabilization", and Balaban[37-39] as "push–pull substitution". Actually, this type of stabilization was first examined theoretically by Dewar[40] in 1952. Other experimentalists and theoreticians have more recently confirmed the pronounced stabilizing effect on radicals by captodative substitution.[41-46] In any event, with respect to reactions of Reissert hydrofluoroborate salts, merostabilization of the biradicaloid intermediates, which predisposes the occurrence of this mechanism in these [4 + 2] cycloaddition reactions, makes possible the prediction of preferred regioselectivity in favorable cases *and even permits cycloaddition to occur at room temperature with some of the poorest of all known dienophiles or dipolarophiles, viz. ethylene and acetylene.* The recent suggestion[47] that a more appropriate term for a "1,3-dipolar" compound would be a "zwitterionic diradical hybrid" seems to be singularly appropriate for the conjugate bases, **2**, of Reissert hydrofluoroborate salts, as well as for the cations, **4**, themselves.

Steric Considerations

Although major emphasis has been placed on stabilization of the spin-paired diradical unstable intermediates by delocalization in providing rationalizations for regiochemical results and relative rate data, steric effects also

(32) Firestone[13] has provided a table of $\Delta H^{\ddagger}$ values for many different 1,3-dipolar addition reactions. The values do not vary greatly and the average of nine values is $\Delta H^{\ddagger}$ = 14.6 ± 1.2 kcal/mol. By use of this value and the well known equations $E_a = H^{\ddagger} + RT$ and $\log k = -(E_a/2.303RT) + (A/2.303)$, it is possible to calculate normalized values of k for a given temperature. For 50 °C, the calculated values of k for reactions of 4 with the alkenes and alkynes (for the nonequilibrium reactions) listed in Table I are as follows (in L mol^{-1} s^{-1}): ethyl acrylate, 4.64; styrene, 8.02×10^{-1}; diethyl maleate, 2.80×10^{-3}; 1-hexene, 6.90×10^{-4}; 1-phenylpropene, 4.72×10^{-4}; cyclohexene, 3.00×10^{-5}; *trans*-stilbene, 2.42×10^{-5}; phenylacetylene, 2.02×10^{-3}; diphenylacetylene, 5.15×10^{-6}; ethyl cinnamate,[33] 7.94×10^{-4}. The rate ratios given in the main text were calculated by use of these values.

(33) The value of k for the reaction of ethyl cinnamate with 4 (R = C_6H_5) in DMF at 32.7 °C was reported[12] to be 20.85×10^{-5} L mol^{-1} s^{-1}.

(34) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 565–598.
(35) Stella, L.; Janousek, Z.; Merényi, R.; Viehe, H. G. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 691–692.
(36) Baldock, R. W.; Hudson, P.; Katritzky, A. R.; Soti, F. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1422–1427.
(37) Balaban, A. T. *Rev. Roum. Chim.* **1971**, *16*, 725–737.
(38) Balaban, A. T.; Caproiu, M. T.; Negoita, N.; Baican, R. *Tetrahedron Lett.* **1974**, 4091–4094.
(39) Balaban, A. T.; Caproiu, M. T.; Negoita, N.; Baican, R. *Tetrahedron* **1977**, *33*, 2249–2253.
(40) Dewar, M. J. S. *J. Am. Chem. Soc.* **1952**, *74*, 3353–3354.
(41) Bennett, R. W.; Wharry, D. L.; Kock, T. H. *J. Am. Chem. Soc.* **1980**, *102*, 2345–2349.
(42) Klessinger, M. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 908–909.
(43) Viehe, H. G.; Merényi, R.; Stella, L.; Janousek, Z. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 917–932.
(44) Deuchert, K.; Hünig, S. *Angew. Chem., Int. Ed. Chem.* **1978**, *17*, 875–958.
(45) Stella, L.; Merényi, R.; Janousek, Z.; Viehe, H. G. *J. Phys. Chem.* **1980**, *84*, 304–306.
(46) Burns, J. M.; Wharry, D. L.; Koch, T. H. *J. Am. Chem. Soc.* **1981**, *103*, 849–856.
(47) Harcourt, R. D. *Tetrahedron* **1978**, *34*, 3125–3127.

