The residue was crystallized from ethyl acetate–heptane or acetone–methanol–water.

Reductive Tritiation. The mesylate (**1**, **2**, respectively) (0.05 mmol), zinc powder (20 mg), sodium iodide (20 mg), and 1,2-dimethoxyethane (2 mL containing 10 mg of tritium oxide, activity 6 Ci) were heated in a sealed tube at 80 °C for 6 h. The cooled tubes was opened, and the reaction mixture worked up as described for deuteriation (vide supra). The crude product was purified by column chromatography by using silica gel (Merck, 1 g) and a mixture of light petroleum ether–acetone–diethyl ether (90:5:5). The specific activity of tritiated compounds, **11** (5.49 Ci/mmol) and **13** (5.3 Ci/mmol), was detd. by a conventional liquid scintillation technique.

Purification of 16 and 17. The olefin containing products **16** and **17** were dissolved in chloroform and treated with *m*-chloroperoxybenzoic acid at 20 °C overnight. After a standard workup, the mixture of **16** and **17** was separated from the epoxides on a silica gel column (elution with light petroleum ether).

The labeled compounds **10–15**, **16** + **17**, and **18** + **19** were identified by mixture melting points with the corresponding unlabeled derivatives. **20** + **21** were identified by comparing the retention time and mass spectrum of each with those of *tert*-butylcyclohexane (column SE-30, 3% on Chromosorb, 70 °C).

Registry No. **1**, 20576-45-8; **2**, 82427-84-7; **3**, 6677-96-9; **4**, 23712-51-8; **5**, 1182-65-6; **6**, 3381-52-0; **7**, 85749-83-3; **8**, 7453-05-6; **9**, 53042-75-4; **10**, 55487-61-1; **11**, 35481-45-9; **12**, 85749-84-4; **13**, 85749-85-5; **14**, 85749-86-6; **15**, 62743-60-6; **16**, 54482-38-1; **17**, 20810-53-1; **18**, 85749-87-7; **19**, 85749-88-8; **20**, 17553-36-5; **21**, 53042-76-5; Zn, 7440-66-6; NaI, 7681-82-5; T, 10028-17-8.

Benzo[*f*]isobenzofuran. Mechanistic Aspects of Isobenzofuran Formation from Acetals and Ortho Esters

Bagher Mir-Mohamad-Sadeghy and Bruce Rickborn*

Department of Chemistry, University of California, Santa Barbara, California 93106

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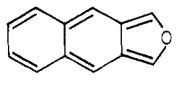
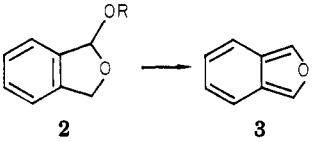
Benzo[*f*]isobenzofuran (**1**) is generated as a reactive intermediate by using the acetal **8** (R = Me, Et) with carboxylic acid catalysts, as shown by the formation of Diels–Alder adducts when the reaction is carried out in the presence of dienophiles ranging in reactivity from maleic anhydride to norbornene. Results with **8** generally parallel those observed earlier with 1-alkoxy-1,3-dihydroisobenzofuran (**2**). In contrast to the lower homologue 1,1-dialkoxy-1,3-dihydroisobenzofuran (**4**), which like the acetals gives Diels–Alder reactions, the ortho ester **9** fails to yield cycloadducts. With acetal **2**, various kinetic parameters were explored. The rate of loss of **2** is half-order in mesitoic acid catalyst and follows second-order behavior with *N*-phenylmaleimide (NPM); i.e., the rate is proportional to the concentrations of **2** and NPM. The reaction of **2** appears to be zero order in dienophile with the less reactive norbornene. An alternative product must be formed reversibly under these conditions, and an oligomeric structure is suggested for this material. In the absence of dienophile a similar rate is observed, leading eventually to the presumed polymer in an irreversible reaction. Deuterium incorporation in recovered **2** when treated for a short time with CH_3OD and acid catalyst provides evidence for the rapid reversible formation of isobenzofuran under the usual reaction conditions. This was further substantiated by deuterium incorporation in the Diels–Alder adducts from a reaction of **2** with norbornene in the presence of CH_3OD. Ortho ester **4** reacts with various acids to give phthalide and ring-opened diesters, and these pathways are shown to dominate the reactions of **9**. The different behavior of **4** and **9** in attempted Diels–Alder reactions is shown to be due to a higher barrier for formation (or lower stability) of 1-alkoxybenzo[*f*]isobenzofuran, rather than more facile ring opening of **9** relative to **4**.

Although several years have passed since Cava's report of the isolation of the reactive 1,3-diphenyl derivative[1] and although the unsubstituted thia[2,3] and aza[4] analogues have been generated and trapped in situ, the parent linearly fused isonaphthofuran (**1**; INF, benzo[*f*]isobenzofuran, or naphtho[2,3-*c*]furan) remains unknown. Given suitable



1

precursors, **1** is in principle accessible through the elegant flash vacuum pyrolysis technique,[5] but this approach has apparently not been attempted. We have reported[6] that the cyclic acetal **2** can be converted to isobenzofuran (IBF, **3**) in two ways. Treatment with lithium diisopropylamide allows the isolation of solutions of **3**, or heating **2** in the presence of a carboxylic acid catalyst and dienophile gives Diels–Alder adducts, implicating **3** as the reactive intermediate. Both the base-induced and acid-catalyzed pro-



2 **3**

(1) Cava, M. P.; VanMeter, J. P. *J. Org. Chem.* **1969**, *34*, 538. Cava, M. P.; VanMeter, J. P. *J. Am. Chem. Soc.* **1962**, *84*, 2008. See also: Haddadin, M. J.; Agha, B. J.; Tabri, R. F. *J. Org. Chem.* **1979**, *44*, 494.

(2) MacDowell, D. W. H.; Jeffries, A. T.; Meyer, M. B. *J. Org. Chem.* **1971**, *36*, 1416.

(3) Cava, M. P.; Pollack, N. M.; Mamer, O. A.; Mitchell, M. J. *J. Org. Chem.* **1971**, *36*, 3932. Low-temperature isolation and the ^1H NMR spectrum have been reported recently: Bornstein, J.; Hardy, R. P.; Remy, D. E. *J. Chem. Soc., Chem. Commun.* **1980**, 612.

(4) Remy, D. E.; Bissett, F. H.; Bornstein, J. *J. Org. Chem.* **1978**, *43*, 4469. Shields, J. E.; Bornstein, J. *Chem. Ind. (London)* **1967**, 1404. The *N*-*tert*-butyl derivative is reported to be stable at room temperature: Kreher, R.; Use, G. *Heterocycles* **1982**, *19*, 637.

(5) For a recent review and references, see: Wiersum, U. E. *Aldrichimica Acta* **1981**, *14* (3), 53. An exhaustive review of isobenzofuran chemistry is found in: Freiedrichsen, W. *Adv. Heterocycl. Chem.* **1980**, *26*, 135.

(6) Naito, K.; Rickborn, B. *J. Org. Chem.* **1980**, *45*, 4061. A related approach for the acid-catalyzed process that presumably involves a 2-like intermediate has been developed by Rodrigo and co-workers.[7]

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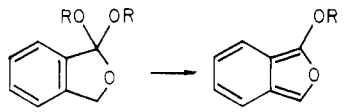
cedures have been applied[8,9] to the related ortho ester 4 to give the more reactive 1-alkoxyisobenzofuran (5); we



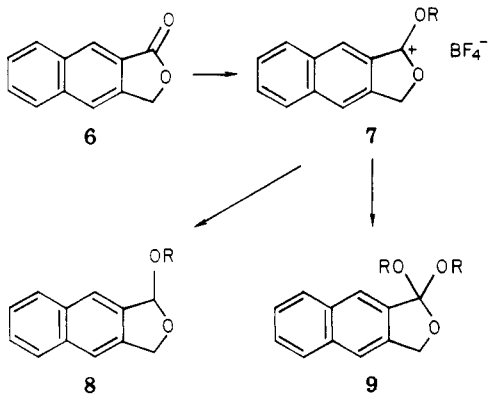
4 5

were unable to isolate 5 even in dilute solution using the strong base method but obtained evidence for its formation through Diels-Alder reactions under both sets of conditions.[8]

The linearly annulated homologue 1 is of theoretical interest as a 14-π-electron system,[10,11] and both 1 and its 1-alkoxy derivative have prospective synthetic utility along the lines already demonstrated for 3 and 5. We report here results of applying the acid-catalysis method developed for IBF to the naphthalene analogues. In addition, mechanistic aspects of the acid-catalyzed reactions of 2 and 4 are presented.

Results and Discussion

Naphthalide 6 was prepared from 2,3-naphthalic anhydride by using Cava's procedure.[3] Alkylation using freshly prepared diethoxycarbenium tetrafluoborate[12] gave results superior to those obtained with triethyloxonium tetrafluoborate, due, we believe, in part to the very poor solubility characteristics of lactone 6. The carbenium ion 7 served as the precursor to both the acetal 8 and the ortho ester 9. The latter was readily formed by adding 7 to



6 7 8 9

excess sodium ethoxide in ethanol, as described for the benzene analogue by Meerwein and co-workers.[15] Crude 9 is freed from the much less soluble 6 by trituration with ether. Initial attempts to reduce 7 to the acetal 8 with $NaBH_4$ in pyridine[8] gave low and erratic yields. Use of an improved procedure recently developed in our laboratory[16] ($NaBH_4$, DMF, 0 °C), however, gave 8 in good yield.

