by distillation under reduced pressure (9-OCH_3, 91%; 9-CH_3, 76%) or by silica gel chromatography (9-C_6H_5, 26%). The last reaction was noted to proceed sluggishly.

Hydrolytic Incorporation of Oxygen-18. To a solution of the acetal in anhydrous THF (10 mL) was added 1.2 equiv of $H_2{}^{18}O$ (50% isotopically enriched) followed by 2 drops of concentrated H_2SO_4. The reaction mixture was stirred at room temperature, and the progress of the hydrolysis was monitored by TLC. When complete, triethylamine (4 drops) was added, stirring was continued for 5 min, and solvents were carefully removed on a rotary evaporator. The labeled ketone was distilled from the flask under reduced pressure. For R = OCH_3: reaction time of 24 h; 4.8 equiv of $H_2{}^{18}O$ utilized; 3.0 g of acetal furnished 1.59 g (72%) of 2-methoxycyclohexanone containing 40% of ^{18}O. For R = C_6H_5: reaction time of 20 min; 1.08 g of acetal gave 806 mg (94%) of 2-phenylcyclohexanone containing 45% of ^{18}O. For R = CH_3: reaction time of 25 min; 3.0 g of acetal afforded 1.999 g (94%) of 2-methylcyclohexane containing 39% of ^{18}O.

Alkylation and Hydroboration of the Labeled 2-Substituted Cyclohexanones. These reactions were performed in the previously described manner with essentially identical efficiencies. For 1-OCH_3: $^{13}C-^{16}O$, 72.72 ppm; $^{13}C-^{18}O$, 72.69 ppm. For 1-C_6H_5: $^{13}C-^{16}O$, 72.26 ppm; $^{13}C-^{18}O$, 72.22 ppm. For 1-CH_3: $^{13}C-^{16}O$, 72.68 ppm; $^{13}C-^{18}O$, 72.65 ppm. For 2-OCH_3: $^{13}C-^{16}O$, 73.56 ppm; $^{13}C-^{18}O$, 73.53 ppm. For 2-C_6H_5: $^{13}C-^{16}O$, 73.79 ppm; $^{13}C-^{18}O$, 73.75 ppm. For 2-CH_3: $^{13}C-^{16}O$, 73.68 ppm; $^{13}C-^{18}O$, 73.65 ppm.

Acid-Catalyzed Cyclization of the Labeled Diols. These cyclizations were carried out as described previously. The product ratios were determined by GC analysis. The diastereomeric tetrahydrofurans were separated by column chromatography on silica gel. All reactions were performed in duplicate. See Table I. For 5-OCH_3: $^{13}CH_2-^{16}O$, 67.77 ppm; $^{13}CH_2-^{18}O$, 67.75 ppm. For 5-C_6H_5: $^{13}CH_2-^{16}O$, 67.97 ppm; $^{13}CH_2-^{18}O$, 67.95 ppm. For 5-CH_3: $^{13}CH_2-^{16}O$, 67.55 ppm; $^{13}CH_2-^{18}O$, 67.52 ppm. For 6-OCH_3: $^{13}CH_2-^{16}O$, 67.67 ppm; $^{13}CH_2-^{18}O$, 67.65 ppm. For 6-C_6H_5: $^{13}CH_2-^{16}O$, 67.34 ppm; $^{13}CH_2-^{18}O$, 67.32 ppm. For 6-CH_3: $^{13}CH_2-^{16}O$, 67.21 ppm; $^{13}CH_2-^{18}O$, 67.18 ppm.

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Acid-Catalyzed Cyclization of 1,4-Diols Tethered to (Butadiene)iron Tricarbonyl Segments. Isotopic Labeling as a Mechanistic Probe of Stereochemical Retention during Tetrahydrofuran Formation

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Abstract: 1,4-Butanediols can undergo acid-catalyzed dehydrative cyclization by either of two pathways. Selected 1-(3-hydroxypropyl)cyclohexanols have previously been shown to prefer the intramolecular S_N2 option where displacement of water by the more highly substituted carbinol oxygen atom operates. All four ^{18}O-labeled 1,4-diols prepared in this study, constructed so as to carry the secondary hydroxyl immediately adjacent to a tricarbonyliron-complexed diene, choose the alternative S_N1 option. As a consequence, all of the isotopic content is absent in the tetrahydrofuran products, and stereochemical integrity is not preserved. Control experiments performed under the same mild conditions reveal product equilibration to be facile. Consequently, the opposite mechanistic extreme is followed by these systems. Other ground-state and transition-state considerations are discussed.

The ability of selected 1-(3-hydroxypropyl)cyclohexanols carrying electron-withdrawing 2-substituents to undergo acid-catalyzed conversion to spirocyclic tetrahydrofurans preferentially via an intramolecular S_N2 mechanism is now an established fact.[2] Even in those cases where the resident proximal group is capable of favorable inductive contributions (e.g., methyl), the alternative S_N1 option is not adopted exclusively. This remarkable departure from conventional mechanistic behavior has prompted us to examine structural building blocks other than cyclohexane rings for their capability to promote ionization via one or the other of these competing processes.

A systematic extension to tricarbonyl(*trans*-π-pentadienyl)iron systems forms the basis of the present report. Unsymmetrically substituted dienes selectively complexed to $Fe(CO)_3$ are playing increasingly utilitarian roles in organic synthesis.[3] Their intrinsic chirality and ability to be produced conveniently in optically pure condition have further broadened the range of interest.[3b,4]

No less impressive is the recent report[5] that the epimeric alcohols **1** and **4** are transformed in the presence of ethereal tetrafluoroboric acid to the optically active cyclized products **3** and **6**, respectively, with clean retention of stereochemistry. These results were attributed to the intervention of intermediate Fe(CO)$_3$-complexed pentadienyl cations **2** and **5**, which were formed stereoselectively because of anchimerically assisted departure of the protonated tertiary hydroxyl group with recapture of the ethereal oxygen from the same face as the departed water molecule. These observations are, however, also consistent with operation of the intramolecular S_N2 pathway.

Considerably earlier, the solvolytic studies of Clinton and Lillya showed definitively that the ionization of 3,5-dinitrobenzoates **7**

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[‡] Evans Chemical Laboratories.

(1) Merck Postdoctoral Fellow, 1992.
(2) (a) Negri, J. T.; Paquette, L. A. *J. Am. Chem. Soc.*, preceding paper in this issue. (b) Paquette, L. A.; Negri, J. T. *J. Am. Chem. Soc.* **1991**, *113*, 5072.
(3) (a) Fatiadi, A. J. *J. Res. Natl. Inst. Stand. Technol.* **1991**, *96*, 1. (b) Franck-Neumann, M. *Organometallics in Organic Synthesis*; de Meijere, A., tom Dieck, H., Eds.; Springer-Verlag: Berlin, 1987; pp 247-264. (c) Koerner von Gustorf, E. A.; Grevels, F. W.; Fischler, I. *The Organic Chemistry of Iron*; Academic Press: New York, 1981; Vol. 2, pp 1-154.
(4) Grée, R. *Synthesis* **1989**, 341.
(5) Teniou, A.; Toupet, L.; Grée, R. *Synlett* **1991**, 195.

