70–75 °C) afforded 13.4 g of the phenyl carbamate as a viscous, colorless oil: IR (film) 2910 (br), 1725, 1590, 1500, 1455, 1425, 1340, 1290, 1245, 1205, 1165, 1130, 1075, 750, 690 cm^{-1}; ^1H NMR ($CDCl_3$) 1.6 (6 H, br s), 2.1 (2 H, m), 3.6 (2 H, t, J = 5 hz), 3.8 (2 H, m), 7.1 (5 H, m). To a solution of 3.0 g (13.0 mmol) of the phenyl carbamate in 40 mL of dry THF was added 2.0 g (36.0 mmol) of freshly powedered KOH and 0.18 g (5 mol %) of 18-crown-6. The reaction mixture was refluxed under argon for 16 h. Upon cooling, the solution was extracted with CH_2Cl_2, and the organic phase was washed several times with 20% aqueous KOH solution. The organic layer was dried over anhydrous K_2CO_3 and concentrated, and the crude product was distilled bulb-to-bulb (20 torr; 75 °C) to provide 0.89 g (67%) of 3,4-dimethyl-1,2,5,6-tetrahydropyridine as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.58 (6 H, m), 2.00 (3 H, m), 2.90 (2 H, t, J = 5.9 Hz), 3.14 (2 H, br s). p-Nitrobenzamide derivative, mp 84–86 °C, recrystallized from ether/hexanes. Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76; Found: C, 64.70; H, 6.24; N, 10.61.

Formamidine 19. Using **18**, the formamidine **19** was prepared in the same manner as the unsubstituted tetrahydropyridine **9**: oil, purified by flash chromatography on silica gel eluting with 5% Et_3N in hexanes; IR (film) 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (6 H, d, J = 6.8 Hz), 1.15 (9 H, s), 1.63 (6 H, m), 1.80 (1 H, m), 2.04 (2 H, m), 2.67 (1 H, m), 3.17 (1 H, m), 3.29 (2 H, t, J = 5.8 Hz), 3.50 (1 H, m), 3.61 (2 H, m), 7.28 (1 H, s); $[\alpha]^{25}_D$ −51.6° (c 2.85 in $CHCl_3$).

(*S*)-2-(4-Methoxybenzyl)-3,4-dimethyl-1,2,5,6-tetrahydropyridine, 20: prepared by the general procedure described for metalation and alkylation of **9** (to give **14**); oil, purified by bulb-to-bulb distillation (0.05 torr; 105 °C); ^1H NMR ($CDCl_3$) δ 1.66 (3 H, br s), 1.71 (3 H, br s), 1.99 (2 H, m), 2.76 (6 H, m), 3.78 (3 H, s), 6.84 (2 H, d, J = 8.8 Hz), 7.13 (2 H, d, J = 8.5 Hz); $[\alpha]^{25}_D$ −88.0° (c 1.8, ether). The ee was determined as 99 ± 1% (Figure 1) from the α-naphthamide **22**.

(*S*)-*N*-Methyl-2-(4-methoxybenzyl)-3,4-dimethyl-1,2,5,6-tetrahydropyridine, 23. A solution of 1.0 mmol of **20** in 2 mL of ethyl formate was heated at 40 °C for 12 h. The reaction mixture was concentrated in vacuo, and the crude formamide was dissolved in 5 mL of diethyl ether to which 2.0 mmol of $LiAlH_4$ was added. After stirring for 2 h at room temperature, the reaction was quenched successively with 10 drops of water, 6 drops of 20% aqueous KOH solution, and 10 drops of water. The solution was filtered and concentrated, and the crude product was subjected to bulb-to-bulb distillation under high vacuum to provide the *N*-methylamine as a colorless oil (0.05 torr; 105 °C): ^1H NMR ($CDCl_3$) δ 1.56 (3 H, s), 1.60 (3 H, s), 2.05 (2 H, m), 2.33 (3 H, s), 2.50 (1 H, m), 2.73 (2 H, d, J = 5.6 Hz), 2.93 (2 H, m), 3.73 (3 H, s), 6.78 (2 H, d, J = 6.6 Hz), 7.14 (2 H, d, J = 8.5 Hz); ^{13}C NMR ($CDCl_3$) δ 17.2, 18.8, 28.4, 36.2, 42.6, 46.6, 54.9, 67.0, 113.1, 124.9, 126.5, 129.7, 133.0, 157.3; $[\alpha]^{25}_D$ −6.8° (c 1.5, ether).