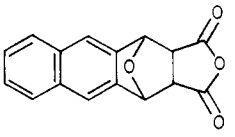
(a) Reactions of 8. Formation of 1. Preliminary attempts with $LiNR_2$ to effect 1,4-elimination of 8 to give solutions of 1 have not been successful; we have also not been able to demonstrate the formation of 1 under these conditions in the presence of the dienophile norbornene. The reasons for this remain unclear, and further work is planned on this strong-base approach.

The acid-catalyzed conditions, however, gave positive evidence for the formation of INF (1) as a reactive intermediate, through Diels–Alder adduct formation with the dienophiles described below. In general, these reactions were carried out in refluxing solvent (toluene or chlorobenzene) under nitrogen, and the progress of the reaction was monitored by examination of NMR spectra of samples removed at intervals. Either acetic or mesitoic acid was used as the catalyst, typically 0.1 equiv relative to the acetal. Mesitoic acid offers the advantages of being accurately weighable, being nonvolatile, providing internal reference peaks in the NMR, and avoiding potential esterification with the alcohol generated in the reaction. Unless otherwise noted, the dienophile was used in slight (5–10%) excess.

Diels–Alder product formation under these conditions was observed by using maleic anhydride (MA), dimethyl acetylenedicarboxylate (DMAD), α-acetoxyacrylonitrile (AAN), and butenolide (BL). Most products were isolated for further characterization, while others were identified by NMR only, where conclusions are based on spectral comparisons with products from the lower homologue 3.[8]

Working with the sulfur analogue of 1, Cava[3] found that the major Diels–Alder adducts with *N*-phenylmaleimide were the exo and endo isomers of reaction at the thiophene ring, but a third minor product was also isolated in which cycloaddition had occurred at the central ring (the stereochemistry of this material was not established). Examination of the crude reaction mixtures in our work did not indicate the formation of a similar product from reaction involving the central ring. Since thiophene has greater resonance stabilization energy than furan and Diels–Alder reactions of polycyclic aromatics tend to form the more stable products preferentially, these observations are in line with expectations. However, since there is uncertainty regarding the anticipated chemical shifts for central ring adducts, we cannot completely rule out the possibility of minor amounts being formed.

The reaction of 8 with MA was carried out in refluxing toluene without added catalyst. The anhydride invariably contains traces of acid sufficient to initiate reaction, and the alcohol generated in the elimination of 8 to give 1 can attack MA to give a half-acid ester which will in turn function as a catalyst. In four runs with reaction times varying from 17 to 43 h, we found that when the mixture was cooled to room temperature, crystals were deposited which accounted for 24–40% yield. This material provided to be the nearly pure exo adduct of structure 10. Re-



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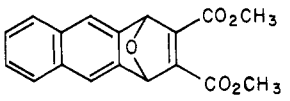
crystallization gave analytically pure product. Its NMR showed the expected[8] singlets for the bridgehead protons and those adjacent to the carbonyl groups. The residues from filtration were evaporated and examined by NMR.

(7) Keay, B. A.; Lee, D. W. K.; Rodrigo, R. *Tetrahedron Lett.* **1980**, *21*, 3663.
(8) Makhlouf, M. A.; Rickborn, B. *J. Org. Chem.* **1981**, *46*, 2734.
(9) Contreras, L.; Slemon, C. E.; MacLean, D. B. *Tetrahedron Lett.* **1978**, 4237. Contreras, L.; MacLean, D. B.; Faggiani, R.; Lock, C. J. L. *Can. J. Chem.* **1981**, *59*, 1247.
(10) Dewar, M. J. S.; Harget, A. J.; Trinajstic, N.; Worley, S. D. *Tetrahedron* **1970**, *26*, 4505.
(11) Julg, A.; Sabbah, R. *C. R. Hebd. Seances Acad. Sci., Ser. C* **1977**, 421.
(12) The general procedure of Borch[13] was followed, with stoichiometric amounts of reagents, to prepare the dialkoxycarbenium tetrafluoborates. These materials have been found to react with substances which are resistant to alkylation by Meerwein salts.[14]
(13) Borch, R. F. *J. Org. Chem.* **1969**, *34*, 627.
(14) Kabuss, S. *Angew. Chem, Int. Ed. Engl.* **1968**, *7*, 64.
(15) Meerwein, H.; Borner, P.; Fuchs, O.; Sasse, H. J.; Schrodt, H.; Spille, J. *Chem. Ber.* **1956**, *89*, 2060.
(16) Moss, R. J.; Rickborn, B. *J. Org. Chem.* **1982**, *47*, 5391.

These showed small amounts of *exo*-**10**, along with the major endo isomer of **10**, identified by analogy with the lower homologue, in the position and appearance of the AA'XX' pattern.[6] The overall yields for this reaction are excellent, and the *exo*-/*endo*-**10** ratio was approximately 40/60 in all four runs.

DMAD reacts with **8** to give adduct **11** in moderate yield. With 0.1 equiv of mesitoic acid catalyst in refluxing chlorobenzene, the reaction requires ca. 30 h to approach completion.



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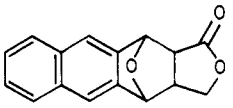
Similarly, BL and AAN give products **12** and **13**, as



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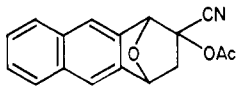

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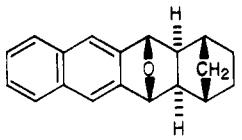
mixtures of exo and endo isomers. With BL, the exo/endo ratio is approximately 60/40. These isomers were difficult to separate by column chromatography, but the less soluble endo adduct was easily isolated by recrystallization. The AAN reaction gave an exo/endo ratio of ca. 3/1; the stereochemical designations refer to the position of the cyano group, with assignments based on the higher field NMR shift of the *endo*-acetoxy group. The major isomer was isolated for further characterization by chromatography.

The reactions with MA, AAN, and BL occur in high yield to give the products shown. No evidence for cycloaddition at the central ring was found with any of the dienophiles employed.

We had previously shown that norbornene (NB) could be used as a dienophile with IBF when the latter was generated by the $LiNR_2$-induced 1,4-elimination method.[8] It was of interest to determine whether this reaction could be effected under the acid-catalyzed conditions. Sealed tubes were used to avoid the loss of NB, and, indeed, we find that both acetals **2** and **8** give the anticipated cycloadducts. Those from **2** (via IBF formation) have been previously characterized.[8] The reaction of **8** follows an analogous course, giving *exo,exo*-**14** and *endo,exo*-**15** as the



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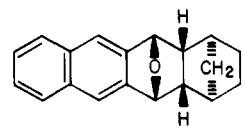

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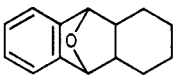
only products in a 4/1 ratio after chromatographic separation. The high exo face selectivity of NB is once again reflected in these results. The **14**/**15** ratio is somewhat higher than that observed for the reaction of IBF with NB. Adduct **14** exhibits the expected singlet for the ethereal bridghead protons at 5.12 ppm, while **15** shows the AA'XX' pattern anticipated for these protons. The latter compound also shows the interesting shielding pattern for the protons on the bridging methylene group, which appear as broadened doublets at 0.17 (anti to the aromatic) and -1.03 ppm (syn to the aromatic). Corrected values for the analogous protons of the lower homologue[8] from IBF are 0.20 and -1.25 ppm, both in $CDCl_3$ solvent.

The acid-catalyzed reactions of **8** closely parallel those of the acetal **2**, supporting the view that the same general mechanisms apply to both and therefore providing evidence that INF **1** is formed as a reactive intermediate. As shown below, the Diels–Alder reaction of **2** can be extended to the simple olefin cyclohexene, which would normally rank as a very poor dienophile. However, we have been unable to effect Diels–Alder reaction of **8** with cyclohexene (8 equiv, 140 °C, 240 h). This represents the first significant divergence in the reactions of the two acetals, and we believe this is due to the greater difficulty in generating INF (lower expected stability) compared to IBF. In spite of this limitation, both acetals are shown to be suitable precursors for reaction with a very wide range of dienophiles, from MA to cyclohexene with the lower and MA to NB with the higher homologue.

(b) Mechanism of the Acid-Catalyzed Reaction of the Acetal. Because of the availability of sizeable quantities of the acetal **2** (R = Me), we have used it to explore mechanistic features of the acid-catalyzed reaction. To test the limits of cycloaddition utility, we carried out a sealed tube reaction using cyclohexene (5 equiv) and mesitoic acid (0.1 equiv) in chlorobenzene at 140 °C. After 229 h the tube was opened, the solvent evaporated, and the residue chromatographed to give the cycloadduct **16**



16

in 60% isolated yield. Interestingly, the endo adduct is strongly favored (exo/endo ratio of 1/11) with this dienophile. Similar selectivity has been reported by Jones and Kneen[17] for reaction of IBF, generated in situ in a different manner, with cyclopentene and cycloheptene (only endo adducts were isolated, but small amounts of exo products were not excluded). These authors also found that reaction with norbornadiene gave preferentially exo,exo product, with selectivity similar to that which we have observed using norbornene.[8] The factors controlling these selectivities are not obvious.[17]

Although the reaction of **2** with cyclohexene was somewhat slower, as judged by examination of a sealed-tube aliquot, than, e.g., reaction with norbornene, the times needed for complete reaction with the whole range of dienophiles used in this and earlier work[8] suggested that any differences in rate were not very large. In considering plausible mechanisms, it appeared possible that IBF formation might be rate limiting, especially with the more reactive dienophiles. Examination of kinetic parameters was needed to answer this and related questions.