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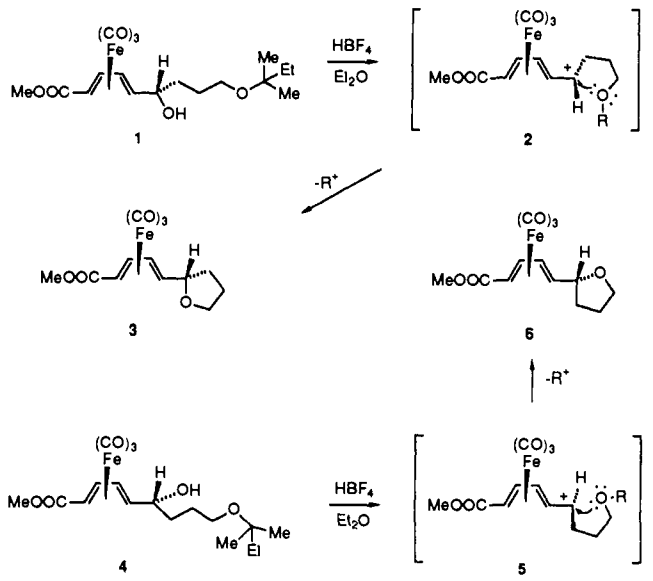
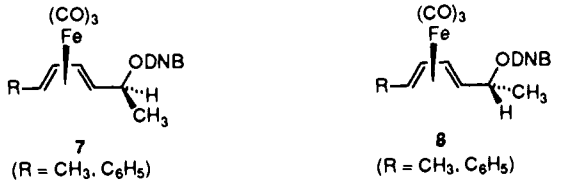


and **8** to carbocations is greatly facilitated in 80% aqueous acetone relative to their uncomplexed counterparts.[6] Estimated minimum

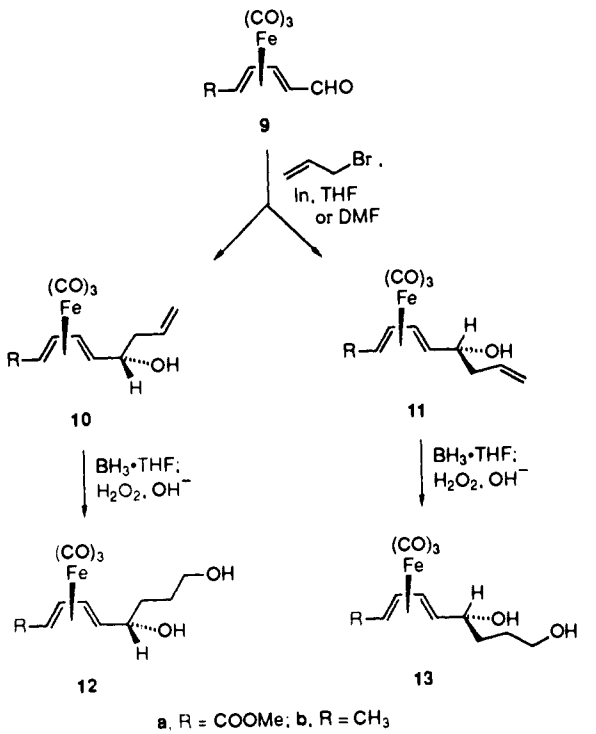


rate differences ran as high as 8700. In these examples, S_N1 behavior with exclusive alkyl–oxygen cleavage was clearly adhered to, (*trans*-π-pentadienyl)iron cations were formed in all cases, and complete retention of configuration was observed in the products.

The crux of the present issue is which of two limiting alternatives accurately represents the manner in which 1,4-diols related to **1** and **4** undergo intramolecular acid-catalyzed dehydration. At the outset, it was already clear that cations related to **2** and **5** are capable of being produced much more readily than cyclohexyl carbenium ions. Consequently, our purposes would be best served if both electropositive and electronegative R groups were incorporated into the molecules to be studied. In this way, some assessment of the extent of inductive transmission through the complexed dienyl unit might also be possible.

Results

Synthesis of the Requisite Diols. Regiospecific ^{18}O Incorporation. When the addition of allylmagnesium bromide to **9a** was found to proceed with unsatisfactory chemoselectivity, recourse was made instead to indium-promoted allylation.[7,8] Upon exposure of **9a** dissolved in THF to allyl bromide in the presence of indium powder at room temperature, a very clean and rapid reaction ensued to generate the readily separable ψ-endo and ψ-exo alcohols[9] **10a** and **11a** in a 45:55 ratio. The stereochemical assignments follow from the relative R_f values of the epimers,[10] with the ψ-endo complex **10a** being less polar than **11a** and consequently eluting more rapidly from the column.



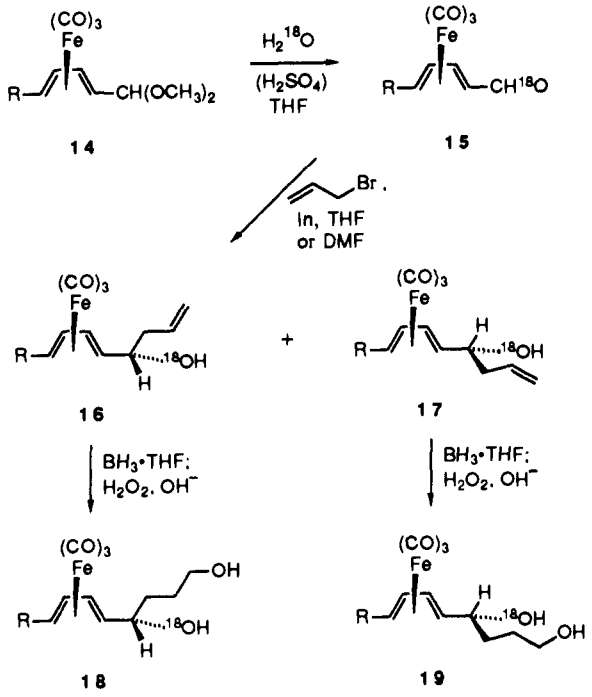
a, R = COOMe; b, R = CH_3

Preliminary hydroboration–oxidation experiments involving **11a** for the purpose of generating diol **13a** showed it to be a problematic process when carried out conventionally. Since alkaline hydrogen peroxide is known to decomplex (η^4-diene)$Fe(CO)_3$ systems, we resorted to the use of 1 M potassium hydroxide (instead of the standard 3 M) and very short reaction times (1 min) in order to limit the extent to which degradation occurred.[11a] Although minor amounts of decomplexation proved to be unavoidable, **12a** and **13a** could be isolated in 90% and 91% yields, respectively, provided that chromatographic purification was not attempted.[11b] Adoption of a similar protocol for **10b** and **11b**, but with DMF as solvent, permitted comparably efficient conversion to **12b** (76%) and **13b** (83%). Alcohols **10b** and **11b** were likewise produced (72%, ratio 44:56) by indium-promoted allylation of (±)-**9b**.