(+)-Metazocine, 24. A solution (0.5 M) of 0.160 g of **23** in 48% HBr was heated at 135 °C for 25 h. The cooled solution was diluted in 5 mL of water and made alkaline with saturated ammonium hydroxide. Extraction with CH_2Cl_2, drying, and concentration gave a solid which was purified by PTLC (silica, 60:15:25 hexane–Et_3N–ethyl acetate) to give 0.090 g (60%): mp 178–179 °C (acetone–water, 1:1); ^1H NMR ($CDCl_3$) δ 0.852 (3 H, d, J = 7.0 Hz), 1.31 (3 H, s), 1.90 (3 H, m), 2.17 (1 H, d of t, J = 3.0, 12.2 Hz), 2.41 (3 H, s), 2.50 (1 H, m), 2.68 (1 H, dd, J = 5.5, 18.2 Hz), 2.91 (1 H, m), 2.97 (1 H, d, J = 18.6 hz), 6.59 (1 H, dd, J = 2.5, 8.2 Hz), 6.69 (1 H, d, J = 2.5 Hz), 6.94 (1 H, d, J = 8.2 Hz); $[\alpha]^{25}_D$ +81.8° (c 0.83, ethanol).[11]

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Factors Influencing Conformational Preferences in Cyclohexenes

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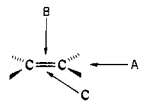
Abstract: Conformational preferences have been measured for the first time for 4-substituted cyclohexenes in a solvent of low polarity. Measurements were made for the substituents Cl, Br, I, OH, $OSiMe_3$, and CN and were compared with conformational preferences in cyclohexyl and *exo*-methylenecyclohex-3-yl. In the nearly nonpolar solvent CF_2Cl_2, in which intramolecular interactions are maximized, there is a much larger axial population for cyclohexen-4-yl than in cyclohexyl or *exo*-methylenecyclohex-3-yl. In particular, the dipolar interaction of the endocyclic double bond is reduced from that of the exocyclic double bond. This observation is confirmed by the almost negligible effect of symmetrizing the endocyclic double bond through 1,2-dimethyl substitution, in contrast with the large effect of symmetrizing the exocyclic double bond through 7,7-dimethyl substitution. Polar solvents increase the proportion of the axial conformer to a smaller extent for the endocyclic than for the exocyclic system, again in agreement with a lower dipolar effect in the endocyclic case. These results emphasize the anisotropic nature of the steric effects of double bonds.

Steric interactions between distant groups within a molecule have been studied primarily in the context of saturated systems. The presence of a double bond in the interacting groups has a major influence on the nature of the steric effect. Whereas rapidly rotating alkyl groups like methyl and simple atoms like chloride or iodide interact with perturbing groups almost isotropically, i.e., independently of the direction of approach, a double bond should interact anisotropically. One can image three extreme modes of approach (**1**): from the end (A), face (B), or side (C). Sus-



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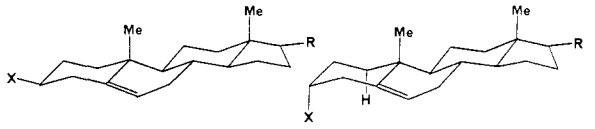
ceptibility to induction of dipoles via van der Waals interactions is anisotropic in double and triple bonds. Moreover, if the bond is polar, particularly in carbonyl or imino groups, electrostatic interactions (dipole–dipole, dipole–quadrupole) should also be anisotropic. Thus the double bond presents a very complex surface to perturbing groups.

An example of the steric effect of double bonds may be found in 3-substituted cholest-5-enes, **2**. The α (axial) conformer has a gauche interaction with only one syn-axial hydrogen, since the



2-α **2-β**

other has been replaced by the double bond. How does the

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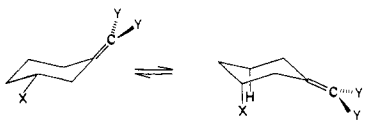
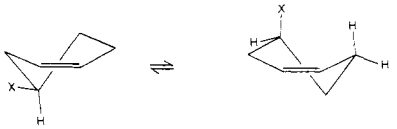
presence of the double bond affect the α/β equilibrium constant? The first comprehensive study of steric intrusion on a double bond like that in **2** was our investigation of 3-substituted *exo*-methylenecyclohexanes (eq 1).[2-4] We found that for polar



(1)

substituents (X) at the 3 position the proportion of axial conformation decreases (compared with cyclohexyl) as the result of a repulsive electrostatic interaction. This repulsive interaction is diminished in polar solvents.[2] Replacement of *exo*-methylene with isopropylidene (eq 1, Y = CH_3) gives an essentially nonpolar double bond that offers little steric interaction with the 3 substituent, resulting in increased proportions of axial substituent.[4]

In terms of diagram **1**, intrusion of the 3 substituent on the double bond in eq 1 occurs off the midpoint of the double bond and above the nodal plane, somewhat of a cross between A and B. The endocyclic double bond of cyclohexene provides a different perspective on the steric interactions of double bonds. This material exists in the half-chair conformation, in which 4 substituents may exist in axial or equatorial arrangements (eq 2). The axial



(2)

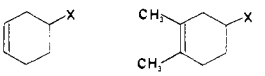
substituent is more along the side of the double bond than it is in *exo*-methylenecyclohexane, a cross between B and C this time. The distance from the axial X group to the midpoint of the double bond is slightly shorter in the endocyclic case (eq 2, 2.88 Å when X = H) than in the exocyclic case (eq 1, 3.23 Å when X = H). The distance from the axial X group to the single axial hydrogen is quite similar in the two systems (2.66 Å for eq 2 vs. 2.64 Å for eq 1).[5] Thus the exocyclic and endocyclic systems differ in terms of angular orientation and distance of the axial substituent with respect to the double bond. In both systems, the equatorial substituent is well removed from the double bond (3.66 Å for eq 2 vs. 3.99 for eq 1) and should have only small interactions with it.