deserve some consideration. Steric interactions between the two atoms that form the first bond of the unstable biradicaloid intermediate (i.e., those that unite during the rate-determining step) should be of importance. This concept helps to explain the relative reactivities of styrene vs. stilbene, ethyl acrylate vs. diethyl maleate, 1-hexene vs. cyclohexene, ethyl acrylate vs. ethyl cinnamate, and phenylacetylene vs. diphenylacetylene. Minisci[48] has pointed out that, in the formation of radicals by addition reactions to alkenes, there is a very high sensitivity to steric effects, as well as to inductive effects and to conjugative polar effects. Furthermore, even though frontier MO theory has been used with some success to rationalize regiochemical results in some 1,3-dipolar addition reactions,[49] Giese has stated that such calculations should be applied, with respect to radical reactions, only to those with early transition states, in which reacting molecules are still comparatively far apart. The 1,3-dipolar reactions which we have studied do not seem to comply with this condition. Thus, the steric effect mentioned above also plays a significant role in controlling the regiochemistry of the reactions of Reissert hydrofluoroborate salts with alkenes and alkynes.

Experimental Section

(A) Preparation of Reissert Hydrofluoroborate Salts. 2-Benzoyl-1,2-dihydroisoquinaldonitrile Hydrofluoroborate (4, R = C_6H_5). This compound (mp 196–198 °C dec) was prepared as described previously.[19]

2-Benzoyl-1-cyano-1,2-dihydrophthalazine Hydrofluoroborate (11). This compound (mp 225–227 °C dec) was prepared as described previously.[14]

2-Benzoyl-1,2,3,4-tetrahydroisoquinaldonitrile Hydrofluoroborate (14). This compound (mp 197–199 °C dec) was prepared as described previously.[14]

(B) Reactions of Reissert Hydrofluoroborate Salt 4 (R = C_6H_5) with Alkenes and Alkynes. In all cases, except that with ethylene and acetylene, the procedure described previously[21] for the reaction of 4 (R = C_6H_5) with styrene was employed. The reactions of 4 (R = C_6H_5) with 1-hexene,[12] *cis*-2-heptene,[12] cyclohexene,[12] diethyl maleate,[12] *trans*-stilbene,[12] ethyl acrylate,[26] phenylacetylene,[21] and diphenylacetylene[21] have been reported previously. For the reactions of 4 (R = C_6H_5) with *cis*-stilbene, 1-phenylpropene, and 1-hexyne, the percent yield of the product, spectral evidence, elemental analyses, the melting point, and reaction conditions are reported.

For the pyrroles, δ values for the N–H peaks are not reported, but they are ordinarily found in the range δ 10–14. Addition of 1 drop of deuterium oxide to the solution resulted in all cases in the disappearance of the broad N–H peak.

The reaction of 4 (R = C_6H_5) with ethylene was carried out in Me_2SO solution at 25 °C, the gaseous alkene being bubbled through the solution for various periods of time. A 3-h reaction period afforded 2-(1-isoquinolyl)-5-phenylpyrrole (**9e**) in 10% yield, while a 24-h reaction period increased the yield to 24%. Increasing the time of reaction to 80 h had little effect, the yield of pyrrole increasing to 28%; mp 136–137 °C (lit.[26] mp 140–141 °C). The use of DMF as solvent in place of Me_2SO also had little effect on the yield. The reaction of 4 (R = C_6H_5) with acetylene was carried out in a similar manner in both DMF and Me_2SO. An 80-h reaction period in DMF solution at 25 °C afforded 3-phenylpyrrolo[2,1-*a*]isoquinoline (**12**, R = R′ = H) in 9.8% yield. The use of Me_2SO as the solvent in place of DMF increased the yield to 19%; mp 98–99 °C (lit.[19] mp 98.5–99 °C).