Incorporation of an ^{18}O label into these diols was achieved by hydrolysis[12] of dimethyl acetals **14a** and **14b** in ^{18}O-enriched water (ca. 48% $H_2{}^{18}O$). The levels of isotopic incorporation into aldehydes **15a** and **15b** were ascertained by ^{13}C NMR analysis, taking advantage of the $^{16}O/^{18}O$ isotopic effect on the chemical shift of the carbonyl carbon.[13] Suitable integration of the respective singlets indicated the level of ^{18}O present in **15a** (45%) to be somewhat more elevated than in **15b** (40%).

From this point, the requisite three-carbon chain was introduced as before. Whereas distinctively different carbon signals could be discerned in the spectra of **16a** (45% ^{18}O), **17a** (45% ^{18}O), and **16b** (40% ^{18}O), they were unresolved in **17b** (assumed also to be at the 40% level). Such overlapping persisted in diols **18a** and **19a**, but not in their methyl-substituted counterparts **18b** (36% ^{18}O) and **19b** (20% ^{18}O). Since some loss of heavy oxygen was quite clearly occurring during the hydroboration step, it was mandatory that the extent of residual ^{18}O in **18a** and **19a** be known

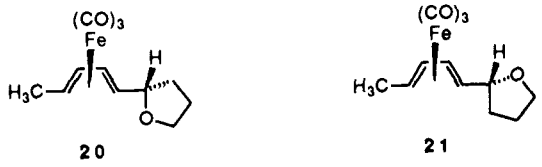
(6) Clinton, N. A.; Lillya, C. P. *J. Am. Chem. Soc.* **1970**, *92*, 3065.
(7) Butsugan, Y.; Araki, S.; Ito, H. *J. Org. Chem.* **1988**, *53*, 183. Le Marrec, N.; Mosset, P. Unpublished results.
(8) Efficient kinetic resolutions of aldehydes **9a** and **9b** during asymmetric allylboration have been described: Roush, W. R.; Park, J. C. *Tetrahedron Lett.* **1990**, *31*, 4707.
(9) The ψ-exo and ψ-endo nomenclature was introduced by Clinton, N. A.; Lillya, C. P. *J. Am. Chem. Soc.* **1970**, *92*, 3058.
(10) This so-called TLC method has seen extensive use and has proven itself to be very reliable (see refs 4, 5, 6, and 9). In the present instance, further corroboration was available by spectral comparison with homologous alcohols whose structures had been established crystallographically.[5]
(11) (a) Vigorous stirring of the two-phase reaction mixture is required to achieve this rate level. If stirring is slowed, longer reaction times (up to 15 min) are observed for completion of the reaction. (b) The borane samples available to the French group gave rise to **12a** at levels of 85% purity. The other product formed was the regioisomer. The same minor complication did not surface with **11a**.
(12) (a) Goering, H. L.; Josephson, R. R. *J. Am. Chem. Soc.* **1962**, *84*, 2779. (b) Finne, E. S.; Gunn, J. R.; Sorensen, T. S. *J. Am. Chem. Soc.* **1987**, *109*, 7816. (c) Kirchen, R. P.; Ranganayakulu, K.; Sorensen, T. S. *J. Am. Chem. Soc.* **1987**, *109*, 7811. (d) Buffam, D. J.; Sorensen, T. S.; Whitworth, S. M. *Can. J. Chem.* **1990**, *68*, 1889.
(13) (a) Risley, J. M.; Van Etten, R. L. *J. Am. Chem. Soc.* **1979**, *101*, 252. (b) Risley, J. M.; Van Etten, R. L.; Uncuta, C.; Balaban, A. T. *J. Am. Chem. Soc.* **1984**, *106*, 7836. (c) Wilgis, F. P.; Neumann, T. E.; Shiner, V. J., Jr. *J. Am. Chem. Soc.* **1990**, *112*, 4435.



a, R = COOMe; **b**, R = CH_3

with reasonable certainty. As discussed below, cyclization via the monotosylate allows the tertiary hydroxyl group in these diols to remain resident. Once these ring closures were performed, **22** and **23** were found to contain 27% and 24%, respectively, of the isotopic label. It is therefore very likely that their precursor diols are similarly enriched. We choose not to speculate on the mechanism by which C–O bond heterolysis operates to some degree at the tertiary carbinol site in the presence of the borane–tetrahydrofuran complex. Fortunately, the residual amounts of ^{18}O in all four diols were more than sufficient for our intended purposes.

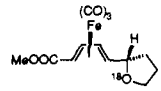
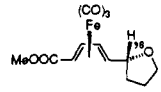
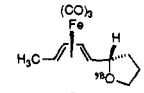
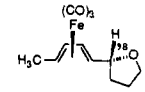
Cyclization Studies. For standardization purposes, all four unlabeled diols were first cyclized efficiently via their monotosylates so as to preclude stereochemical randomization. In this way, definitive characterization of **3**, **6**, **20**, and **21** was made possible. The ordering of polarity originally observed in the allylic alcohols **10** and **11** was again found to be a useful diagnostic of relative stereochemistry, the ψ-endo diastereomer being less polar.



Analogous cyclization of **18a,b** and **19a,b** gave good yields of the four isotopically labeled analogues **22–25**. A consequence of the presence of the ^{18}O atom was immediately apparent in their ^{13}C NMR spectra, since the signals of both carbon atoms linked to oxygen were now twinned in response to the isotope effect. The relevant data are collected in Table I, and an example is illustrated in Figure 1. The ultimate mechanistic test was whether comparable levels of stereoselectivity *and* isotopic content would prevail under acidic conditions.