In chlorobenzene solvent, the NMR absorption of the methanol CH_3 singlet appears slightly upfield of the peak for the methoxy group in **2**, and this offered a way to follow the rate of loss of this starting material. The errors inherent in this method are rather large (those of NMR integration), especially so at the early and late stages of reaction, but nonetheless the procedure appeared to be sufficiently accurate to determine major kinetic features. Reactions were carried out in sealed tubes immersed in an oil bath, and the tubes were cooled in ice–water before being opened to prevent losses of volatile materials. Two substrates were chosen for these studies, NB and *N*-phenylmaleimide (NPM), to represent poorer and better dienophiles, respectively.

These studies have led to interesting and rather curious observations that suggest a complex mechanistic picture. Bearing in mind that the process examined is the rate of loss of **2**, it was found that the rate is dependent on the

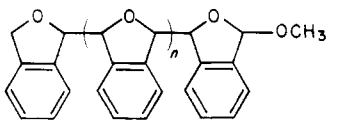
(17) Jones, D. W.; Kneen, G. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1647.

nature of the dienophile. Thus the reaction, with other variables held constant, is faster with NPM than with NB, although the difference is not large; both reactions are conveniently followed over a period of hours at 140 °C by using ca. 0.5 M substrate and 0.05 M mesitoic acid. Furthermore, the rate of the NPM reaction is dependent on the concentration of this dienophile. Tripling the initial concentration of NPM from 1 to 3 equiv/mol of **2** caused a distinct increase in rate of loss of **2**. Second-order rate constants for the two runs, assuming $-d[2]/dt = k'[2][NPM]$, were identical within experimental error ($k' = 4.9$ and 4.7×10^{-4} M^{-1} s^{-1}); note that k' is a composite that includes a term for mesitoic aid concentration, which was the same for both runs. These observations are those expected for a mechanism involving a rapid preequilibrium between **2** and IBF (plus methanol), with cycloaddition being rate determining.

Since the rate was proportional to the concentration of the better dienophile NPM, it was expected that similar behavior would be exhibited by NB. However, kinetics runs involving a three-fold variation in NB concentration (again, from 1 to 3 equiv) failed to show any influence on the rate of loss of acetal. Similar results were obtained at 110 and 140 °C. Instead, apparent overall first-order kinetics, $-d[2]/dt = k'[2]$, were observed, even though the aliquots examined by NMR indicated the consumption of NB and the formation of Diels–Alder adducts.

This behavior requires the intervention of an alternative mechanism for loss of **2**, one which occurs more rapidly than Diels–Alder reaction with NB. The product of this reaction must be capable of reversibly forming IBF to account for the fact that substantial yields of cycloadducts are formed under these conditions. For verification of this, a kinetic run was carried out in the absence of dienophile. The rate of loss of **2** was indeed comparable, or even somewhat faster, than in runs where NB was present. This reaction also differed in that significant darkening occurred with time, such that the final sample examined (19 h), which showed ≤10% residual **2**, was black. A strong peak at the free methanol position was evident. To test the possible reversibility of reaction at this stage. we added 1 equiv of NB, and the mixture was again heated in a sealed tube. NMR peaks corresponding to NB cycloadducts were indeed observed after 38 h, but these amounted to less than 10% of the methanol peak, and no further change was observed when the heating was repeated for an additional 24 h. We are thus uncertain whether IBF is formed from residual **2** or another reaction product that is capable of reversal to this species. It appears, however, that the strong darkening is associated with a process that is effectively irreversible under these reaction conditions.

A plausible explanation for these observations would be the rate-determining formation of oligomers of generalized structure **17**, which must at lower stages of polymerization



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be able to revert to IBF (to account for the yields of NB cycloadducts formed) but which in the absence of a dienophile eventually lead to unreactive material, perhaps simply a higher polymer of limited solubility, or products lacking the acetal function needed for reversibility. With the more reactive dienophile NPM, second-order behavior would thus be ascribed to a combination of activation energies and concentrations of reagents and intermediates which allows the Diels–Alder process to be the kinetically observed reaction. With the less reactive NB, the oligomerization process is the more facile option. A reasonable rate expression for formation of oligomer would be $d[17]/dt = k[C^+][IBF]$, where $[C^+]$ represents the concentration of the various carbenium ions formed by loss of methoxide from either **2** or its higher homologues of general structure **17**. One might expect $[C^+]$ to be approximately constant over the course of reaction, and if rapid prior equilibrium formation of IBF is assumed, the first-order (in **2**) kinetic behavior for loss of acetal is rationalized.

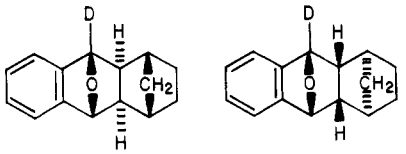
The role of acid catalyst was examined under the "first order" conditions in three runs with **2** and NB in equal concentration and with variation of the mesitoic acid concentration (0.1, 0.25, and 1.0 equiv). Increasing the acid concentration caused a more rapid loss of **2**, but the factors (1, 1.7, and 3.1, respectively) were significantly lower than those required by first-order dependence on mesitoic acid. The observed values would in fact correspond closely to a process that is one-half order in acid. This would be expected if mesitoic acid exists predominantly as a hydrogen-bonded dimer, in rapid equilibrium with monomer, with the latter being the kinetically active species.[18]

Further evidence on the question of a rapid prerate-determining equilibrium between **2** and IBF was obtained by carrying out a sealed-tube experiment in which **2** (R = Et), 0.1 equiv of mesitoic acid, and 4 equiv of CH_3OD were heated in chlorobenzene solvent at 140 °C for 0.9 h. These are conditions which, in the absence of added methanol, cause negligible loss of **2**. After room-temperature evaporation of the solvent, the product was first examined by ^1H NMR. Using the mesitoic acid methyl peaks as an internal reference, it was found that over 90% of **2** was recovered; the ratio of methyl (84%) to ethyl **2** (16%), reflected complete equilibration of acetal with alcohol (also in separate experiments, alkoxy equilibration was shown to be complete in less than 10 min under these conditions). The recovered sample was then examined by ^2H NMR. Deuterium was present *in equal amounts* at all three exchangeable positions, i.e., at the acetal carbon and at the cis and trans benzylic methylene sites. It is difficult to conceive of a mechanism to accommodate this pattern of exchange other than by formation of IBF and readdition of alcohol to form **2**. That all three sites contain the same amount of deuterium is strong evidence that the process has undergone numerous cycles, i.e., that IBF and alcohol are in rapid acid-catalyzed equilibrium with **2** and that this equilibration is substantially faster than the reactions followed in kinetic runs. The actual amount of deuterium at each position was estimated, through the use of an internal standard (cyclohexane-d_{12}), to be 40 ± 10%. Although this is lower than the statistical level (57%) anticipated from complete equilibration of known exchangeable D,H sources, the difference may be ascribable to adventitious proton sources (purity of CH_3OD, traces of moisture); no indication of deuterium incorporation into the aromatic ring of **2** was observed in the ^2H NMR, and such exchange with chlorobenzene is expected to be an even slower process.

The experiment using 4 equiv of CH_3OD was repeated with the modification of using **2** (R = Me) and adding 1 equiv of NB to the starting mixture. An aliquot was taken

(18) Alternatively, half-order behavior would be observed if the acid dimer is both the dominant and kinetically active species, if the reaction of acetal and dimer leads to monomer which then rapidly dimerizes. The two possibilities are kinetically indistinguishable.

after 18 h (140 °C), the solvent evaporated, and the residue chromatographed on neutral alumina. The exo,exo adduct **18** was cleanly separated (26%) and shown by ^2H NMR



18 **19**

to contain 0.4 ± 0.1 atom of D/mol **18** at the bridgehead position(s) shown. The endo,exo isomer **19** (estimated 17%) was not separated from material which appeared to be **2** (ca. 21% by ^1H NMR). The ^2H NMR of this mixture also indicated the presence of deuterium at the bridgehead position(s) of **19**, but this absorption occurs at nearly the same chemical shift as that of the methylene deuterons of **2**, and quantitative evaluation was not feasible. Curiously, this sample did not display a measurable peak for incorporation of deuterium at the acetal center. No other signals were evident in either sample. A second aliquot taken after 96.5 h showed, by proton NMR, and **2** had been consumed (<10% remaining). Chromatography gave **18** and **19** in 49% and 11% isolated yields, respectively. These samples were then examined by ^2H NMR and found to contain 49% and 51% deuterium at the positions indicated; these are, within experimental error (±10%), the same as the first sample of **18** examined.