Under the reactions conditions employed for the reaction of 4 (R = C_6H_5) with styrene,[21] the Reissert salt 4 (R = C_6H_5) failed to react with 1,2-dichloroethylene, 1-phenylpropyne, and 2-hexyne. All alkenes and alkynes used in the preparation of the pyrroles are either available commercially or are known compounds which were synthesized by known procedures.

Reaction of 4 (R = C_6H_5) with *cis*-Stilbene. The procedure utilized for the reaction between 4 (R = C_6H_5) and styrene was used.[21] When 2 equiv of *cis*-stilbene, a reaction time of 6 h, and a reaction temperature of 90 °C were employed, the yield of 2-(1-isoquinolyl)-3,4,5-triphenylpyrrole (**9d**) was 13%. Use of 30 equiv of *cis*-stilbene, a reaction time of 24 h, and a reaction temperature of 100 °C increased the yield to 23%; mp 264–266 °C (lit.[50] mp 262.5–263.5 °C).

This compound showed no depression in a mixture melting point test with authentic 2-(1-isoquinolyl)-3,4,5-triphenylpyrrole (**9d**), and the infrared spectra of the two samples, taken in chloroform solution, were identical.

Reaction of 4 (R = C_6H_5) with 1-Phenylpropene. The procedure utilized for the reaction between 4 (R = C_6H_5) and styrene was used.[21] When 2 equiv of 1-phenylpropene, a reaction time of 6 h, and a reaction temperature of 25 °C were employed, the yield of 2-(1-isoquinolyl)-4-methyl-3,5-diphenylpyrrole (**9i**) was 21%. Use of 2 equiv of 1-phenylpropene, a reaction time of 24 h, and a reaction temperature of 80 °C increased the yield of 42%; mp 211–212 °C; IR (KBr) 3050, 1600, 1490, 1350, 1020, 820, 765, 750, 700, 505 cm^{-1}; NMR ($CDCl_3$) δ 2.4 (s, 3 H), 7.4 (m, 15 H), 8.2 (d, 1 H, J = 6.0 Hz), 11.5 (br s, 1 H). The broad singlet at δ 11.5 disappeared on the addition of 1-drop of deuterated water to the NMR sample.

Anal. Calcd for $C_{26}H_{20}N_2$: C, 86.63; H, 5.59; N, 7.77. Found: C, 86.92; H, 5.55; N, 7.51.

Reaction of 4 (R = C_6H_5) with 1-Hexyne. The procedure utilized for the reaction between 4 (R = C_6H_5) and phenylacetylene was used.[21] When 3 equiv of 1-hexyne, a reaction time of 48 h, and a reaction temperature of 55 °C were employed, the yield of the product, 1-*n*-butyl-3-phenylpyrrole[2,1-*a*]isoquinoline (**12** R = *n*-Bu; R′ = H), was 4.0%. Use of 10 equiv of 1-hexyne under the same reaction conditions increased the yield of the product to 26%: mp 56–57 °C; IR (KBr) 2960, 2920, 2850, 1600, 1480, 1470, 1450, 1340, 780, 770, 680 cm^{-1}; NMR ($CDCl_3$) δ 0.9–2.0 (m, 7 H), 3.1 (m, 2 H), 6.7 (s, 1 H), 7.1–7.7 (m, 9 H), 7.9 (d, 1 H, J = 7.0 Hz), 8.2 (d, 1 H, J = 7.0 Hz).

Anal. Calcd for $C_{22}H_{21}N$: C, 88.24; H, 7.07; N, 4.68. Found: C, 88.19; H, 7.23; N, 4.59.