When **18a** dissolved in anhydrous benzene containing a catalytic quantity of Amberlyst 15 was heated in a Soxhlet apparatus containing calcium hydride as desiccant, conversion to a 1.0:1.2 mixture of **3** and **6** materialized. Relevantly, *neither tetrahydrofuran contained any residual ^{18}O within the limits of detection of the NMR spectrometer*. Consequently, recourse was next made to a lower reaction temperature. Stirring **18a** in CH_2Cl_2 containing Amberlyst 15 with or without powdered 4-Å molecular sieves at room temperature did lead to improved yields. Although a somewhat higher percentage of inverted diastereomer **6** was produced (1.0:1.9), neither product showed evidence of being isotopically labeled (Table II). The results with **19a** were entirely comparable.

Table I. Selected ^{13}C NMR Spectral Data for **22–25**[a]

labeled tetrahydrofuran	carbon shifts in ppm (relative % intensity) >CH-^{16}O	>CH-^{18}O	>CH_2-^{16}O	>CH_2-^{18}O
 **22**	79.56(74)	79.53(26)	67.73(73)	67.71(27)
 **23**	80.76(74)	80.73(26)	68.67(78)	68.64(22)
 **24**	80.06(61)	80.03(39)	67.77(59)	67.74(41)
 **25**	81.80(80)	81.77(20)	68.68(80)	68.66(20)

[a] Spectra were run at 75 MHz in C_6D_6 solution.

Table II. Acid-Promoted Cyclizations of Labeled Diols **18** and **19**

diol	solvent	*T*, °C	Ψ-endo: Ψ-exo ratio	combined yield, %
18a	C_6H_6	80	1.0:1.2	40
	CH_2Cl_2	20	1.0:1.9	58
19a	C_6H_6	80	1.0:1.1	41
	CH_2Cl_2	20	1.0:1.7	62
18b	C_6H_6	80	1.0:1.4	51
	CH_2Cl_2	20	1.0:1.4	57
19b	C_6H_6	80	1.0:1.7	52
	CH_2Cl_2	20	1.0:1.9	55

For the purpose of determining whether the reaction products were interconverting under the reaction conditions, **3** was stirred in CH_2Cl_2 at 20 °C as described above for 13 h.[14] This treatment led to the isolation of a 1.0:1.5 mixture of **3** and **6**. Similarly, resubmission of **6** to the acidic ion-exchange resin at room temperature returned a 1.0:1.6 mixture of the same two heterocycles.

The response of methyl derivatives **18b** and **19b** proved to be equally lacking in both stereocontrol and retention of the ^{18}O isotope. Under no conditions was residual labeling noted. As in the earlier series of experiments, the ψ-exo tetrahydrofuran was favored in each instance. Thus, **21** invariably dominated over **20**. The control experiments involving **20** and **21** gave evidence that the equilibrium ratio was very likely in the range 1.0:1.7–1.9.

Discussion

The demonstration that 1,4-diols tethered to (butadiene)iron tricarbonyl components as in **18** and **19** undergo acid-catalyzed cyclization with the loss of their tertiary hydroxyl groups, irrespective of relative configuration and the electronic nature of the R group, supports the conclusion that formation of coordinated (*trans*-π-pentadienyl)iron cations is product-determining. The overwhelming extent to which site-specific alkyl–oxygen cleavage occurs validates expectations whose foundation is in the enhanced solvolytic behavior of **7** and **8**.[6] The ψ-exo ester **8** enters into S_N1 ionization approximately 90 times faster than the structurally related ψ-endo isomer **7**. Since **8** is also at least 8700 times more reactive than the uncomplexed 3,5-dinitrobenzoate, the capacity of both diastereomeric esters for anchimerically assisted ionization is seen to be impressively high. In actuality, the innate capacity

(14) The rate of equilibration is actually quite fast, such that equilibrium is attained in approximately 1 h.