Calculations by MM2 on the nonisolable axial isomer of 3-methoxy-*exo*-methylenecyclohexane and 4-methoxycyclohexene generally corroborated these conclusions. By MM2, the distance from the axial oxygen to the midpoint of the double bond is slightly shorter for the endocyclic (3.08 Å) than for the exocyclic (3.19 Å) system. The distances from the axial oxygen to the single opposed axial proton again are very similar (2.78 Å for endocyclic, 2.73 Å for exocyclic). The oxygen in the equatorial isomer is quite far from the double bond (3.93 Å for endocyclic, 4.22 Å for exocyclic). The MM2 calculations are probably more reliable than the earlier structural data, which were not on methoxyl. MM2 indicates that the methoxy group is slightly closer to the double bond and to the axial proton in the endocyclic case, but not by very much.

The importance of interactions between the double bond and the substituent in 4-substituted cyclohexenes was first pointed out by Kugatova-Shemyakina and Ovchinnikov.[6] One previous study of 4-substituted cyclohexenes reported axial/equatorial equilibrium constants, but only for halogen substituents.[7] The solvent used in this early study was the relatively polar vinyl chloride.[7] We found that equilibrium constants for the *exo*-methylenecyclohexanes (eq 1) were strongly dependent on solvent polarity and that polar solvents gave values that primarily reflected intermolecular interactions.[2] Only in the nearly nonpolar CF_2Cl_2 did we observe equilibrium constants that reflected the intramolecular interactions. In the present study we have examined 4-substituted cyclohexenes in the nonpolar solvent in order to focus on intramolecular interactions. We have obtained a variety of halogen, oxygen, and carbon substituents. In order to remove dipolar interactions of the double bond, we also have prepared a second series in which the double bond is 1,2-dimethyl substituted. We report the equilibrium constants for these systems by direct examination of the resonances from the two conformers below the coalescence temperature to ring reversal by proton NMR spectroscopy at 500 MHz.

Results

4-Substituted cyclohexenes (**3**) were prepared, in which X was Cl, Br, I, OH, OCD_3, OAc, $OSiMe_3$, CN, CHO, and CH_3. The



3 **4**

nitrile and aldehyde were commercially available. The remaining materials were prepared by standard procedures, details of which are given in the Experimental Section. Wolff–Kishner reduction of the aldehyde gave the CH_3 derivative. Oxidation of the aldehyde to the carboxylic acid and reduction of the acid with lead tetraacetate in the presence of LiCl gave the chloride. 1,4-Cyclohexanediol gave the bromide on treatment with PBr_3. Nucleophilic displacement by iodide on the bromide gave the iodide. Treatment of the epoxide from 1,4-cyclohexadiene with $LiAlH_4$ gave the alcohol, which was converted to the methoxy, acetoxy, and trimethylsilyloxy derivatives.

The key starting material for the 1,2-dimethylcyclohexenes (**4**) was 3,4-dimethylanisole. Birch reduction, hydrolysis, and hydride reduction gave the alcohol, which was converted to the methoxy, tosyloxy, and trimethylsilyloxy derivatives. Displacement of tosylate by halide gave the chloride, bromide, and iodide. The remaining derivatives were obtained by Diels–Alder reactions with 2,3-dimethyl-1,3-butadiene (from 2,3-dimethyl-2,3-butanediol). Dienophiles acrolein, vinyl acetate, and acrylonitrile respectively gave the aldehyde, acetate, and nitrile. The aldehyde was reduced to the methyl derivative by the Wolff–Kishner method.

All samples were examined at 500 MHz at temperatures below the coalescence for ring reversal (123–128 K) in 1–2% solutions in dichlorodifluoromethane (dielectric constant $\epsilon = 2.13$). Coalescence temperatures were not recorded, since the process of ring reversal in cyclohexenes has already been studied thoroughly.[7] Axial–equatorial equilibrium constants were measured by direct integration of the CHX resonance. The chloro, cyano, and methoxy derivatives were examined also in the more polar solvents $CHFCl_2$ ($\epsilon = 5.34$) or CHF_2Cl ($\epsilon = 6.11$). Decoalescence was not observed for the aldehydic, methyl, methoxy, acetoxy, or (only for the 1,2-dimethyl series) trimethylsilyloxy derivatives, either because the equilibrium was heavily biased to one extreme (methyl and aldehyde) or because of peak overlap. We prepared the deuterated methoxy derivatives (OCD_3) for both **3** and **4** but still observed no spectral changes. The measured free energy differences are given in Table I.

Discussion

Our experiments with the *exo*-methylenecyclohexanes (eq 1) demonstrated that the axial/equatorial equilibrium constant for substituents at the 3 position is determined primarily by dipole–dipole interactions.[2-4] Polar substituents in the axial position are repelled by the *exo*-methylene group, resulting in a larger proportion of equatorial conformer.[2] The cyano substituent was

(1) This work was supported by the donors of the Petroleum Research Fund, administered by the American Chemical Society, and by the National Science Foundation (Grant No. CHE83-12285). We thank Mr. Li-ang Xue for carrying out the MM2 calculations.