In addition, use of 10 equiv of 1-hexyne yielded 3.0% of a byproduct, 2-(1-isoquinolyl)-3-*n*-butyl-5-phenylpyrrole (**9g**), mp 122–123 (C (lit.[12] mp 123–124 °C).

Reaction of 2-Benzoyl-1-cyano-1,2-dihydrophthalazine Hydrofluoroborate (11) with Dimethyl Acetylenedicarboxylate. Dimethyl 3-phenylpyrrolo[2,1-*a*]phthalazine-1,2-dicarboxylate (**13**, R = R′ = CO_2Me) was prepared in the same manner as described by Popp,[27] mp 175–177 °C (lit.[27] mp 168–169 °C).

Reaction of 2-Benzoyl-1-cyano-1,2-dihydrophthalazine Hydrofluoroborate (11) with Ethyl Phenylpropiolate. Ethyl 1,3-diphenylpyrrolo[2,1-*a*]phthalazine-2-carboxylate (**13**, R = C_6H_5; R′ = CO_2Et) was prepared in the same manner as described by Popp;[27] mp 153–154 °C (lit.[27] mp 151–151.5 °C).

Reaction of 2-Benzoyl-1,2,3,4-tetrahydroisoquinaldonitrile Hydrofluoroborate (14) with Dimethyl Acetylenedicarboxylate. A mixture of 4.0 g (0.12 mmol) of 2-benzoyl-1,2,3,4-tetrahydroisoquinaldonitrile hydrofluoroborate (**14**), 2.5 g (0.18 mmol) of dimethyl acetylenedicarboxylate, and 60 mL of anhydrous *N*,*N*-dimethylformamide was stirred for 20 h at 90 °C. The reaction mixture was poured into 500 mL of water, and the aqueous suspension was extracted with ten 100-mL portions of benzene. The benzene extract was dried over anhydrous magnesium sulfate and filtered, and the filtrate was concentrated almost to dryness. The concentrated solution was chromatographed on neutral alumina, with a benzene–chloroform mixture (3:1) being used as the eluent. The eluent from the first fraction gave a 66% yield of dimethyl 4,5-dihydro-3-phenylpyrrolo[2,1-*a*]isoquinoline-1,2-dicarboxylate (**15**, R = R′ = CO_2Me): mp 162–163 °C; IR ($CHCl_3$) 3010, 2940, 1710, 1605, 1580, 1560, 1530, 1475, 1435, 1405, 1340, 1300, 1245, 1195, 1160, 1100, 1050, 990, 940, 910, 830, 690 cm^{-1}; NMR ($CDCl_3$) δ 2.78 (t, 2 H, J = 6.0 Hz), 3.59 (s, 3 H), 3.71 (t, 2 H, J = 6.0 Hz), 3.86 (s, 3 H), 7.05–7.51 (m, 9 H).

(48) Minisci, F. *Top. Curr. Chem.* **1976**, *62*, 1–48.
(49) Giese, B. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 125–136.
(50) Liao, T. K.; McEwen, W. E. *J. Org. Chem.* **1966**, *31*, 4110–4118.

Anal. Calcd for $C_{22}H_{19}NO_4$: C, 73.13; H, 5.26; N, 3.87. Found: C, 73.10; H, 4.96; N, 3.91.

Reaction of 2-Benzoyl-1,2,3,4-tetrahydroisoquinaldonitrile Hydrofluoroborate (14) with Ethyl Phenylpropiolate. A mixture of 4.0 g (0.12 mmol) of 2-benzoyl-1,2,3,4-tetrahydroisoquinaldonitrile hydrofluoroborate (14), 3.5 mL of ethyl phenylpropiolate, and 100 mL of anhydrous *N,N*-dimethylformamide was stirred for 15 h at 100 °C. Use of a similar workup procedure to that employed for the reaction with dimethyl acetylenedicarboxylate gave 2.3 g (51%) of ethyl 4,5-dihydro-1,3-diphenylpyrrolo[2,1-*a*]isoquinoline-2-carboxylate (**15**, R = C_6H_5; R′ = CO_2Et): mp 139–140 °C; IR ($CHCl_3$) 3010, 1700, 1610, 1580, 1560, 1490, 1465, 1450, 1425, 1385, 1345, 1300, 1225, 1170, 1040, 925, 860, 695 cm^{-1}; NMR ($CDCl_3$) δ 0.76 (t, 3 H, *J* = 8.0 Hz), 2.87 (t, 2 H, *J* = 6.0 Hz), 3.68–4.09 (m, 4 H), 6.82–7.58 (m, 14 H).