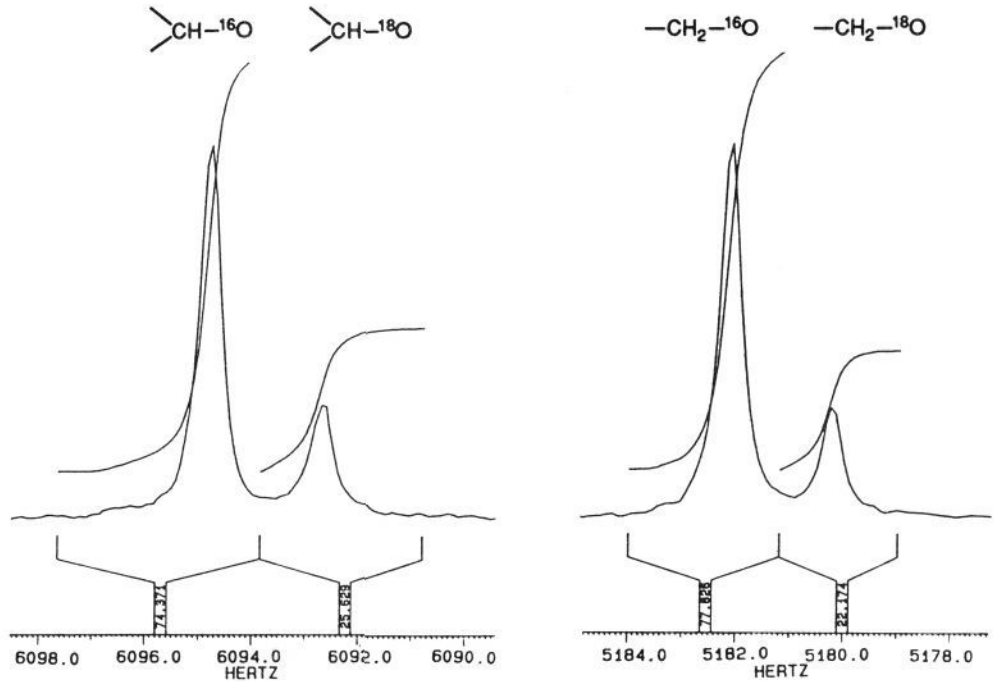


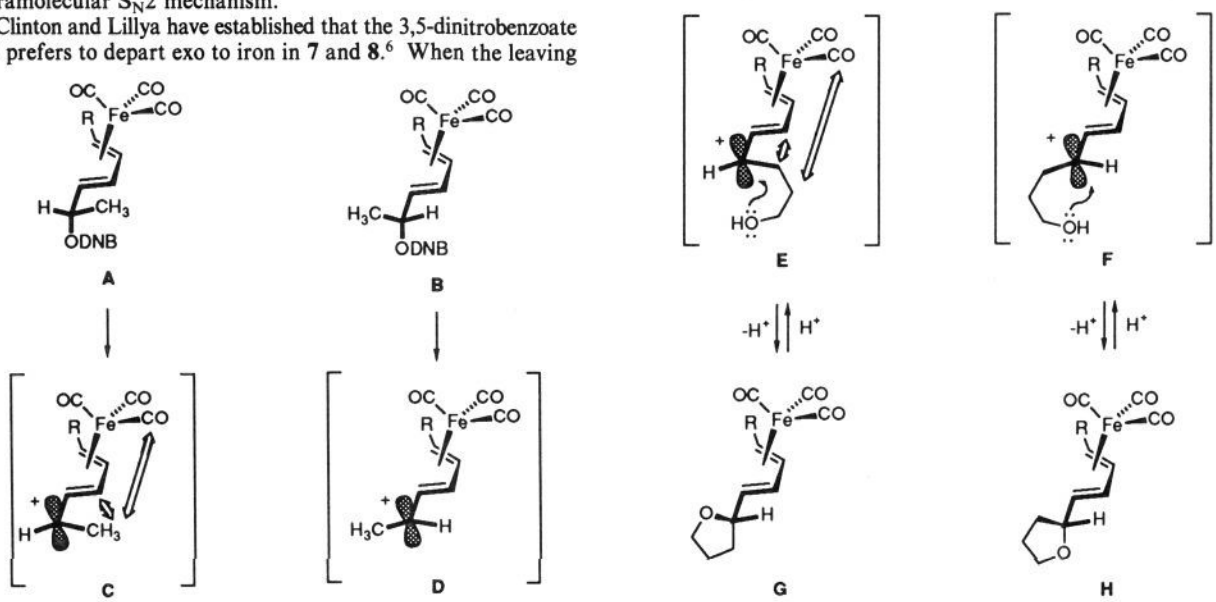
Figure 1. Partial expanded ^{13}C NMR spectrum of isotopically labeled **6** showing the level of precision attainable by integration of those signals derived from the α- and α'-tetrahydrofuranyl carbons.

of these systems for effective hyperconjugative interaction is adequate to override the completely competitive operation of the intramolecular S_N2 process so prevalent in cyclohexyl systems.[2]

The significant issue here would appear to be the realization that we have succeeded in bracketing the limits of both reactivity extremes. With this groundwork in place, it will be of interest to elucidate the extent to which other less electronically biased structural networks are suited for ring closure to tetrahydrofurans along one mechanistic extreme or the other. It should be stressed that unstinting adherence to S_N1 ionization in the present examples persists in those cases where R is carbomethoxy. A reasonable conclusion is that the capacity of the iron atom for neighboring group participation remains respectably high irrespective of the nature of R. This is not to say that hyperconjugative contributions are not attenuated. Unfortunately, rate data are not available to provide quantitative insight into this issue. It is clear nonetheless that the carbomethoxy groups in **18a** and **19a** do not retard S_N1 ionization adequately to allow for the competitive incursion of the intramolecular S_N2 mechanism.

Clinton and Lillya have established that the 3,5-dinitrobenzoate ion prefers to depart exo to iron in **7** and **8**.[6] When the leaving group is aligned so as to take maximum advantage of edge-on participation by the metal center, **7** is required to adopt a conformation (see **A**) more sterically congested than that associated with **8** (as in **B**). The transition-state destabilization resulting from the indicated methyl/dienyl and methyl/carbonyl interactions in **C** was offered as an explanation for the slower rate of ionization of **7**. Although similar modest steric retardation could be operative in the present study, it is hardly sufficient to deter ionization via the S_N1 pathway.

The failure of **18** and **19** to undergo conversion to the tetrahydrofurans with retention of configuration reveals an overall lack of stereochemical constraint. In light of the fact that **7** and **8** experience solvolysis with essentially complete retention of configuration under short-life conditions,[6] it is entirely possible that intramolecular cyclization within **E** and **F** is similarly well behaved at the outset.[5] However, these ring closures are comparatively slow, such that the long-life conditions needed to complete the conversion permit return from **G** and **H** to **E** and **F**. The potential



for σ-bond rotation within these cations leads to eventual loss of stereochemistry. Suitable control experiments have indeed revealed that **3** and **6** as well as **20** and **21** do interconvert at room temperature under the reaction conditions. The ψ-exo isomers are favored at or near equilibrium. We attribute this behavior to the existence of steric compression in **E** that is not present in **F**. The greater polarity of the ψ-exo isomer can be rationalized in terms of greater accessibility to the nonbonded oxygen lone pairs in **H**.

Conclusions

By subjecting **18a,b** and **19a,b** to acid-catalyzed ring closure, we have demonstrated that S_N1 ionization can indeed dominate over the intramolecular S_N2 process that is so strongly favored in less electronically biased systems. The tell-tale consequences of classical ionization are complete loss of the isotopic label and randomization of product stereochemistry. Our ability to equilibrate the tetrahydrofurans represents the first available opportunity to evaluate ground-state energy imbalances in (butadiene)iron tricarbonyl derivatives. The extent to which ψ-exo diastereomers are favored (ca. 2:1) may originate from the electronically beneficial antiperiplanar arrangement of the polar C–O bond and electron-rich $Fe(CO)_3$ group as depicted in **H**.

Now that the extremes of both possible mechanistic modes of ring closure have been observed, we are hopeful that the response of many structurally diverse 1,4-diols will be defined by similar means in the years ahead.

Experimental Section

Melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 1320 spectrometer. ^1H NMR spectra were recorded at 300 MHz and ^{13}C NMR spectra at 75 or 22.5 MHz, as indicated. Mass spectra were recorded on a Kratos MS-30 instrument at The Ohio State University Chemical Instrument Center. Elemental analyses were performed at the Scandinavian Microanalytical Laboratory, Herlev, Denmark, and by the Service de Microanalyses (IDRS, Suresnes). All separations were carried out either under flash chromatographic conditions on Merck silica gel HF_{254} or by MPLC on Lobar Lichroprep Si 60 prepacked glass columns (40–63 μm silica gel). The organic extracts were dried over anhydrous magnesium sulfate. Solvents were reagent grade and in many cases dried prior to use. The Amberlyst 15 resin was dried by azeotropic removal of water from a slurry in refluxing benzene followed by overnight drying in vacuo at 25 °C.

Alkylation of 9a. A 250-mL flask containing powdered indium (1.72 g, 14.9 mmol) was flame-dried and cooled under nitrogen. Following the addition of dry THF (70 mL) and allyl bromide (70 mL, 43 mmol), the mixture was vigorously stirred for 5 min prior to the dropwise addition of **9** (4.0 g, 14.3 mmol) dissolved in anhydrous THF (70 mL). Upon completion of the addition, the reaction mixture was stirred for 15 min, diluted with water, and extracted with ether. The combined organic phases were washed with water, dried, and concentrated under reduced pressure. Flash chromatography of the residual oil (elution with ether–petroleum ether, 1:1) afforded **10a** (1.9 g, 41%) as a viscous yellow-orange oil that solidified on prolonged standing, mp 45–46 °C, and **11a** (2.3 g, 50%) as a yellow crystalline solid, mp 98–100 °C.