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Table I. Free Energy Differences for the Axial/Equatorial Equilibrium in 4-Substituted Cyclohexenes (**3**) and 1,2-Dimethylcyclohexenes (**4**)

system	X	solvent	concn, wt %	temp, K	$-\Delta G°$,[a] kcal/mol
cyclohexene (**3**)	Cl	CF_2Cl_2	2	128	0.31
	Cl	CHF_2Cl	2	128	−0.02
	Br	CF_2Cl_2	2	128	0.27
	I	CF_2Cl_2	2	128	0.16
	OH	CF_2Cl_2	2	123	0.22
	OTMS	CF_2Cl_2	2	123	0.31
	CN	CF_2Cl_2	1	123	0.15
	CN	CHF_2Cl	1	123	0.02
1,2-dimethyl-cyclohexene (**4**)	Cl	CF_2Cl_2	2	128	0.38
	Cl	$CHFCl_2$	2	128	0.06
	Br	CF_2Cl_2	2	123	0.30
	I	CF_2Cl_2	2	128	0.20
	OH	CF_2Cl_2	2	123	0.70
	CN	CF_2Cl_2	2	128	0.14
	CN	$CHFCl_2$	2	128	0.14

[a] A positive number implies that the equatorial isomer is favored. The error on these measurements is ±0.03 kcal/mol.

exceptional, in that the axial/equatorial equilibrium constant was about the same for the cyclohexyl and *exo*-methylenecyclohexyl systems, either because the electronegative nitrogen end of the substituent dipole is much further removed from the *exo*-methylene group than for hydroxy derivatives or because the directionality of the cyano triple bond is different from that of the hydroxy derivatives.[3] Introduction of methyl groups on the exocyclic double bond removes its repulsive properties, allowing enhanced amounts of the polar 3-axial substituents.[4] The tetrasubstituted double bond has little or no dipole but retains its quadrupole. Thus the electrostatic interaction between double bond and 3-axial substituent appears to be primarily dipole–dipole rather than quadrupole–dipole.

The axial/equatorial free energy differences are relatively small for the 4-substituted cyclohexenyl systems (Table I). In the nonpolar CF_2Cl_2 ($\epsilon = 2.13$), the values are 0.31, 0.27, 0.16, 0.22, and 0.15 respectively for Cl, Br, I, OH, and CN, compared with 0.53, 0.48, 0.47, 0.97, and 0.24 for cyclohexyl systems in the nonpolar CS_2 ($\epsilon = 2.64$).[8] Comparable data for the 3-substituted *exo*-methylene system are available only for OH (1.12) and CN (0.26). The endocyclic double bond clearly offers a less repulsive interaction than the exocyclic double bond for OH. The distance from the axial substituent to the midpoint of the double bond is slightly shorter in the endocyclic case. The distance from the substituent to the single axial hydrogen shown in eq 1 and 2 is nearly identical in the two cases. The dipolar properties of the endocyclic and exocyclic double bonds may be different. Thus the dipole moment of isobutylene is 0.50 D (model for exocyclic double bond), whereas that of *cis*-2-butene is 0.33 D (model for endocyclic double bond).[9]

Apparently the effect of a dipole concentrated along the axis of the double bond, as in the exocyclic system, is much more pronounced than that of a dipole directed perpendicular to the axis, as in the endocyclic system. As a result, the dipole–dipole repulsion between the double bond and a 4-axial substituent in **3** is reduced because the dipole moment of the endocyclic double bond is less than that of the exocyclic double bond.

These observations are confirmed by the effect of dimethyl substitution at the 1 and 2 positions (**4**). In contrast to the exocyclic system, in which *exo*-dimethyl substitution essentially eliminates the repulsive interaction, the methyl groups in the endocyclic system have very little effect on the axial/equatorial equilibrium constant. The nonmethylated endocyclic values for Cl, Br, I, and CN in CF_2Cl_2 are 0.31, 0.27, 0.16, and 0.15, respectively; the respective dimethylated values are 0.38, 0.30, 0.20, and 0.14. The much smaller endocyclic values thus reflect a smaller dipolar effect of the double bond. Since the quadrupole of the double bond is not strongly altered by introduction of the methyl groups, the insensitivity of the free energy differences to methyl substitution does not eliminate the possibility that the endocyclic double bond still interacts with the substituents by a small quadrupole–dipole interaction.

Whereas CF_2Cl_2 probes intramolecular interactions, more polar solvents probe intermolecular interactions. In the nonmethylated, endocyclic case (**3**), the group dipoles of the double bond and the axial substituent reinforce to give a larger molecular dipole than that of the equatorial conformer. Thus a more polar solvent favors the axial form. For Cl, the values are 0.31 in CF_2Cl_2, 0.20 in vinyl chloride,[7] and −0.02 in CHF_2Cl. For CN, the values are 0.15 in CF_2Cl_2 and 0.02 in CHF_2Cl. For Br and I, the CF_2Cl_2 values of 0.27 (Br) and 0.16 (I) compared with the vinyl chloride values of 0.08 (Br) and −0.02 (I). It is clear from these results that the vinyl chloride results of Jensen and Bushweller responded largely to intermolecular as well as intramolecular interactions.