Anal. Calcd for $C_{27}H_{23}NO_2$: C, 82.44; H, 5.85; N, 3.56. Found: C, 82.36; H, 5.85; N, 3.60.

(C) Proofs of Structure by Independent Syntheses. 3-Phenylpyrrolo[2,1-*a*]phthalazine-1,2-dicarboxylic Acid (13, R = R′ = CO_2H). This compound (mp 258–259 °C) was prepared in the same manner as described by Popp[27] (lit.[27] 248–250 °C).

3-Phenylpyrrolo[2,1-*a*]phthalazine (13, R = R′ = H). A mixture of 1.0 g (3.0 mmol) of 3-phenylpyrrolo[2,1-*a*]-phthalazine-1,2-dicarboxylic acid (**13**, R = R′ = CO_2H), 7 mL of quinoline, and 50 mg of copper chromite was stirred for 80 min at 250 °C. The reaction mixture was poured onto 20 g of ice and neutralized with 10% hydrochloric acid. The aqueous suspension was extracted with five 200-mL portions of benzene. The benzene extract was washed with 10% sodium bicarbonate, dried over anhydrous magnesium sulfate, and filtered, and the filtrate was concentrated almost to dryness. The concentrated solution was chromatographed on neutral alumina, with a benzene–chloroform mixture (3:1) being used as the eluent. The eluent from the first fraction gave a 94% yield of 3-phenylpyrrolo[2,1-*a*]phthalazine (**13**, R = R′ = H); mp 107–108 °C; IR ($CHCl_3$) 3010, 1630, 1560, 1515, 1480, 1455, 1350, 1320, 1250, 1200, 1160, 1080, 1060, 1030, 950, 925, 895, 690, 660 cm^{-1}; NMR ($CDCl_3$) δ 6.95 (s, 2 H), 7.25–7.90 (m, 9 H), 8.28 (s, 1 H).

Anal. Calcd for $C_{17}H_{12}N_2$: C, 83.60; H, 4.91; N, 11.47. Found: C, 83.62; H, 4.93; N, 11.39.

3-Phenylpyrrolo[2,1-*a*]phthalazine (13, R = R′ = H). This compound was synthesized independently by treatment of 3-phenylpyrrolo[2,1-*a*]phthalazine-2-carboxamide (**13**, R = H; R′ = $CONH_2$) with phosphoric acid according to a method previously described.[51] This compound showed no depression in a mixture melting point test with 3-phenylpyrrolo[2,1-*a*]phthalazine (**13**, R = R′ = H) obtained by the decarboxylation of 3-phenylpyrrolo[2,1-*a*]phthalazine-1,2-dicarboxylic acid (**13**, R = R′ = CO_2H), and the infrared spectra of the two samples, taken in chloroform solution, were identical.