For **10a**: IR ($CHCl_3$, cm^{-1}) 3600, 2080, 2000, 1710; ^1H NMR (300 MHz, $CDCl_3$) δ 5.82 (m, 2 H), 5.41 (dd, J = 8.6, 5.1 Hz, 1 H), 5.20 (s, 1 H), 5.16 (m, 1 H), 3.69 (m, 1 H), 3.65 (s, 3 H), 2.46 (m, 1 H), 2.26 (m, 1 H), 1.84 (br s, 1 H), 1.33 (t, J = 7.3 Hz, 1 H), 0.96 (d, J = 8.0 Hz, 1 H); ^{13}C NMR (22.5 MHz, C_6D_6) δ 209.5, 172.5, 134.3, 118.4, 84.2, 83.1, 71.7, 69.8, 51.3, 46.0, 45.1; MS m/z (M^+) calcd 322.0140, obsd 322.0140. Anal. Calcd for $C_{13}H_{14}FeO_6$: C, 48.48; H, 4.38. Found: C, 48.55; H, 4.19.

For **11a**: IR ($CHCl_3$, cm^{-1}) 3600, 2080, 2000, 1710; ^1H NMR (300 MHz, $CDCl_3$) δ 5.83 (m, 2 H), 5.50 (m, 1 H), 5.20 (m, 2 H), 3.67 (s, 3 H), 3.66–3.58 (m, 1 H), 2.46 (m, 1 H), 2.31 (m, 1 H), 2.02 (br s, 1 H), 1.28 (m, 1 H), 1.04 (d, J = 7.6 Hz, 1 H); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 210.1, 172.6, 134.4, 118.3, 85.3, 83.9, 72.0, 67.3, 51.4, 46.3, 43.7; MS m/z (M^+) calcd 322.0140, obsd 322.0124. Anal. Calcd for $C_{13}H_{14}FeO_6$: C, 48.48; H, 4.38. Found: C, 48.44; H, 4.28.

Alkylation of 9b. To a mixture of **9b** (253 mg, 1.08 mmol) and indium powder (186 mg, 1.62 mmol) in dry DMF (3 mL) was added allyl bromide (139 μL, 1.62 mmol) dissolved in DMF (1.5 mL) via cannula. After 40 min, the reaction mixture was quenched with 0.1 N HCl (2 mL), diluted with ether and water, and processed in the manner described above. Isolated were 112 mg (37%) of **10b** as a yellow oil and 142 mg (48%) of **11b** as a yellow solid, mp 54–55 °C.

For **10b**: IR ($CHCl_3$, cm^{-1}) 3600, 2050, 1980; ^1H NMR (300 MHz, C_6D_6) δ 5.55 (m, 1 H), 4.95 (m, 2 H), 4.68 (dd, J = 8.6, 4.9 Hz, 1 H), 4.40 (dd, J = 8.8, 5.0 Hz, 1 H), 3.27 (m, 1 H), 2.06 (m, 2 H), 1.18 (d, J = 3.3 Hz, 1 H), 1.06 (d, J = 6.2 Hz, 3 H), 0.72 (m, 1 H), 0.66 (m, 1 H); ^{13}C NMR (75 MHz, C_6D_6) δ 134.0, 118.5, 85.3, 80.7, 72.7, 67.2, 57.9, 44.5, 19.0 ($Fe(CO)_3$ not seen); FAB MS m/z (M^+) calcd 278.09, obsd 278.10. Anal. Calcd for $C_{12}H_{14}FeO_4$: C, 51.83; H, 5.07. Found: C, 52.01; H, 5.25.

For **11b**: IR ($CHCl_3$, cm^{-1}) 3600, 2048, 1980; ^1H NMR (300 MHz, C_6D_6) δ 5.75 (m, 1 H), 5.05 (m, 2 H), 4.76 (dd, J = 8.0, 3.5 Hz, 1 H), 4.38 (dd, J = 8.8, 4.9 Hz, 1 H), 3.25 (m, 1 H), 2.24 (m, 1 H), 2.07 (m, 1 H), 1.18 (d, J = 4.4 Hz, 1 H), 1.03 (d, J = 6.2 Hz, 3 H), 0.72 (m, 1 H) (OH proton not observed); ^{13}C NMR (75 MHz, C_6D_6) δ 134.0, 118.9, 86.5, 82.2, 72.9, 63.4, 58.3, 43.1, 19.1 ($Fe(CO)_3$ not seen); FAB MS m/z (M^+) calcd 278.09, obsd 278.09. Anal. Calcd for $C_{12}H_{14}FeO_4$: C, 51.83; H, 5.07. Found: C, 52.03; H, 5.22.

Hydroboration–Oxidation of the Allylic Alcohols. A. 10a. To a solution of **10a** (385 mg, 1.20 mmol) in cold (0 °C), dry THF (4 mL) was added borane·THF complex (1.26 mL of 1.0 M in THF, 1.26 mmol). The mixture was stirred at 0 °C for 1 h and treated all at once with 1.26 mL of 1.0 M KOH and 1 mL of 30% hydrogen peroxide; 1 min later it was poured into a separatory funnel containing brine (15 mL) and ether (15 mL). The separated organic layer was washed with water (2×) and brine, dried, and evaporated to give **12a** as an orange oil that solidified on prolonged standing, mp 102 °C (from ether) (369 mg, 90%): IR ($CHCl_3$, cm^{-1}) 3400, 2060, 2000, 1715, 1170; ^1H NMR (300 MHz, C_6D_6) δ 5.53 (ddd, J = 8.0, 5.2, 0.9 Hz, 1 H), 4.93 (dd, J = 8.6, 5.2 Hz, 1 H), 3.33 (s, 3 H), 3.30–3.08 (m, 3 H), 2.33 (br s, 1 H), 1.46–1.22 (series of m, 4 H), 0.96 (ddd, J = 8.8, 5.3, 0.8 Hz, 1 H), 0.96 (dd, J = 8.1, 0.9 Hz, 1 H), 0.45 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.4, 172.5, 85.5, 84.0, 73.0, 66.9, 62.7, 51.7, 46.1, 36.2, 28.6; MS m/z ($M^+ - H_2O$) calcd 322.0139, obsd 322.0148. Anal. Calcd for $C_{13}H_{16}FeO_7$: C, 45.91; H, 4.74. Found: C, 45.99; H, 4.58.