These solvent effects for **3** are smaller than those observed in the exomethylene series, reflecting the lower dipolar effect of the endocyclic double bond. The free energy difference for methoxyl, for example, decreased from 0.80 to 0.11 between CF_2Cl_2 and $CHFCl_2$ in the exocyclic system.[2] The fact that a small solvent effect is observed in the methylated system (**4**) as well as in the unmethylated system (**3**) suggests that the quadrupole of the double bond might supply part of the electrostatic interaction with the 4 substituent.[10]

Summary

An axial substituent at the 4 position of cyclohexene (eq 2) has a higher population than an axial substituent at the 3 position of *exo*-methylenecyclohexane (eq 1). The dipole–dipole interaction between double bond and axial substituent is substantially reduced because of a smaller double bond dipole in the endocyclic case. The reduced size of the dipolar interactions also is seen by smaller solvent effects (CF_2Cl_2 vs. $CHFCl_2$ or CHF_2Cl) and almost no effect from symmetrization of the double bond through 1,2-dimethyl substitution with concomitant removal of the double bond dipole. Residual effects may be due to the quadrupole of the double bond.[10]

Experimental Section

Low-temperature NMR spectra were taken at the Regional NMR Facility at Yale University, sponsored by the National Science Foundation (Grant No. CHE79-16210).

4-Methylcyclohexene. 1,2,3,6-Tetrahydrobenzaldehyde (Aldrich, 5.5 g, 0.05 mol) was added to 10.0 g (0.2 mol) of 85% hydrazine hydrate in a 50-mL round-bottomed flask equipped with a condenser. The solution was heated to reflux for 2 h, cooled, and extracted with 3 × 25 mL of diethyl ether. These extracts were combined, washed once with 40 mL of H_2O, and dried over $MgSO_4$. After filtration the ether was removed by rotary evaporation, and the remaining oil was dissolved in 25 mL of reagent grade ethylene glycol. This mixture was again placed in a 50-mL round-bottomed flask fitted with a condenser and KOH (3.0 g, 0.05 mol) was added to the solution, which was then heated to 150 °C for 90 min. The condenser was replaced by a short-path distillation head, and 4-methylcyclohexene was distilled (bp 102 °C) along with a small amount of H_2O. This two-phase mixture was taken up in pentane and dried over Na_2CO_3. Filtration and distillation afforded 3.7 g (76%) of pure 4-methylcyclohexene: bp 102 °C (lit.[11] bp 100.8–101.5 °C (736 mm Hg); ^1H NMR ($CDCl_3$) δ 5.65 (s, 2, vinyl), 2.04, 1.65 (br s, 6, H3, H5, H6), 1.21 (m, 1, $HCCH_3$), 0.95 (d, 3, CH_3); ^{13}C NMR ($CDCl_3$) δ 126.8, 126.7 (sp^2 carbons), 33.9 (C4), 31.0 (C3), 28.7, 25.4 (C5, C6), 22.1 (C4 methyl).

Cyclohexene-4-carboxylic Acid. Silver oxide (20.0 g, 0.086 mol) was placed in a 250-mL Erlenmeyer flask along with 100 mL of H_2O. Sodium hydroxide pellets (17.0 g, 0.40 mol) were then dissolved in the solution. 1,2,3,6-Tetrahydrobenzaldehyde (Aldrich, 10.0 mL, 9.4 g, 0.085 mol) was added in two portions. After 1 min a vigorous exothermic reaction took place, and the mixture changed from black to gray. The

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resulting thick suspension was stirred for 1 h, the contents of the flask were filtered, and the filtrate was acidified to a pH of 2 with concentrated HCl. This aqueous solution was extracted with 4 × 50 mL of diethyl ether, and the combined extracts were dried ($MgSO_4$) overnight. The ether was removed by distillation at atmospheric pressure, and the acid was distilled under high vacuum (bp 98 °C (1 mm Hg)) (lit.[12] bp 235–238 °C). The yield was 9.50 g (89%): ^{1}H NMR ($CDCl_3$) δ 12.25 (s, 1, CO_2H), 5.50 (br s, 2, vinyl), 3.40 (m, 1, methine), 1.20–1.70 (br m, 6, H3, H5, H6).