Several features of these data deserve comment. First, the incorporation of deuterium is in keeping with rapid equilibration of **2** with CH_3OD, via IBF, and the apparently unchanged percentages of deuterium incorporation with time imply that this process is completed at an early stage of reaction, prior to cycloaddition. The actual amounts of deuterium incorporated, however, are lower by about a factor of 2 than those expected on the basis of the earlier experiment. This may in some way be associated with the longer times involved in obtaining cycloadducts with NB, but the mechanism for dilution of deuterium remains unclear. The absence of deuterium in the acetal position of recovered (presumed) **2** is also unexplained. However, we have found that samples of **2** (R = Me) when treated with CH_3OD (2 and 4 equiv) and acid catalyst for longer periods (18 h) than that used for the complete exchange (0.9 h) also gave unusual results. Substantial decomposition of **2** occurs with this longer heating, and recovery was effected by neutral alumina chromatography. In both cases, ^2H NMR indicated a much higher level of deuterium at the benzylic methylene positions than at the acetal center; the ratio was ca. 4/1 for each of the cis and trans benzylic positions relative to the acetal site. Other than the time of heating, the only apparent difference in treatment between the equal incorporation and low acetal ratio samples was chromatography of the latter. To test for possible exchange at this stage, we subjected a portion of the material containing 40% deuterium at each position, which was described earlier, to chromatography, using a freshly opened container of neutral alumina. Unfortunately, only traces of apparent acetal survived this treatment. We are thus uncertain as to whether the longer heating or chromatography is responsible for the apparent selective loss of deuterium.

The possible reversibility of the Diels–Alder reaction of IBF and NB was explored by heating a sample of pure endo,exo adduct in chlorobenzene (ca. 0.1 equiv of mesitoic acid was added to approach more closely the conditions of formation) at 140 °C for 30 h (sealed tube). No decomposition of the starting material was observed, and no detectable exo,exo isomer was formed. We assume the exo,exo adduct to be the more stable of the pair, and its bridgehead proton singlet would allow the detection of relatively small amounts. The Diels–Alder step with this dienophile is thus effectively irreversible under our reaction conditions.

We and others[5] have observed that solutions of preformed IBF (no acid present) give cycloadducts rapidly at room temperature with better dienophiles such as MA and NPM. The reaction with NB under these conditions is much slower, requiring several days to approach completion. An NMR tube kinetic run for this reaction exhibited the expected second- order behavior, with $k = 1.5 \times 10^{-5}$ M^{-1} s^{-1} at 22 °C.[19] If one assumes a value for $\Delta S^{\ddagger} = -30$ cal mol^{-1} deg^{-1} (characteristic of many Diels–Alder reactions[20]), the second-order rate constant for this reaction at 140 °C would be ca. 3×10^{-2} M^{-1} s^{-1}, i.e., very much faster than any of the acid-catalyzed reactions of **2** examined. The much slower reactions actually observed, even with NPM where cycloaddition is rate determining, indicate that the equilibrium concentration of IBF is very low under the typical acid-catalyzed reaction conditions with **2**.

In earlier work[8] with the ortho ester **4** it was found that acetic acid was suitable, while the stronger trifluoroacetic and methanesulfonic acids were ineffective for causing Diels–Alder reactions; the reasons for this are clarified in the next section of this paper. It was not evident from these results what to expect from the use of strong acids for reactions of acetals. This question was briefly explored in NMR tube experiments by using **2** and various dienophiles (ambient temperature, $CDCl_3$ solvent) by adding 1 equiv of trifluoroacetic acid. In each case the acetal was rapidly consumed (within 1 h), and the reactions are marked by intense color development. Interestingly, with the two better dienophiles MA and NPM peaks corresponding to Diels–Alder adducts with IBF were observed (plus other absorptions), while no indication of cycloadduct formation was found with DMAD (stability?) or NB. On consideration of NPM and NB, these results parallel those found with mesitoic acid at higher temperature in that cycloaddition is competitive with other processes with the more reactive dienophile but not with NB. Again IBF is implicated as an intermediate in the trifluoroacetic acid catalyzed reactions, but the stronger acid is, not unexpectedly, more effective at causing loss of acetal through polymerization. We also noted that over the several hours these mixtures were observed a singlet developed which we attribute to methyl trifluoroacetate. Its formation would deplete both a product (methanol) and the catalyst.

An overall mechanism which accommodates the various observations on acid-catalyzed reactions of **2** is shown in Scheme I. The half order in mesitoic acid is explained by step 1. Steps 1–4 are rapidly established equilibria, as shown by the deuterium-incorporation results with added CH_3OD. Step 5 is rate determining for the faster reacting dienophiles such as NPM, whereas the reversible formation of a product (oligomer) is rate determining for loss of acetal

(19) This rate constant was determined by Dr. M. A. Makhlouf, using IBF generated with LDA in ether/hexane solvent. The downfield singlet of IBF and the vinyl protons of NB are clearly disinguishable, and integrals for the product (aromatic protons) were normalized by assuming 1:1 stoichiometry for the reaction. The actual yield of cycloadducts was estimated to be ≥70%; some polymerization of IBF may have occurred. The true rate constant for the Diels–Alder reaction is likely ±30% of the value given in the text.

(20) For example, see: Lowry, T. H.; Richardson, K. S. "Mechanism and Theory in Organic Chemistry", 2nd ed.; Harper and Row: New York, 1981; p 848.

Scheme I

$$(HA)_2 \underset{}{\overset{K_1}{\rightleftharpoons}} 2HA \quad (1)$$

$$2 + HA \overset{K_2}{\rightleftharpoons} A^- + \text{I} \quad (2)$$

I

$$\text{I} \overset{K_3}{\rightleftharpoons} CH_3OH + \text{II} \quad (3)$$

II

$$\text{II} + A^- \overset{K_4}{\rightleftharpoons} HA + IBF \quad (4)$$

$$IBF \xrightarrow{\text{dienophile}} \text{Diels-Alder product} \quad (5)$$

$$IBF \overset{+\text{II},\ CH_3OH}{\rightleftharpoons} \text{dimer/oligimer} \quad (6)$$

$$\text{oligimer} \xrightarrow{\text{acid, IBF}} \text{polymer} \quad (7)$$

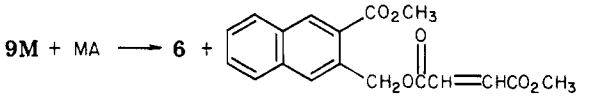
either in the absence of dienophile or in the presence of a poorer dienophile such as NB (step 6). Step 7 invokes the effectively irreversible formation of a product, presumably polymeric, to account for loss of the acetal in the absence of dienophile; this is likely to be a competitive side reaction with poorer dienophiles and accounts for the diminished yields of cycloadducts.

The much faster reactions with trifluoroacetic acid require that a higher concentration of IBF be formed with this catalyst than with mesitoic acid to account for the rapid formation of cycloadducts with MA and NPM. The known slow rate of Diels–Alder reaction of NB and IBF at room temperature would not allow this process to compete effectively with steps 6 and 7 of Scheme I.

From a synthetic standpoint for Diels–Alder applications, the use of acetal **2** (and by inference the higher homologue **8**) is shown to be dependent on the nature of the acid catalyst employed, and the reasons for this are explicable in terms of the competing processes outlined in Scheme I. While simple carboxylic acids of pK_a ca. 5 are satisfactory for a wide range of dienophiles, they may not represent the best catalysts for each dienophile. Stronger acids will generate higher operational levels of IBF but will also speed polymerization. When the desired Diels–Alder reaction is either unaffected or subject to a lower degree of acid catalysis than polymerization, weaker acids should be the more useful.

(c) Reactions of Ortho Esters. The Diels–Alder reactions of acetals **2** and **8** under acid catalysis are similar in conditions and times needed to effect conversions with various dienophiles. Since ortho ester **4** (R = Me or Et) had given satisfactory cycloadditions with several reactive dienophiles (but not NB), there was reason to expect that **9** would similarly serve as a precursor to 1-alkoxyisonaphthofuran adducts. This was a desirable synthetic goal since the ketal function in the adducts can be used for further elaboration at two defined centers. However, to summarize the results of many attempts, we have been unable to effect the conversion of **9** to Diels–Alder products with a variety of dienophiles and reaction conditions. We conclude that 1-alkoxyisonaphthofuran is inaccessible under acid-catalyzed conditions, because of the intervention of lower activation energy pathways available to the ortho ester function. The results obtained with **9** and some new observations on the reactions of **4** are outlined below, and the basis for the differences in reactions of the two seemingly closely related systems is discussed.

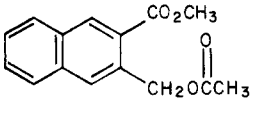
Initial attempts involved the use of MA as the dienophile with either the dimethyl (**9M**) or diethyl (**9E**) derivative of **9**. The starting material is rapidly consumed on heating; for example, no **9E** remained after 0.5 h in refluxing benzene with 1 equiv or more of MA. The resulting NMR spectrum indicated the formation of naphthalide **6** and material which appeared to be an ethyl ester. Higher temperatures (refluxing toluene or chlorobenzene) and longer reaction times did not materially affect the outcome. Use of **9M** gave similar results, with NMR peaks attributable to methyl esters. Recrystallization of the residue from a reaction carried out in refluxing toluene gave an analytically pure sample of the major product **20**. This



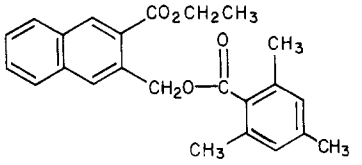
20

material is presumably formed by the following sequence: (a) reaction of traces of maleic acid with **9M** to give carbenium ion intermediate and methanol; (b) methanol attack on MA to give the half-ester of maleic acid; (c) reaction of the latter, as the anion, at the benzylic methylene position of the carbocation to generate **20**.