B. 11a. Hydroboration of **11a** (373 mg, 1.16 mmol) according to the above procedure gave 360 mg (91%) of **13a** as a yellow crystalline solid, mp 86–87 °C (from ether): IR ($CHCl_3$, cm^{-1}) 3400, 2060, 2000, 1715, 1170; ^1H NMR (300 MHz, C_6D_6) δ 5.53 (ddd, J = 8.0, 5.2, 1.0 Hz, 1 H), 4.93 (dd, J = 8.6, 5.2 Hz, 1 H), 3.33 (s, 3 H), 3.30–3.18 (m, 3 H), 2.33 (br s, 1 H), 1.46–1.22 (series of m, 4 H), 0.92 (m, 2 H), 0.45 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.5, 172.5, 85.5, 84.0, 73.0, 66.9, 62.7, 51.7, 46.1, 36.2, 28.6; MS m/z ($M^+ - H_2O$) calcd 322.0139, obsd 322.0148. Anal. Calcd for $C_{13}H_{16}FeO_7$: C, 45.91; H, 4.74. Found: C, 45.65; H, 5.08.

C. 10b. Following the procedure outline above, 189 mg (0.685 mmol) of **10b** was converted into diol **12b** (183 mg, 90%) as a yellow oil that solidified on prolonged standing, mp 74–75 °C: IR ($CHCl_3$, cm^{-1}) 3610, 3405, 2025, 1970; ^1H NMR (300 MHz, $CDCl_3$) δ 5.15 (br m, 1 H), 5.04 (br m, 1 H), 3.66 (br m, 2 H), 3.48 (m, 1 H), 2.26 (br s, 2 H), 1.70 (br m, 4 H), 1.40 (d, J = 5.8 Hz, 3 H), 1.30–0.85 (series of m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 85.3, 80.6, 73.7, 68.4, 62.8, 58.0, 37.0, 29.2, 19.0 ($Fe(CO)_3$ not seen); MS m/z (M^+) calcd 296.0347, obsd 296.0353. Anal. Calcd for $C_{12}H_{16}FeO_5$: C, 48.68; H, 5.45. Found: C, 48.76; H, 5.47.

D. 11b. From 649 mg (2.35 mmol) of **11b** was obtained 602 mg (87%) of **13b** as a yellow solid, mp 98–99 °C: IR ($CHCl_3$, cm^{-1}) 3600, 3380, 2055, 1970; ^1H NMR (300 MHz, $CDCl_3$) δ 5.23 (dd, J = 8.4, 4.6 Hz, 1 H), 5.07 (dd, J = 8.7, 4.9 Hz, 1 H), 3.70 (br m, 2 H), 3.47 (m, 1 H), 2.50 (br s, 2 H), 1.90–1.52 (m, 4 H), 1.42 (d, J = 6.2 Hz, 3 H), 1.24 (m, 1 H), 0.99 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 86.4, 82.3, 74.0, 64.5, 62.8, 58.4, 35.8, 28.7, 19.1 ($Fe(CO)_3$ not seen); MS m/z ($M^+ - 2CO$) calcd 240.0448, obsd 240.0386. Anal. Calcd for $C_{12}H_{16}FeO_5$: C, 48.68; H, 5.45. Found: C, 48.91; H, 5.62.

Diol Cyclization via Primary Monotosylates. A. 12a. To a solution of diol **12a** (170 mg, 0.52 mmol) in CH_2Cl_2 (4 mL) were added in turn triethylamine (1 mL), *p*-toluenesulfonyl chloride (108 mg, 0.57 mmol), and 4-(dimethylamino)pyridine. The mixture was stirred at room temperature for 16 h, diluted with ether, and washed successively with 0.5 M HCl, water, and brine prior to drying. Solvent evaporation left a dark orange oil that was purified by chromatography on silica gel (elution with 15% ether in petroleum ether) to give **3** as a clear, unstable yellow oil (73 mg, 54%): IR ($CHCl_3$, cm^{-1}) 2070, 2000, 1710; ^1H NMR (300 MHz, C_6D_6) δ 5.50 (ddd, J = 8.4, 5.1, 1.1 Hz, 1 H), 4.81 (dd, J = 8.3, 5.1 Hz, 1 H), 3.62 (m, 1 H), 3.46–3.32 (m, 2 H), 3.37 (s, 3 H), 1.63–1.26 (series of m, 3 H), 1.13 (m, 1 H), 0.94 (dd, J = 8.0, 5.4 Hz, 1 H), 0.86 (d, J = 8.0 Hz, 1 H); ^{13}C NMR (75 MHz, C_6D_6) δ 209.8, 172.2, 84.3, 83.2, 79.6, 68.3, 67.7, 51.2, 45.9, 34.6, 26.2; MS m/z ($M^+ - CO$) calcd 294.0190, obsd 294.0229.

B. 13a. Following the procedure described above, diol **13a** (86 mg, 0.26 mmol) was transformed into **6**, a clear yellow oil (35 mg, 42%): IR ($CHCl_3$, cm^{-1}) 2070, 2010, 1710; ^1H NMR (300 MHz, C_6D_6) δ 5.49 (dd, J = 8.2, 5.1 Hz, 1 H), 4.83 (dd, J = 8.5, 5.0 Hz, 1 H), 3.63–3.36 (series of m, 3 H), 3.32 (s, 3 H), 1.69 (m, 1 H), 1.52–1.22 (series of m, 3 H),

0.94 (m, 2 H); ^{13}C NMR (75 MHz, C_6D_6) δ 210.2, 172.0, 85.9, 84.6, 80.8, 68.7, 65.4, 51.2, 46.8, 34.2, 26.5; MS m/z (M^+) calcd 322.0140, obsd 322.0172.

C. **12b**. Treatment of **12b** (105 mg, 0.36 mmol) in an analogous fashion followed by MPLC purification of the crude product (SiO_2, elution with 10% ether in petroleum ether) afforded **20** as a clear, yellow oil (35.5 mg, 36%): IR ($CHCl_3$, cm^{-1}) 2020, 1970, 1050; ^1H NMR (300 MHz, C_6D_6) δ 4.82 (dd, J = 8.4, 4.9 Hz, 1 H), 4.42 (dd, J = 8.5, 4.9 Hz, 1 H), 3.71 (AB q, J = 14.6, 7.4 Hz, 1 H), 3.55 (AB q, J = 13.8, 6.2 Hz, 1 H), 3.45 (AB q, J = 14.2, 7.8 Hz, 1 H), 1.70–1.15 (series of m, 4 H), 1.09 (d, J = 6.2 Hz, 3 H), 0.81 (m, 1 H), 0.68 (m, 1 H); ^{13}C NMR (300 MHz, C_6D_6) δ 85.0, 80.4, 80.1, 67.8, 65.8, 56.9, 34.6, 26.0, 19.1 ($Fe(CO)_3$ not seen); MS m/z (M^+) calcd 278.0241, obsd 278.0235.