4-Chlorocyclohexene. A solution of cyclohexene-4-carboxylic acid (15.0 g, 0.119 mol) in 250 mL of anhydrous benzene was placed in a 500-mL 3-necked round-bottomed flask, which was fitted with 2 rubber stoppers and a condenser. The flask was flushed with dry N_2; the reaction was performed under this inert atmosphere. To this solution anhydrous LiCl (5.3 g, 0.125 mol) was added. Lead tetraacetate (recrystallized from HOAc, 52.72 g, 0.119 mol) was dropped into the flask over a 30-min period. Upon contact of the first portions of $Pb(OAc)_4$ the solution turned bright yellow, and after several minutes CO_2 began to evolve. After complete addition of $Pb(OAc)_4$, the solution was heated to reflux for 7 h, the flask was cooled, and the contents were washed with 300 mL of H_2O. The organic layer was scrubbed with 200 mL of 10% NaOH and 200 mL of H_2O and subsequently was dried over $MgSO_4$. The benzene was removed at room temperature by a water aspirator. Pure 4-chlorocyclohexene (4.8 g, 35%) was distilled at 50 °C (10 mm Hg) (lit.[7] 69 °C (74 mm Hg)); ^{1}H NMR ($CDCl_3$) δ 5.50 (d, 2, vinyl), 3.9–4.3 (m, 1, methine), 1.5–2.6 (br m, 6, H3, H5, H6).

4-Bromocyclohexene was prepared by the procedure of Jensen and Bushweller[7] from 1,4-cyclohexanediol to give 16.6 g (24%): bp 65 °C (25 mm Hg) (lit.[7] bp 52–53 °C (12 mm Hg)).[13] An analytically pure sample was obtained through preparative VPC (25% DEGS on Chromosorb W, 8 ft × $^3/_4$ in., 120 °C, He flow 75 mL/min); ^{1}H NMR ($CDCl_3$) δ 5.5 (br s, 2, vinyl), 4.2 (m, 1, methine), 2.3–2.7 (br s, 2, H3), 1.8–2.2 (br s, 4, H5, H6); ^{13}C NMR ($CDCl_3$) δ 127.0, 124.0 (sp^2 carbons), 49.0 (C4), 36.0, 33.0, 25.0 (C3, C5, C6).

4-Iodocyclohexene was obtained by the displacement of sodium iodide on 4-bromocyclohexene (4.3 g, 0.027 mol) in 26% yield: bp 66–70 °C (15 mm Hg) (lit.[7] bp 60 °C (4 mm Hg)); ^{1}H NMR analysis revealed that the oil was a mixture of 4-iodo- and 4-bromocyclohexene in a ratio of 3.7:1. A pure sample of 4-iodocyclohexene was obtained through preparative VPC (25% DEGS on Chromosorb W, 8 ft × $^3/_4$ in., 130 °C, He flow 75 mL/min). The resulting iodide is extremely sensitive to light: ^{1}H NMR ($CDCl_3$) δ 5.4–5.8 (br d, 2, vinyl), 4.5 (m, 1, methine), 2.5–2.9 (m, 2, H3), 2.0–2.2 (m, 4, H5, H6); ^{13}C NMR ($CDCl_3$) δ 126.0, 125.0 (sp^2 carbons), 38.0 (CH_2I), 34.0, 27.0, 26.0 (C3, C5, C6).

Cyclohexa-1,4-diene epoxide was obtained by treatment of 1,4-cyclohexadiene (14.0 g, 0.17 mol) with *m*-chloroperbenzoic acid:[13] 5.8 g (35%); bp 145–155 °C; ^{1}H NMR ($CDCl_3$) δ 5.35 (br s, 2, vinyl), 3.10 (m, 2, H4, H5), 2.40 (br s, 4, allylic).

3-Cyclohexen-1-ol. Reduction of cyclohexyl-1,4-diene epoxide (5.75 g, 0.060 mol) with $LiAlH_4$ (2.2 g, 0.25 mol) yielded 4.3 g (73%) of 3-cyclohexen-1-ol:[12] bp 98–105 °C (20 mm Hg) (lit.[14] bp 164–164.5 °C (763 mm Hg)); ^{1}H NMR ($CDCl_3$) δ 5.55 (s, 2 vinyl), 5.15 (s, 1, OH), 3.80 (m, 1, methine), 1.30–2.40 (br, m, 6, H3, H5, H6).

4-Methoxycyclohexene was prepared by treatment of 3-cyclohexen-1-ol (2.15 g, 0.022 mol) with NaH and CH_3I.[13] The yield was 0.90 g (37%); bp 62–65 °C (30 mm Hg) (lit.[15] bp 135.5–136.5 °C (760 mm Hg)); ^{1}H NMR ($CDCl_3$) δ 5.52 (br, s, 2, vinyl), 3.30 (m, 1, methine), 3.27 (s, 3, methoxy), 1.30–2.40 (br m, 6, H3, H5, H6).

4-Methoxy-d_3-cyclohexene. The preparation was identical with that of 4-methoxycyclohexene, except that methyl-d_3 iodide (Aldrich) was used as the electrophile instead of CH_3I:[13] ^{1}H NMR ($CDCl_3$) δ 5.60 (d, 2, vinyl), 3.93 (br, s, 1, methine), 1.40–2.50 (br m, 6, H3, H5, H6).