To avoid complications due to opening of MA, reactions were attempted by using NPM, AAN, and DMAD with acetic, mesitoic, trifluoroacetic, and other acid catalysts, but no evidence of Diels–Alder product formation was obtained. Instead, varying amounts of lactone **6** and ring-opened diester products analogous to **20** were formed. For example, use of **9M**, AAN, and acetic acid (ca. 1 equiv) gave complete consumption of ortho ester with formation of **6** (ca. 25%) and diester **21** (ca. 75%). Similarly, **9E** in



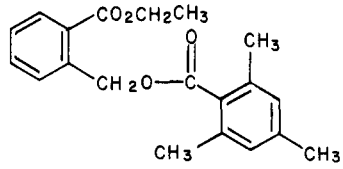
21



22

the presence of various dienophiles and mesitoic acid gave NMR evidence for the formation of diester **22**. By using larger than catalytic amounts of the acid, it was possible to isolate this material for complete characterization.

To gain a better understanding of the mechanisms involved, we turned to the simpler ortho ester **4**. Unlike **9**, **4** had been shown[8,9] to give moderate to good yields of cycloadducts with several activated dienophiles. This was reiterated by treating the ethyl derivative **4E** with 1 equiv of DMAD and 0.1 equiv of mesitoic acid in refluxing chlorobenzene for 1 h (no reaction occurs at room temperature). The major product is the ketal cycloadduct, part of which has been further converted to the aromatized naphthol described earlier.[8,9] Thus mesitoic acid is an effective catalyst for the formation of 1-alkoxyisobenzofuran (1-RO-IBF), and this process occurs rapidly at 131 °C (all **4E** consumed in less than 1 h). Interestingly, however, when **4E** is treated under the same conditions (0.1 equiv of acid) with the dienophile omitted, the mesitoic acid is totally consumed in less than 1 h, with approximately 20% loss of **4E**; longer heating (up to 92 h) does not cause any further change in the NMR spectrum. Integration of the spectrum indicated that, within measurement error, all of the mesitoic acid is accounted for by formation of diester **23**. The remainder of **4E** consumed is accounted for by the formation of phthalide, ca. 10% by integration. Thus competitive pathways exist for the loss of **4** and these also occur rapidly under conditions



23

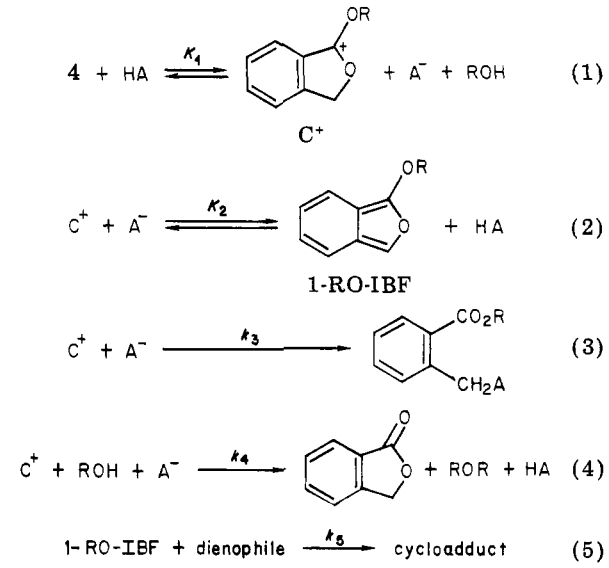
where cycloadducts are obtained with reactive dienophiles.

When **4E** is treated with 1 equiv of mesitoic acid in refluxing chlorobenzene (no dienophile), the ortho ester is entirely consumed in less than 0.5 h, with **23** and phthalide being formed in a ca. 3/1 ratio. Again the material balance is good, as judged by integration of the mesitoate methyl peaks vs. those for **23** and phthalide, indicating that little if any loss of **4E** occurs by alternative routes, e.g., polymerization of 1-RO-IBF. Comparison of the benzylic methylene integral of **23** with the ethyl ester absorptions showed that the only ester present was **23**; although ethyl mesitoate absorptions occur at the same chemical shifts as the corresponding peaks for **23**, as shown by admixture of an authentic sample, no measurable amount of the simpler mesitoate is formed in these reactions. Thus the phthalide arises by a process other than mesitoate anion attack on the ethyl group of the cationic intermediate. It appears that the anionic nucleophile exhibits a strong preference for attack at the benzylic methylene position of the cation, whereas ethanol (the only other obvious nucleophile present) gives phthalide by attack at the ethyl group under these conditions. While the formation of diethyl ether has not been unambiguously demonstrated, peaks corresponding to this expected product are seen in the NMR spectra of sealed-tube reaction mixtures, and these peaks are lost on evaporation of the solvent.

A sample of pure **23** with 1 equiv of DMAD was refluxed in chlorobenzene for 30 h. No change in the NMR spectrum was observed. Therefore, the formation of **23** is irreversible. Scheme II outlines a mechanism which accounts for the observations described. The presumed dissociation of acid dimer step is omitted for simplicity. The common intermediate for all processes is the oxacarbenium ion (C^+), which presumably exists as an ion pair in the relatively nonpolar solvents used in this work. The formation of C^+ is shown as a concerted process rather than as stepwise protonation–dissociation, although evidence on this point is lacking under our reaction conditions. The products of step (1) may either revert to starting materials (rapid equilibrium) or form phthalide via step 4. Alternative reactions of C^+ are elimination to 1-RO-IBF (step 2) or nucleophilic opening to form **23** (step 3). To account for both the rapid reactions of cycloaddition (with better dienophiles) and formation of **23** irreversibly, with good material balance in the absence of dienophiles, the formation of 1-RO-IBF must be readily reversible (step 2).

There is no reason to expect that the reactions of **4** should differ in mechanism from those of the naphthalene analogue **9**. The question therefore remains as to why **4** gives Diels–Alder reactions and **9** does not. In terms of Scheme II, the answer must lie in relative rate differences. This point was explored by treating an equimolar mixture of ***9E*** and ***4E*** with 0.5 equiv (relative to total ortho ester) of mesitoic acid in refluxing chlorobenzene. The NMR spectrum showed that the major products, diesters **22** and **23**, are formed in equal amounts, and the corresponding lactones are also formed, as minor components, in essentially equal amounts. Thus the overall activation energies for steps 1, 3, and 4 of Scheme II are identical for both ***4E*** and ***9E***. The failure of **9** to give Diels–Alder products must

Scheme II



therefore represent a change in either step 2 or the cycloaddition step (step 5). It is unlikely that 1-RO-INF is unreactive as a diene partner in cycloaddition, in view of the parallel reactions exhibited by IBF and INF generated from the corresponding acetals. In fact, in both systems the 1-alkoxy substituent would normally be expected to enhance cycloaddition reactivity. Thus it appears that the failure of **9** to give Diels–Alder reactions is a reflection of a very unfavorable equilibrium for formation of 1-RO-INF (step 2).

As noted earlier, strong acids fail to catalyze Diels–Alder reactions of **4**, and **9** behaves simiarly. The reason for this became apparent when ***4E*** was treated with trifluoroacetic acid in chlorobenzene or $CDCl_3$ at room temperature. A very rapid reaction, complete within a few minutes, occurs. When less than 1 equiv of acid is used, the acid is totally consumed. The products are the trifluoroacetate analogue of **23** (identification based on a singlet at 5.8 ppm in $CDCl_3$), ethanol, phthalide, and ethyl trifluoroacetate, the last two being formed in equal amounts; in addition, there is residual ***4E***. No diethyl ether is formed. It was shown by a control experiment using ethanol and trifluoroacetic acid in $CDCl_3$ that esterification is too slow to account for the ethyl trifluoroacetate, so this product must be formed by attack of trifluoroacetate anion at the ethyl group of the carbenium ion, giving also phthalide in an equal amount. When the reaction is done in the presence of NPM or DMAD, no cycloaddition is observed. Since we expect the Diels–Alder reactions of 1-RO-IBF to be very rapid with these dienophiles (cf. results with acetal **2** under these conditions), it appears that no significant level of this species is formed under the strong acid conditions. The overall much faster reaction, relative to those involving acetic or mesitoic acid, is explicable in terms of Scheme II by recognizing that strong acid will generate a higher concentration of carbenium ion (step 1), while the trifluoroacetate ion as a weak base will be less effective for the elimination process (step 2). The failure of strong acids to initiate cycloadditions is thus explained by very rapid alternative reactions which consume the acid. In our earlier work[8] this was not apparent because of the small (catalytic) amounts of acid employed.

The requirements of a catalyst to favor elimination to 1-RO-IBF or -INF at the expense of these alternative routes can be simply stated but not so easily attained for the higher homologue. The ideal catalyst must be a strong enough acid to facilitate carbenium ion formation, while

its conjugate base must be effective in causing elimination but not nucleophilic displacement. Various amine salts would seem to meet these requirements, and this reasoning led us to examine the use of pyridinium, 2,6-di-*tert*-butylpyridinium, and ethyldiisopropylammonium tetrafluoborates. Use of 0.1 equiv of each of these salts with **4*E*** and DMAD caused complete loss of the ortho ester when refluxed in chlorobenzene for 0.5–1 h. Aromatized Diels–Alder product was detected by NMR in yields of ca. 35%, <5%, and 60%, respectively. Phthalide is the major product with the first two salts and accounts for most of the balance of **4*E*** with the Hunig's base salt. When **4*E*** and 1 equiv of the latter salt were heated in the absence of dienophile, reaction was complete in less than 0.3 h (131 °C). The mixture darkened, and a large amount of phthalide was produced. This reaction was repeated in a sealed tube (140 °C, 1 h) with 0.1 equiv of the salt; again the **4E** was nearly all consumed, leading to phthalide and diethyl ether (as shown by peak enhancement on addition of this material), along with a small amount of what appears to be the product of ethanol attack at the benzylic methylene group. It is clear that efforts to diminish the nucleophilicity of the conjugate base of the catalyst are thwarted by ethanol, generated in the formation of carbenium ion, filling the role of nucleophile.