D. **13b**. Analogous processing of **13b** (143 mg, 0.48 mmol) gave **21** as a clear, yellow oil (73 mg, 54%) after MPLC purification: IR ($CHCl_3$, cm^{-1}) 2060, 1980, 1050; ^1H NMR (300 MHz, C_6D_6) δ 4.79 (m, 1 H), 4.37 (dd, J = 8.8, 4.9 Hz, 1H), 3.69 (m, 1 H), 3.58–3.45 (m, 2 H), 1.86 (m, 1 H), 1.55–1.32 (m, 3 H), 1.04 (d, J = 6.2 Hz, 3 H), 0.77 (m, 2 H); ^{13}C NMR (75 MHz, C_6D_6) δ 86.6, 83.3, 81.8, 68.7, 63.5, 58.2, 34.3, 26.6, 19.9 ($Fe(CO)_3$ not seen); MS m/z (M^+) calcd 278.0241, obsd 278.0210.

Preparation of Dimethyl Acetals 14a and 14b and Hydrolytic Incorporation of Oxygen-18. A. 15a. A solution containing **9a** (2.78 g, 10 mmol), trimethyl orthoformate (1.2 g, 11.3 mmol), and *p*-toluenesulfonic acid (30 mg) in 50 mL of anhydrous methanol was stirred at room temperature for 5 h. Triethylamine (0.5 mL) was introduced, followed by water (25 mL). Following extraction with ether, the combined organic layers were washed with brine, dried, and evaporated to give **14a** as an orange oil (3.1 g, 96%), homogeneous by TLC.

This acetal (3.1 g, 9.6 mmol) dissolved in anhydrous THF (50 mL) was treated with $H_2{}^{18}O$ (48% enriched, 209 μL, 11 mmol) and then with concentrated H_2SO_4 (2 drops). The reaction mixture was stirred at room temperature for 16 h, triethylamine (5 drops) was introduced, and the solvent was carefully removed under reduced pressure. The residual yellow solid was stirred in a 70:30 mixture of petroleum ether and ether, and the solution was decanted from the insoluble salts. Solvent evaporation gave **15a** as a yellow crystalline solid (2.52 g, 94%). ^{13}C NMR analysis showed the level of ^{18}O incorporation to be approximately 45%: $^{13}C{=}{}^{16}O$, 195.40 ppm; $^{13}C{=}{}^{18}O$, 195.37 ppm.

B. 15b. Treatment of **9b** (2.57 g, 10.9 mmol) in comparable fashion afforded the dimethyl acetal as an orange oil (2.96 g, 97%). Hydrolysis of this material in heavy water (48% ^{18}O) as described above resulted in the isolation of **15b** as an orange oil (1.99 g, 94%) into which 40% of the ^{18}O label had been incorporated: $^{13}C{=}{}^{16}O$, 196.31 ppm; $^{13}C{=}{}^{18}O$, 196.27 ppm.

Preparation of the Labeled Allylic Alcohols and 1,4-Diols. These reactions were performed in the previously described manner with essentially identical efficiencies. For **16a**: $^{13}C{-}{}^{16}O$, 71.68 ppm; $^{13}O{-}{}^{18}O$, 71.66 ppm. For **17a**: $^{13}C{-}{}^{16}O$, 71.85 ppm; $^{13}O{-}{}^{18}O$, 71.82 ppm. For **16b**: $^{13}C{-}{}^{16}O$, 72.26 ppm; $^{13}O{-}{}^{18}O$, 72.24 ppm. For **17b**: unresolved signals. For **18a**: unresolved signals. For **19a**: unresolved signals. For **18b**: $^{13}C{-}{}^{16}O$, 73.54 ppm; $^{13}O{-}{}^{18}O$, 73.52 ppm. For **19b**: $^{13}C{-}{}^{16}O$, 73.95 ppm; $^{13}O{-}{}^{18}O$, 73.92 ppm.

Acid-catalyzed cyclization of the diols was achieved as before. The relevant spectroscopic data for **22–25** are compiled in Table I.

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Evidence for Intermediates and a Change in Rate-Limiting Step in the Aminolysis of the Carcinogen *N*-Methyl-*N'*-nitro-*N*-nitrosoguanidine by Cyclic Amines[1]

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Abstract: Rate constants and products are reported for the decomposition of *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG) stimulated by cyclic amines in aqueous solutions at 40 °C, ionic strength 1 M (KCl). Plots of k_{obs} against nucleophile are linear to a concentration of nucleophile up to 0.3 M. The slopes of the plots change as a function of pH. There is no evidence of significant buffer catalysis of the reactions in control experiments containing up to 0.5 M buffer. In the pH region from 4 to 8.5, the second-order rate constants, corrected for concentration of the acid form of MNNG and free base of the amine, increase with increasing pH and level off to a pH-independent reaction in the cases of imidazole, 3,5-dimethylpyrazole, and pyrazole. The downward break in the pH rate profiles and the absence of buffer catalysis require a change in the rate-limiting step involving two, presumably tetrahedral, intermediates that are in protonic equilibrium in the pH-dependent region. It is concluded that the rate-limiting step for the pH-independent reaction involves nucleophilic attack on MNNG while leaving group expulsion from an anionic intermediate, T^-, is rate-limiting for the pH-dependent region. This represents the first evidence for reaction intermediates in the nucleophile-stimulated decomposition of MNNG. The corrected second-order rate constants for the reactions of 1,2,3- and 1,2,4-triazoles are strictly pH-dependent over the same pH range. A comparison of the rate constants for the reaction of 1,2,4-triazole with those of pyrazole indicates that the reaction of triazoles involves a direct attack of triazole anion on MNNG with subsequent rate-limiting leaving group expulsion from T^-. These conclusions require that the *N*-nitrosomethylamine anion is a worse leaving group from the intermediate T^- than the 1,2,4-triazole anion in spite of the fact that the triazole anion is estimated to be more than 3 orders of magnitude more basic. The unreactivity toward MNNG of certain amine nucleophiles, such as 4-(dimethylamino)pyridine, that are incapable of proton loss subsequent to nucleophilic attack further substantiates the conclusion that the *N*-nitrosomethylamine anion is an unexpectedly poor leaving group.

Introduction

The compound *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG) is a powerful direct-acting carcinogen. Its biological activity is believed to be the result of formation, in the course of its decomposition, of an electrophilic methyl group that reacts with DNA.[2,3] MNNG has demonstrated a cancer chemotherapeutic

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(2) The crystal structure of MNNG has recently been determined. It proves the nitrimino form in the solid state. Rice, S.; Cheng, M. Y.; Cramer, R. E.; Mandel, M.; Mower, H. F.; Seff, K. *J. Am. Chem. Soc.* **1984**, *106*, 239.

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