3-Phenylpyrrolo[2,1-*a*]phthalazine-2-carboxamide (13, R = H; R′ = $CONH_2$). A solution of 13.0 mL of phenylithium (2.2 M in ether–benzene) was added dropwise to a mixture of 7.89 g (30.0 mmol) of 2-benzoyl-1-cyano-1,2-dihydrophthalazine, prepared in the same manner as described by Popp,[52] and 70 mL of anhydrous tetrahydrofuran at −20 °C with stirring. After the mixture had been stirred for 40 min at −20 °C under a nitrogen atmosphere, a solution of 1.80 g (34.0 mmol) of freshly distilled acrylonitrile in 20 mL of tetrahydrofuran was added dropwise. The reaction mixture was then stirred for 3 h at −20 °C and finally overnight at room temperature. After addition of dry ice and water, the resulting aqueous mixture was extracted with five 200-mL portions of benzene. The benzene extract was dried over anhydrous magnesium sulfate and filtered, and the filtrate was concentrated almost to dryness. Crystallization of the residue from chloroform–95% ethanol gave 4.5 g (52%) of 3-phenylpyrrolo[2,1-*a*]phthalazine-2-carboxamide (**13**, R = H; R′ = $CONH_2$): mp 210–211 °C; IR ($CHCl_3$) 3480, 3370, 3000, 1630, 1605, 1595, 1555, 1535, 1495, 1460, 1380, 1320, 1285, 1185, 1175, 1155, 1130, 930, 885, 690 cm^{-1}.

Anal. Calcd for $C_{18}H_{13}N_3O$: C, 75.26; H, 4.53. Found: C, 75.60; H, 4.52.

1,3-Diphenylpyrrolo[2,1-*a*]phthalazine-2-carboxylic Acid (13, R = C_6H_5; R′ = CO_2H). This compound (mp 257.5–258 °C) was prepared in 92% yield from ethyl 1,3-diphenylpyrrolo[2,1-*a*]phthalazine-2-carboxylate (**13**, R = C_6H_5; R′ = CO_2Et) and potassium hydroxide according to the procedure used in the preparation of 3-phenylpyrrolo[2,1-*a*]phthalazine-1,2-dicarboxylic acid (**13**, R = R′ = CO_2H): IR ($CHCl_3$) 2910, 2860, 1685, 1615, 1550, 1525, 1450, 1370, 1275, 1250, 1195, 840, 740, 685 cm^{-1}.

Anal. Calcd for $C_{24}H_{16}N_2O_2$: C, 78.26; H, 4.35; N, 7.62. Found: C, 78.10; H, 4.60; N, 7.89.

1,3-Diphenylpyrrolo[2,1-*a*]phthalazine (13, R = C_6H_5; R′ = H). This compound (mp 167.5–169 °C) was prepared in 93% yield from 1,3-diphenylpyrrolo[2,1-*a*]phthalazine-2-carboxylic acid (**13**, R = C_6H_5; R′ = CO_2H), copper chromite, and quinoline according to the procedure used in the preparation of 3-phenylpyrrolo[2,1-*a*]phthalazine (**13**, R = R′ = H): IR ($CHCl_3$) 3010, 1620, 1545, 1490, 1475, 1455, 1395, 1300, 1245, 1200, 1070, 1025, 940, 900, 820, 685, 655 cm^{-1}; NMR ($CDCl_3$) δ 6.92 (s, 1 H), 7.25–8.11 (m, 14 H), 8.33 (s, 1 H).

Anal. Calcd for $C_{23}H_{16}N_2$: C, 86.25; H, 5.00; N, 8.75. Found: C, 86.25; H, 5.30; N, 8.80.

Independent Synthesis of 1,3-Diphenylpyrrolo[2,1-*a*]phthalazine (13, R = C_6H_5; R′ = H). This compound was synthesized independently by treatment of 1,3-diphenylpyrrolo[2,1-*a*]phthalazine-2-carboxamide **13** (R = C_6H_5; R′ = $CONH_2$), with phosphoric acid according to the method previously described.[51] This compound showed no depression in a mixture melting point test with 1,3-diphenylpyrrolo[2,1-*a*]phthalazine (**13**, R = C_6H_5; R′ = H), obtained by the decarboxylation of 1,3-diphenylpyrrolo[2,1-*a*]phthalazine-2-carboxylic acid (**13**, R = C_6H_5; R′ = COOH), and the infrared spectra of the two samples, taken in chloroform solution, were identical.