Since the trialkylamine salt gave the best cycloaddition results with **4E**, we used this material (0.05 equiv) in an attempt to catalyze a similar reaction of **9E** with DMAD. As anticipated, however, no Diels–Alder reaction was observed, while **9E** was converted to naphthalide **6** as the nearly exclusive product.

The Hunig's base salt has one potential advantage over carboxylic acids as a catalyst in that it is not consumed by the alternative reactions which accompany the latter. This might be useful in cases where cycloaddition is especially facile. However, it appears that the rate of reaction with ethanol is also enhanced by the use of the amine salt (presumably because the amine is a more efficient proton acceptor), with the net result that the carboxylic acids will in most instances lead to better yields of cycloadducts.

Experimental Section

Proton NMR spectra were recorded on a Varian T-60 with $CDCl_3$ as the solvent unless otherwise specified. Proton noise decoupled ^2H NMR spectra were obtained on a Nicolet NT-300 instrument, with CCl_4 as the solvent containing a known quantity of cyclohexane-d_{12} to calibrate chemical shifts and to obtain quantitative estimates of deuterium content. Melting point were determined in open capillary tubes on a Mel-Temp apparatus and are uncorrected. IR spectra were run on a PE-283 instrument, and mass spectral data were obtained on a VG Micromass ZAB-2F instrument. Combustion analyses were done by Galbraith Laboratories.

1(3*H*)-Benzo[*f*]isobenzofuranone (6). The general procedure of Cava[1,3] was followed. Commerical 2,3-naphthalenedicarboxylic accid (25 g) was heated in refluxing acetic anhydride containing a small amount of acetyl chloride for 8 h. When the mixture cooled, the anhydride (98%; mp 251–252 °C, lit.[1] mp 250–251 °C) was isolated by vacuum filtration. Sodium borohydride reduction gave naphthalide **6**: 88% yield; mp 212–213 °C (lit.[3] mp 207–209 °C).

1-Ethoxy-1,3-dihydrobenzo[*f*]isobenzofuran (8, R = Et). Alkylation of **6** to **7** (R = Et) was effected by treating a slurry of 6.3 g (34 mmol) of naphthalide in 140 mL of CH_2Cl_2 (distilled from $LiAlH_4$) with 51 mmol of freshly prepared diethoxycarbenium tetrafluoborate[12] in 20 mL of CH_2Cl_2. This mixture was stirred for 48 h at room temperature, giving a burgundy-colored clear solution.

This solution was added dropwise (0.5 h) to an ice-cooled well-stirred solution of $NaBH_4$ (58 mmol) in 80 mL of dry DMF. After an additional 0.5 h of stirring, the contents were poured into excess water and extracted three times with ether. The organic phase was washed with small volumes of water and brine, dried over K_2CO_3, and rotary evaporated to give 7.3 g (quantitative) of solid; the ^1H NMR of this material indicated that it consisted of 85% **8** and 15% **6**.

A column was prepared by using 120 g of neutral Type I alumina (Sigma) and pentane/ether (1:1, with ca. 1% triethylamine added), and the crude acetal was rapidly eluted with this same solvent to give 2.95 g (40%) of analytically pure **8**. Other than recovered **6**, the remaining material was lost on the column, and we have found that, in general, significant losses of acetals occur regardless of column packing used or efforts to maintain neutral or basic conditions. Acetal **8** (R = Et) crystallizes as colorless leaflets on evaporation of solvent: mp 126–127 °C; ^1H NMR δ 1.25 (t, J = 7 Hz, 3 H), 3.4–4.1 (m, resembling a pair of quartets, diastereotopic protons OCH_2CH_3), 4.98–5.50 (AB pattern, downfield peaks broadened by W coupling with acetal proton, larger peaks appearing as broadened singlets at 5.20 and 5.30, $ArCH_2$), 6.35 (sl br s, 1 H, acetal), 7.3–7.9 (m, 6 H, aromatic); MS, m/z 214.0994 (calcd), 214.0997 (found). Anal. Calcd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.58. Found: C, 78.22; H, 6.63.

1,3-Dihydro-1-methoxybenzo[*f*]isobenzofuran (8, R = Me). A mixture of **8** (R = Et; 0.935 g, 4.4 mmol), 40 mL of methanol, and 0.2 mL of trifluoroacetic acid was stirred at room temperature for 12 h under nitrogen. It was then poured into excess dilute bicarbonate solution and extracted with ether. The usual washing, drying, and evaporation gave 0.785 g (89%) of solid which by NMR was essentially pure product. Recrystallization from methanol gave colorless plates: mp 86–87 °C; ^1H NMR δ 3.40 (s, 3 H), 4.90–5.40 (AB pattern, $ArCH_2$, analogous to ethyl analogue), 6.20 (sl br s, 1 H, acetal), 7.25–7.95 (m, 6H, aromatic); MS, m/z (relative intensity) 200 (M^+, 32), 169 (100). Anal. Calcd for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found: C, 77.88; H, 6.09.

1,1-Diethoxy-1,3-dihydrobenzo[*f*]isobenzofuran (9, R = Et). The carbenium ion **7** (R = Et) was prepared as described above from 2.88 g (15.7 mmol) of **6** with a reaction time of 12 h. The resulting solution was added dropwise to a stirred ice-cooled solution of sodium ethoxide (78 mmol) in 50 mL of absolute ethanol. After being stirred briefly, the mixture was poured into 200 mL of water and extracted with ether. Drying (K_2CO_3) and evaporation gave 3.42 g (85%) of crude **9** which contained ca. 5% of **6** (NMR). Samples from other attempts which contained greater amounts of starting lactone could be partially separated by trituration with small volumes of ether, in which **6** is only slightly soluble. Pure **9** (R = Et) was obtained by recrystallization from aqueous ethanol containing a trace of triethylamine: mp 66–68 °C; ^1H NMR δ 1.18 (t, 6 H), 3.30–3.90 (m, 4 H, diastereotopic OCH_2CH_3), 5.10 (s, $ArCH_2$), 7.25–7.95 (m, 6 H, aromatic); MS, m/z 258.1256 (calcd), 258.1270 (found). Anal. Calcd for $C_{16}H_{18}O_3$: C, 74.39; H, 7.02. Found: C, 74.27; H, 6.99.

The methyl analogue of **9** (R = Me) was similarly prepared by using dimethoxycarbenium tetrafluborate, but efforts to obtain analytically pure material were thwarted by facile conversion to **6** on attempted recrystallization. The best sample obtained (low-temperature crystallization from hexane) had the following: mp 52–54 °C; ^1H NMR δ 3.38 (s, 6 H), 5.25 (s, 2 H), 7.40–8.0 (m, 6 H.) Material of approximately 90% purity, the remainder being **6**, was used in the runs involving **9** (R = Me).

Reactions of 8 with Dienophiles. (a) Maleic Anhydride. Acetal **8** (R = Et; 70 mg, 0.33 mmol) and MA (42 mg, 0.43 mmol) were heated in 2.0 mL of refluxing toluene for 17 h under nitrogen. When the mixture cooled, 34 mg (40%) of solid precipitated, which by NMR was nearly pure exo adduct. Recrystallization from toluene gave *exo*-**10**: mp 285–286 °C; IR (KBr) 1850, 1780 cm^{-1}; ^1H NMR (acetone-d_6) δ 3.60 (s, 2 H), 5.98 (s, 2 H, benzylic), 7.40–8.10 ppm (m, 6 H, aromatic); MS, m/z 267.0609 (calcd for $^{13}CC_{15}H_{10}O_4$), 267.0612 (found). Anal. Calcd for $C_{16}H_{10}O_4$: C, 72.17; H, 3.78. Found: C, 71.95; H, 3.92.

The residual toluene solution was evaporated to give 45 mg (52%) of solid which was largely *endo*-**10**, contaminated with a small amount of exo isomer. Recrystallization from aqueous acetone gave *endo*-**10**: mp 195–198 °C; ^1H NMR δ 3.98 (m, 2H, AA′XX′ pattern for protons adjacent to carbonyls), 5.75 (m, 2 H, AA′XX′, benzylic), 7.3–7.9 (m, 6 H, aromatic); MS, m/z 266.0578 (calcd for $C_{16}H_{10}O_4$), 266.0579 (found).

(b) Dimethyl Acetylenedicarboxylate. The reaction of 8 (R = Et, 394 mg, 1.84 mmol), 2.75 mmol of DMAD, and 0.19 mmol of mesitoic acid in 4.0 mL of refluxing chlorobenzene was followed by NMR, observing the disappearance of the upfield ethoxy triplet and the formation of product peak at ca. 6.0 ppm (benzylic singlet). Unlike acetal reactions with other dienophiles, the mesitoic acid methyl region (2–3 ppm) in DMAD runs exhibited peak broadening and the formation of unexplained new absorptions. Control experiments failed to explain this behavior. When mesitoic acid and DMAD were heated under the reaction conditions for several hours, no changes were observed. Treatment of 8 with 0.23 equiv of mesitoic acid in refluxing chlorobenzene (no dienophile) led to complete consumption of acetal in 10 h, giving a black residue with a complex NMR spectrum which did not, however, show a change in the mesitoic acid peaks. The reaction with all three materials was terminated after 61 h, although no change was observed after 30 h, when it appeared that essentially all of the acetal had been consumed. By NMR the estimated yield of cycloadduct appeared to be modest. The residue after vacuum evaporation was chromatographed on silica gel, yielding a viscous oil which crystallized on standing for several days (27%). Recrystallization from hexane gave 11: mp 116–118 °C; IR ($CHCl_3$) 1743, 1718 (sh) cm^{-1}; ^1H NMR δ 3.75 (s, 6 H), 5.98 (s, 2 H), 7.2–7.8 (m, 6 H), MS, m/z 310.0841 (calcd for $C_{18}H_{14}O_5$), 310.0839 (found).