3-Cyclohexen-1-yl acetate was obtained by treatment of 3-cyclohexen-1-ol (1.50 g, 0.015 mol) with acetic anhydride (1.72 g, 0.017 mol):[13] 1.4 g (65%); bp 71–73 °C (15 mm Hg) (lit.[16] bp 75 °C (20 mm Hg)); ^{1}H NMR ($CDCl_3$) δ 5.60 (br s, 2, vinyl), 4.90 (m, 1, methine), 1.92 (s, 3, $OCOCH_3$), 1.60–2.40 (br m, 6, H3, H5, H6); ^{13}C NMR ($CDCl_3$) δ 170.5 ($OCOCH_3$), 126.8, 123.7 (ring sp^2 carbons), 69.7 (COAc), 30.8, 27.4, 23.4 (C3, C5, C6), 21.3 ($OCOCH_3$).

4-(Trimethylsilyloxy)cyclohex-1-ene. A solution of 3-cyclohexen-1-ol (1.5 mL, approximately 0.013 mol) in 10 mL of dry pyridine (distilled from BaO) was poured into a 50-mL round-bottomed flask. The flask was placed on the receiving end of a distillation apparatus. Trimethylsilyl chloride (Me_3SiCl, Aldrich) was distilled from pyridine directly into the stirred alcoholic solution under an atmosphere of N_2. Pyridinium chloride precipitated immediately upon contact of Me_3SiCl and the alcohol. The disappearance of the alcohol was monitored by gas chromatography; the reaction was complete upon addition of approximately 2 mL of Me_3SiCl. Water (20 mL) was added to quench the reaction and to dissolve the precipitated pyridinium chloride. The material was extracted with diethyl ether, and the organic portion was washed twice with saturated $CuSO_4$ (40 mL) to scavenge any remaining pyridine. The organic phase was then washed with 40 mL of saturated brine and was finally dried over Na_2CO_3. The solids were filtered, and the ether was removed by rotary evaporation. The remaining colorless oil (approximately 1 mL) was purified by preparative VPC (25% DEGS column, 8 ft × $^3/_4$ in., 100 °C, He flow 75 mL/min): ^{1}H NMR ($CDCl_3$) δ 5.55 (m, 2, vinyl), 3.82 (m, 1, methine), 1.40–2.25 (br m, 6, H3, H5, H6), 0.10 (s, 9, $OSi(CH_3)_3$).

2,3-Dimethyl-1,3-butadiene was prepared by the method of Allen et al.[17] from pinacol (Aldrich, 100 g, 0.846 mol). Filtration and fractionation yielded 60 mL of an 85/15 mixture of 2,3-dimethyl-1,3-butadiene/pinacolone (bp 68–75 °C); lit.[17] bp 69–70.5 °C. The overall yield of butadiene was 53%: ^{1}H NMR ($CDCl_3$) δ 5.00, 4.90 (singlets, 4, vinyl), 1.89 (s, 6, CH_3).

3,4-Dimethyl-3-cyclohexen-1-carboxaldehyde. A 5-mL sample (0.044 mol) of 2,3-dimethyl-1,3-butadiene was placed in a 100-mL pyrolysis tube along with acrolein (Aldrich, 3 mL, 2.52 g, 0.045 mol) and a small amount of hydroquinone to inhibit polymerization. The mixture was cooled to −78 °C, and the tube was sealed. The tube was clamped vertically to a ringstand, and the bottom 2 in. of the tube was immersd in an oil bath. The oil bath was heated to 95 °C for 12 h and cooled to room temperature. The tube was cooled to −78 °C again and opened. The contents were poured into a 25-mL round-bottomed flask, and the tube was rinsed with anhydrous diethyl ether (5 mL). The ether was distilled at atmospheric pressure and the product at 92–94 °C (25 mm Hg): 4.8 g (79%); ^{1}H NMR ($CDCl_3$ δ 9.66 (d, 1, aldehyde), 2.48 (m, 1, methine), 1.90–2.15 (br m, 6, H3, H5, H6), 1.65, 1.60 (singlets, 6, CH_3); ^{13}C NMR ($CDCl_3$) δ 204.3 (CHO), 125.8, 123.5 (ring sp^2 carbons), 47.0 (CCHO), 30.6, 30.3, 22.9 (C3, C5, C6), 19.1, 18.9 (C1, C2 methyls).

1,2,4-Trimethylcyclohex-1-ene. 3,4-Dimethyl-3-cyclohexene-1-carboxaldehyde (7.94 g, 0.057 mol) was dissolved in 200 mL of ethylene glycol and placed in a 500-mL round-bottomed flask. Hydrazine hydrate (85% in H_2O, 20 g, 0.53 mol) was added to the stirred mixture with evolution of heat. After 30 min, KOH pellets (20 g, 0.36 mol) were added to the flask. A reflux condenser was attached, and the mixture was heated to 165 °C for 3 h. The mixture was cooled, the reflux condenser was replaced with a distillation head, and the solution was heated slowly to 180 °C. After several hours, approximately 20 mL of a two-phase distillate had been collected. The mixture was transferred to a separatory funnel, and H_2O (50 mL) was added. This largely aqueous phase was extracted with diethyl ether (3 × 50 mL). The extracts were combined, dried over $MgSO_4$, and filtered. Fractionation of the ethereal solution afforded 3.2 g (45%) of 1,2,4-trimethylcyclohex-1-ene, bp 154 °C. The cloudy product was dried over 4 Å molecular sieves; the ^{1}H NMR spectrum of this colorless oil showed no trace of the aldehyde precursor: ^{1}H NMR ($CDCl_3$) δ 1.50–1.65 (br m, 2, C5 methylene), 1.59 (s, 6, C1, C2 methyls), 1.16 (m, 1, methine), 0.92 (d, 3, C4 methyl); ^{13}C NMR ($CDCl_3$) δ 125.1 (C1, C2 methyls), 40.7 (C4), 32.1, 31.9 (C3, C6 allylic), 29.4 (C5), 21.9 (C4 methyl), 19.1, 18.9 (C1, C2 methyls).