1,3-Diphenylpyrrolo[2,1-*a*]phthalazine-2-carboxamide (13, R = C_6H_5; R′ = $CONH_2$). This compound (mp 159–160 °C) was prepared in 21% yield from 2-benzoyl-1-cyano-1,2-dihydrophthalazine,[52] phenyllithium, and cinnamonitrile according to the procedure used in the preparation of 3-phenylpyrrolo[2,1-*a*]-phthalazine-2-carboxamide (**13**, R = H; R′ = $CONH_2$): IR ($CHCl_3$) 3480, 3370, 3000, 1635, 1610, 1555, 1495, 1465, 1380, 1290, 1205, 1130, 1010, 940, 905, 695, 665 cm^{-1}; NMR ($CDCl_3$) δ 6.32 (br s, 2 H), 7.00–7.40 (m, 14 H), 8.05 (s, 1 H).

Anal. Calcd for $C_{24}H_{17}N_3O$: C, 79.33; H, 4.79; N, 11.57. Found: C, 79.06; H, 4.63; N, 11.51.

Kinetics Studies. Cycloaddition Reactions of 4 (R = C_6H_5) with Alkenes and Alkynes. The procedure utilized for the kinetics studies of the cycloaddition reactions of 2-aroyl-1,2-dihydroisoquinaldonitrile hydrofluoroborates with substituted ethyl cinnamates was used.[12] All plots of $1/c$ vs. t were found to be linear. The second-order rate constants which were obtained directly by calculating the slope of each plot are reported in Table I.

Cycloaddition Reactions of 11 and 14, Respectively, with Ethyl Phenylpropiolate. The kinetics procedure was the same as that described previously for reactions of various Reissert hydrofluoroborate salts, **4** (R = aryl), with ethyl phenylpropiolate.[18]

Determination of pK_a Values of Reissert Hydrofluoroborate Salts. The pK_a values of the salts were determined by titrating 1 mmol of each salt, dissolved in 100 mL of methanol, with 0.0885 N methanolic potassium hydroxide solution. The endpoint was determined potentiometrically by using a Corning Model 12 pH meter. A plot of pH vs. milliliters of titrant added was made, and the endpoint was determined from the graph. The pK_a was then taken as the pH at half-completion of titration. During titration, all samples were kept immersed in a constant temperature bath set at 27.5 °C.

Conclusion

We believe that Reissert hydrofluoroborate salts undergo [4 + 2] cycloaddition reactions with alkenes and alkynes by the biradicaloid mechanism, and we have presented orientation and rate data to support this belief. It is our

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hypothesis that merostabilization of the biradicaloid intermediate predisposes these salts to utilize this mechanism rather than the concerted one.