This reaction was repeated with 8 (R = Me) and a reflux time of 35 h, giving 11 in an estimated (NMR) 52% yield. Use of ethyldiisopropylammonium tetrafluoborate as catalyst (0.1 equiv) with 8 (R = Et) similarly gave 11 in 55% yield, as determined by NMR through addition of a weighed amount of mesitoic acid to the crude product.[21]

(c) Butenolide. A chlorobenzene solution of 8 (R = Et; 300 mg, 1.40 mmol), 130 mg (1.54 mmol) of butenolide, and 20 μL of glacial acetic acid was refluxed for 44 h, and the mixture was then placed in a freezer (-15 °C) overnight. The crystalline precipitate was vacuum filtered and recrystallized from hexane to give 113 mg (32%) of *endo*-**12**: mp 194–196 °C; IR ($CHCl_3$) 1775 cm^{-1}; ^1H NMR δ 3.40–4.35 (m, 4 H), 5.45 (d, J = 5 Hz, 1 H, benzylic), 5.65 (d, J = 5 Hz, 1 H, benzylic), 7.25–7.9 (m, 6 H, aromatic); MS, m/z (relative intensity) 252 (M^+, 6), 168 (100). Anal. Calcd for $C_{16}H_{12}O_3$: C, 76.18; H, 4.79. Found: C, 75.96; H, 5.02.

The solution from the initial filtration was evaporated to give 180 mg (45%) of solid which by NMR consisted of ca. 9/1 exo/endo adducts. Recrystallization from $CHCl_3$–hexane (three times) gave *exo*-**12**: mp 265–267 °C dec; IR ($CHCl_3$) 1770 cm^{-1}; ^1H NMR ($CDCl_3$ with Me_2SO-d_6) δ 2.80 (m, 2 H), 4.0–4.4 (br m, 2 H), 5.25 (s, 1 H, benzylic), 5.60 (s, 1 H, benzylic), 7.15–7.65 (m, 6 H); MS, m/z 252.0786 (calcd), 252.0773 (found).

(d) α-Acetoxyacrylonitrile. This reaction was done in refluxing chlorobenzene (2.0 mL), with 200 mg (0.93 mmol) of 8 (R = Et), 1.87 mmol of AAN, and 0.37 mmol of mesitoic acid. No further changes were seen in the NMR spectrum after 57 h, and heating was discontinued after 80 h. After evaporation, the NMR (using mesitoic acid peaks for reference) indicated the presence of 38% exo (cyano) and 13% endo adduct. Chromatography on silica gel by using a graded elution from pentane to CH_2Cl_2 gave 60 mg (23%) of *exo*-**13**: mp 207–208 °C (after recrystallization from hexane); IR ($CHCl_3$) 1760 cm^{-1}; ^1H NMR δ 1.83 (s, 3 H), 2.0 (d, J = 13 Hz, 1 H, endo methylene proton), 3.05 (dd, J = 13, 6 Hz, 1 H, exo methylene proton), 5.60 (d, J = 6 Hz, 1 H, benzylic adjacent to CH_2), 6.15 (s, 1 H, other benzylic), 7.3–7.9 (m, 6 H, aromatic); MS, m/z 279.0895 (calcd for $C_{17}H_{13}O_3N$), 279.0901 (found).

Further elution gave *endo*-**13** contaminated with exo material which was not further purified. The ^1H NMR peaks ascribable to *endo*-**13** (by analogy with the lower homologue from IBF[8]) are δ 2.20 (s, 3 H), 2.53 (s, 1 H, endo methylene proton), 2.58 (d, J = 6 Hz, 1 H, exo methylene proton), 5.60 (d, J = 6 Hz, 1 H, benzylic), 5.75 (s, 1 H, other benzylic), and 7.35–8.0 (m, 6 H, aromatic).

(21) Interestingly, the reactions of acetals 2 and 8 (plus DMAD) are faster with Hunig's base salt than with mesitoic acid as the catalyst, although the yields of cycloadduct are similar. Further work is in progress to clarify the side reactions with DMAD and the enhanced reactivity of the ammonium salt.

(e) Norbornene. The use of a threefold excess of NB (188 mg, 2.0 mmol), 8 (R = Et; 143 mg, 0.67 mmol), and 11 mg of mesitoic acid catalyst in 4.0 mL of refluxing chlorobenzene for 65 h gave on vacuum evaporation of the solvent a residue which was chromatographed on 15 g of silica gel. Exo,exo adduct **14** was eluted by using 9/1 pentane/ether; this nearly pure material weighed 120 mg (46%): mp 144–145 °C (after recrystallaization from hexane); ^1H NMR δ 0.65–1.55 (complex m, 6 H), 1.65 (s, 2 H), 2.30 (br s, 2 H), 5.12 (s, 2 H, benzylic), 7.18–7.85 (m, 6 H, aromatic); MS, m/z 262 (M^+, 12), 168 (100). Anal. Calcd for $C_{19}H_{18}O$: C, 86.98; H, 6.92. Found: C, 86.79; H, 6.95.

Further elution with 1/1 pentane/ether gave 30 mg (11%) of endo,exo adduct **15**, which on recrystallization from hexane had a melting point of 179–180 °C: ^1H NMR δ -1.03 (br d, J = 11 Hz, 1 H, proton of bridge methylene syn to aromatic), 0.17 (br d, J = 11 Hz, 1 H, corresponding anti proton), 0.60–1.60 (m, 4 H), 1.83 (m, 2 H), 2.37 (m, 2 H), 5.22 (m, 2 H, benzylic), 7.18–7.83 (m, 6 H, aromatic); MS, m/z (relative intensity) 262 (M^+, 6), 168 (100). Anal. Found: C, 86.98; H, 7.01.

Reactions of 2 with Dienophiles. (a) Cyclohexene. A mixture of acetal 2 (R = Me; 298 mg, 2.0 mmol), 1.0 mL of cyclohexene (10 mmol), 35 mg (0.21 mmol) of mesitoic acid, and 2.0 mL of chlorobenzene was split into three equal portions which were sealed into Pyrex test tubes. These tubes were fully immersed in an oil bath maintained at 140 ± 2 °C. The tubes were opened after 77, 105, and 230 h and exhibited methoxy singlets corresponding to ca. 35%, 30%, and 12% unreacted acetal, respectively. The contents were pooled, and the solvent was evaporated. Chromatography of the residue on 40 g of neutral Type I alumina gave, with pentane/ether (2/1), 20 mg (5%) of a solid indentified as *exo*-**16**, which was recrystallized from hexane: mp 99–99.5 °C; ^1H NMR (CCl_4) δ 1.20–1.80 (m, 10 H), 4.70 (s, 2 H, benzylic), 7.0 (s, 4 H, aromatic); MS, m/z 118 (100), 119 (12), no parent ion, and no other peaks greater than 5% of base. Anal. Calcd for $C_{14}H_{16}O$: C, 83.96; H, 8.05. Found: C, 83.86; H, 8.27.

Further elution gave the major *endo*-**16** isomer: 220 mg (55%); mp 79–80 °C (after recrystallization from hexane); ^1H NMR (CCl_4) δ 0.3–0.8 (vbr m, 2 H), 1.20–1.55 (m, 6 H), 2.3–2.8 (br m, 2 H), 5.0 (m, 2 H, benzylic), 7.0 (s, 4 H, aromatic); MS, m/z (relative intensity) 118 (100). Anal. Found: C, 83.58; H, 8.36.

(b) Norbornene. Runs were made in refluxing toluene (46 h) and chlorobenzene (22 h) by using 3.0 and 1.5 equiv of norbornene, respectively, with 2 (R = Et) and mesitoic acid catalyst. The use of an efficient reflux condenser and a low nitrogen flow was essential to prevent loss of NB. Yields of adducts were estimated by NMR to be ca. 60% in both runs. These products have been previously characterized[8] (see corrected NMR chemical shifts given in the text for the upfield protons of the endo isomer).

(c) Dimethyl Acetylenedicarboxylate. In a preliminary experiment[22] using acetic acid as the catalyst in refluxing toluene (6 days) and 2 (R = Et), the IBF–DMAD adduct (dimethyl 1,4-dihydro-1,4-oxy-2,3-naphthalenedicarboxylate) was isolated (30%) as a viscous oil: IR ($CHCl_3$) 1742, 1714 cm^{-1}; ^1H NMR (CCl_4) δ 3.76 (s, 6 H), 5.8 (s, 2 H), 6.90–7.11 and 7.27–7.47 (4 H, AA'BB' pattern, aromatic); MS, m/z 260.0684 (calcd), 260.0685 (found). Anal. Calcd for $C_{14}H_{12}O_5$: C, 64.61; H, 4.65. Found: C, 64.76; H, 4.80.