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Registry No. 4 (R = C_6H_5), 68001-26-3; 4 (R = methyl), 68001-32-1; 4 (R = benzyl), 82026-92-4; 4 (R = cyclopropyl), 68001-36-5; 4 (R = *m*-ClC_6H_4), 82026-94-6; 4 (R = *p*-$MeOC_6H_4$), 41745-69-1; 4 (R = 1-naphthyl),, 68001-38-7; 4 (R = styryl), 82043-96-7; **9a**, 82026-95-7; **9c**, 68001-17-2; **9d**, 10425-52-2; **9e**, 13226-09-0; **9g**, 76583-58-9; **9i**, 82026-96-8; **11** (R = C_6H_5), 76456-91-2; **11** (R = *p*-$MeOC_6H_4$), 82026-98-0; **12** (R = R' = H), 20958-78-5; **12** (R = *n*-Bu; R' = H), 82026-99-1; **13** (R = R' = CO_2Me), 76456-96-7; **13** (R = C_6H_5; R' = CO_2Et), 76456-98-9; **13** (R = R' = CO_2H), 76456-97-8; **13** (R = R' = H), 82027-00-7; **13** (R = H; R' = $CONH_2$), 66858-02-4; **13** (R = C_6H_5; R' = CO_2H), 82027-01-8; **13** (R = C_6H_5; R' = H), 82027-02-9; **13** (R = C_6H_5; R' = $CONH_2$), 82027-03-0; **14**, 82027-05-2; **15** (R = R' = CO_2Me), 82027-06-3; **15** (R = C_6H_5; R' = CO_2Et), 82027-07-4; ethylene, 74-85-1; acetylene, 74-86-2; *cis*-stilbene, 645-49-8; 1-phenylpropene, 637-50-3; 1-hexyne, 693-02-7; dimethyl acetylenedicarboxylate, 762-42-5; ethyl phenylpropiolate, 2216-94-6; 2-benzoyl-1-cyano-1,2-dihydrophthalazine, 13925-27-4; acrylonitrile, 107-13-1; cinnamonitrile, 1885-38-7; ethyl acrylate, 140-88-5; styrene, 100-42-5; diethyl maleate, 141-05-9; 1-hexene, 592-41-6; cyclohexene, 110-83-8; *trans*-stilbene, 103-30-0; phenylacetylene, 536-74-3; diphenylacetylene, 501-65-5.

Stereoselectivity in the Epoxide Hydrolase Catalyzed Hydrolysis of the Stereoisomeric 3-*tert*-Butyl-1,2-epoxycyclohexanes. Further Evidence for the Topology of the Enzyme Active Site[1]

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(±)-*cis*-3-*tert*-Butyl-1,2-epoxycyclohexane is converted by rabbit liver microsomal epoxide hydrolase exclusively into the diaxial diol. The 1*S*,2*R*,3*S* enantiomer reacts at a much faster rate to yield the 1*R*,2*R*,3*S* diol, which is isolated at least 96% optically pure in the first stages of the reaction, up to almost 50% conversion. (±)-*trans*-3-*tert*-Butyl-1,2-epoxycyclohexane is a poorer substrate than the cis isomer: only the 1*S*,2*R*,3*R* epoxide undergoes slow enzymatic hydrolysis to produce exclusively optically pure 1*R*,2*R*,3*R* diol, the product of diequatorial opening, in contrast with the acid-catalyzed hydrolysis of the same epoxide that yields both the diequatorial and the diaxial diols. The absolute configurations of the diols and epoxides were established by chiroptical methods on appropriate derivatives. The enantiomeric excesses in the diols were determined with chiral shift reagents. The present results confirm previous hypotheses on the topology of the hydrolase active site, involving a large hydrophobic pocket situated in such a way as to accommodate bulky substituents to the right of the oxirane ring in the ES complex. They also are consistent with and supplement previous evidence on a general-base catalysis in the enzymatic reaction mechanism.

The microsomal epoxide hydrolase (EC 3.3.2.3) is an important enzyme involved in both the detoxification[2,3] and the further metabolic activation[4,5] of epoxides and arene oxides arising by oxidation of olefinic and aromatic substrates by the cytochrome P-450 containing monooxygenases. In spite of its low substrate specificity, the hydrolase exhibits a remarkable regioselectivity[6-10] and in several cases appears to be able to discriminate between substrate enantiomers.[11-13] The latter feature is exceedingly important in view of the well-known influence of stereochemical factors on biological activity. In particular, marked effects of absolute and relative configuration on the mutagenic and carcinogenic activity of stereoisomeric epoxides, dihydrodiols, and diol epoxides formed in the metabolism of polycyclic aromatic hydrocarbons have been reported.[14]

Substituted epoxycyclohexane rings are present in a variety of naturally occurring or metabolically formed products and represent suitable models on which the stereoselectivity of the epoxide hydrolase can be simply investigated by virtue of the rather advanced understanding of steric, electronic, and conformational factors involved in their ring-opening reactions[15] and of the facility of conformational and configurational determinations with

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