Three additional reactions with 2 in refluxing chlorobenzene were carried out, with yields estimated by NMR through addition of phthalide as an internal standard. With mesitoic acid catalyst (0.1 equiv) and 2 (R = Et), the yield after 30 h was 30%. Ethyldiisopropylammonium tetrafluoborate catalyst[21] (0.1 equiv) led to 47% (R = Et) and 57% (R = Me), respectively.

Reactions of 9. (a) Formation of Maleate Ester 20. Ortho ester 9 (R = Me; 1.0 g, 4.3 mmol) and MA (0.51 g, 5.2 mmol) were heated in refluxing toluene (8.0 mL) for 40 h. When the mixture cooled, solid 6 precipitated and was removed. The remaining solution was evaporated to give a solid residue, which was triturated with hot hexane to separate additional slightly soluble 6. On cooling, the hexane solution deposited crystals. This procedure was repeated several times to obtain pure triester 20: mp 86–87 °C; IR ($CHCl_3$) 1725 cm^{-1} (broad complex absorption); ^1H NMR

(22) We thank Dr. M. A. Makhlouf for carrying out the initial work with this system and characterizing the DMAD–IBF cycloadduct.

δ 3.60 (s, 3 H), 3.90 (s, 3 H), 5.65 (s, 2 H, $ArCH_2$), 6.20 (s, 2 H, vinyl), 7.35–7.95 (br m, 5 H, aromatic), 8.45 (s, 1 H, aromatic); MS, m/z 328.0947 (calcd), 328.0969 (found). Anal. Calcd for $C_{18}H_{16}O_6$: C, 65.85; H, 4.91. Found: C, 66.01; H, 4.92.

The same product **20** was identified by NMR, again as the major component, when the reaction was carried out in refluxing benzene. No indication of Diels–Alder adduct formation was seen in the spectra of crude reaction mixtures.

Further evidence of structure was obtained by saponifying **20** with KOH in CH_3OH; when the resulting solution was diluted with water and acidified, naphthalide **6** was obtained in 91% yield.

(b) Acetate 21. The reaction of **9** with acetic acid was observed in attempts to form cycloadducts with DMAD and AAN. Thus **9** (R = Me; 35 mg, 0.13 mmol), DMAD (0.24 mmol), and acetic acid (0.13 mmol) were refluxed in 1.5 mL of toluene for 50 h. The crude reaction mixture after vacuum evaporation showed by NMR the presence of lactone **6** and diester **21**, in approximately a 2/1 ratio. Chromatography on silica gel with a graded pentane–CH_2Cl_2 solvent gave **21**, which was recrystallized from hexane: mp 82–83 °C; IR ($CHCl_3$) 1725 cm^{-1}; ^1H NMR δ 2.10 (s, 3 H), 3.90 (s, 3 H), 5.60 (s, 2 H), 7.35–7.95 (m, 5 H), 8.50 (s, 1 H, aromatic); MS, m/z (relative intensity) 258 (M^+, 8), 215 (24), 183 (100). Anal. Calcd for $C_{15}H_{14}O_4$: C, 69.76; H, 5.46. Found: C, 69.86; H, 5.61.

(c) Mesitoate 22. This product was detected by NMR in attempts to form a cycloadduct from **9** with DMAD by using mesitoic acid as a catalyst. To prepare a sample for subsequent use, a reaction was carried out with no dienophile present; **9** (R = Et; 50 mg, 0.19 mmol) and 0.19 mmol of mesitoic acid were refluxed for 1 h in chlorobenzene (no **9** remaining by NMR). The crude product consisted of **6** and **22** in a ratio of ca. 1/2. After removal of most of the lactone by trituration, the residue was recrystallized from $CHCl_3$–hexane to give pure **22**: mp 63–64 °C; IR ($CHCl_3$) 1725 cm^{-1}; ^1H NMR (CCl_4) δ 1.40 (t, J = 7 Hz, 3 H), 2.25 (s, 9 H, mesitoate CH_3 protons), 4.30 (q, J = 7 Hz 2 H), 5.70 (s, 2 H), 6.65 (s, 2 H, mesitoate aromatic), 7.25–7.90 (m, 5 H), 8.35 (s, 1 H, aromatic); MS, m/z (relative intensity) 229 (50), 184 (58), 147 (100). Anal. Calcd for $C_{24}H_{24}O_4$: C, 76.57; H, 6.43. Found: C, 76.37; H, 6.69.

Diester 23. Ortho ester **4** (R = Et; 50 mg, 0.24 mmol) and 0.24 mmol of mesitoic acid were heated in refluxing chlorobenzene for 0.5 h, and the solvent was then vacuum evaporated. Phthalide and **23** were formed in a ca. 1/3 ratio. Recrystallization from hexane gave pure **23**: mp 77–78 °C; IR ($CHCl_3$) 1720 cm^{-1}; ^1H NMR δ 1.35 (t, J = 7 Hz, 3 H), 2.25 (s, 9 H), 4.30 (q, J = 7 Hz, 2 H), 5.70 (s, 2 H), 6.75 (s, 2 H), 7.1–8.0 (m, 4 H); MS, m/z (relative intensity) 326 (M^+,2), 147 (100), 135 (32). Anal. Calcd for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79. Found: C, 73.72; H, 6.88.

Amine Tetrafluoborate Salts. Commercial (Alfa) tetrafluoboric acid (62%) in ether was diluted 20-fold with anhydrous ether, and an equivalent amount of the amine (pyridine, 2,6-di-*tert*-butylpyridine, ethyldiisopropylamine) was added slowly by syringe with ice-bath cooling under nitrogen. The white crystalline precipitates were filtered and washed several times with ether in a drybox. These salts have limited solubility in chlorobenzene at room temperature but dissolve on heating.

Deuterium Analyses. A standard reference solution was prepared by dissolving 8.0 μL of cyclohexane-d_{12} in 60 mL of CCl_4. The density of perdeuteriocyclohexane (0.89) was assumed to be that of cyclohexane (0.778) corrected by the ratio of molecular weights. This solution thus contained 1.5×10^{-5} mol of deuterium/mL, with the reference ^2H signal appearing at 1.385 ppm. For most samples examined, the solution was used directly, while for others appropriate dilutions were used to give comparable sample/reference peak sizes. The samples, after treatment as described in the text, were evaporated to constant weight and taken up in a measured volume, usually 2.0 mL, of the reference solvent. The ^2H singlets (proton decoupled) appeared as follows: for acetal **2** (R = Me), 6.10 (acetal), 5.10 (methylene D presumed trans to methoxy), and 4.94 ppm (methylene D presumed cis to methoxy), based on assumed W coupling in the proton spectrum of undeuterated material;[8] for **18**, 5.01 ppm; for **19**, 5.07 ppm. These chemical shifts all are in good agreement with those of the corresponding protons in the ^1H NMR spectra.

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Registry No. **1**, 268-51-9; **2E**, 75802-19-6; **2M**, 67536-29-2; **4E**, 70103-17-2; **6**, 4711-50-6; **8E**, 85827-93-6; **8M**, 85827-94-7; **9E**, 85827-95-8; **9M**, 85828-02-0; *endo*-**10**, 85827-96-9; *exo*-**10**, 85880-59-7; **11**, 85827-97-0; *endo*-**12**, 85827-98-1; *exo*-**12**, 85880-60-0; *endo*-**13**, 85827-99-2; *exo*-**13**, 85880-61-1; **14**, 85880-62-2; **15**, 85828-00-8; *endo*-**16**, 85880-64-4; *exo*-**16**, 85880-63-3; **20**, 85828-03-1; **21**, 85849-60-1; **22**, 85828-04-2; **23**, 85828-05-3; MA, 108-31-6; DMAD, 762-42-5; BL, 497-23-4; AAN, 3061-65-2; NB, 498-66-8; cyclohexene, 110-83-8; dimethyl 1,4-dihydro-1,4-oxy-2,3-naphthalenedicarboxylate, 85828-01-9; mesitoic acid, 480-63-7.

Selective Reductions of 3-Substituted Hydantoins to 4-Hydroxy-2-imidazolidinones and Vicinal Diamines[1]

Sergio Cortes and Harold Kohn*[2]

Department of Chemistry, University of Houston, Houston, Texas 77004

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N^3-Substituted hydantoins (**1**) have been shown to undergo $LiAlH_4$ reduction (THF, room temperature, 2 days) to give 4-hydroxy-2-imidazolidinones (**3**) in good yields. Reduction of 3,5-disubstituted hydantoins in which an aliphatic substituent was present at nitrogen 3 led to the preferential formation of the cis adduct **3**. Conversely, disubstituted hydantoins possessing an aryl moiety at nitrogen 3 gave the trans derivative **3** as the major product. Treatment of the N^3-substituted hydantoins (**1**) under more vigorous conditions (THF, reflux, 3 days) led to selective ring opening of **1** to yield *N*-methylethylenediamines (**7**). The scope of both of these reductive processes has been explored, and explanations are offered to account for the observed results. Full spectral (infrared, ^1H and ^{13}C NMR, and mass spectra) data on all three classes of compounds (**1**, **3**, and **7**) have been collected. Together this information provides a consistent data set which is useful in structure elucidation. Moreover, various NMR aids have been discerned for the isomeric *cis*- and *trans*-4-hydroxy-2-imidazolidinones (**3**) which permitted stereochemical assignments for these compounds.

Hydantoins (**1**, Chart I) are important medicinal and synthetic compounds.[3] Although much is known about their chemical reactivity, surprisingly little is known about their reactions with hydride reducing agents.[4-7] Lithium

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