4-Methoxy-1,2-dimethyl-1,4-cyclohexadiene was prepared by Birch reduction of 3,4-dimethylanisole (Aldrich, 50.0 g, 0.367 mol):[13] 33.80 g (67%), bp 35 °C (0.5 mm Hg); ^{1}H NMR ($CDCl_3$) δ 4.68 (br, t, 1, vinyl), 3.50 (s, 3, OCH_3), 2.50–2.80 (br d, 4, C3, C6 allylic), 1.63 (s, 6, methyls).

1,2-Dimethyl-1-cyclohexen-4-one was prepared by hydrolysis of the above vinyl ether (30.0 g, 0.217 mol):[13] bp 96–98 °C (32 mm Hg); ^{1}H NMR ($CDCl_3$) δ 2.74 (s, 2, C3 allylic), 2.40 (m, 4, C5, C6 methylene), 1.73, 1.67 (s, 6, C1, C2 methyls); ^{13}C NMR ($CDCl_3$) δ 209.3 (carbonyl), 125.5, 122.7 (sp^2), 44.4 (C3), 38.1 (C5), 31.0 (C6), 17.9, 17.7 (C1, C2 methyls). ^{1}H NMR revealed the presence of α,β-unsaturated ketone (5%).

1,2-Dimethyl-1-cyclohexen-4-ol.[18] Reduction of the ketone (21.85 g, 0.176 mol) with $LiAlH_4$ gave the alcohol:[13] 30 g (91%), bp 109–112 °C (32 mm Hg) (lit.[18] bp 76 °C (6 mm Hg)); ^{1}H NMR ($CDCl_3$) δ 3.92 (m,

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1, methine), 1.71 (br s, 1, OH), 1.61 (s, 6, C1, C2 methyls), 1.60-2.30 (br m, 6, C3, C5, C6 methylenes); ^{13}C NMR ($CDCl_3$) δ 125.2, 123.0 (sp^2), 67.4 (COH), 40.6 (C3), 31.6, 30.0 (C5, C6), 19.2, 18.6 (C1, C2 methyls). An analytically pure sample was obtained by preparative VPC (25% DEGS, 8 ft × $^1/_4$ in., 120 °C, He flow 75 mL/min).

1,2-Dimethyl-1-cyclohexen-4-yl tosylate[17] was prepared by treatment of the alcohol (4.0 g, 0.032 mol) with tosyl chloride (6.15 g, 0.032 mol) in 57% yield:[13] ^{1}H NMR ($CDCl_3$) δ 7.25-7.90 (d of d, 4, aromatic), 4.70 (m, 1, methine), 2.47 (s, 3, tolyl methyl), 1.58 (br s, 6, C1, C2 methyls), 1.70-2.30 (br m, 6, C3, C5, C6 methylenes).

4-Halo-1,2-dimethyl-1-cyclohexene. Treatment of the tosylate with LiCl (0.40 g, 9.4 mmol), LiBr (0.50 g, 5.8 mmol), or NaI gave the respective halide compounds.[13] Chloride: 45%; ^{1}H NMR ($CDCl_3$) δ 4.20 (m, 1, methine), 1.61 (s, 6, C1, C2 methyls), 1.80-2.50 (br m, 6, C3, C5, C6 methylenes). Bromide: 60%; ^{1}H NMR ($CDCl_3$) δ 4.38 (m, 1, methine), 1.60 (s, 6, C1, C2 methyls), 1.80-2.65 (br m, 6, C3, C5, C6 methylenes). Iodide: 35%; ^{1}H NMR ($CDCl_3$) δ 4.48 (m, 1, methine), 2.62 (br s, 2, C3 methylene), 2.10 (m, 4, C5, C6 methylenes), 1.61 (s, 6, C1, C2 methyl groups).

4-Methoxy-d_3-1,2-dimethyl-1-cyclohexene was prepared from 1,2-dimethyl-1-cyclohexen-4-ol (0.50 g, 4 mmol) by treatment with NaH and CD_3I:[12] ^{1}H NMR ($CDCl_3$) δ 3.42 (m, 1, methine), 1.59 (s, 6, C1, C2 methyls), 1.75-2.35 (br m, 6, C3, C5, C6 methylenes).

1,2-Dimethyl-1-cyclohexen-4-yl acetate was prepared by the Diels-Alder reaction of 2,3-dimethyl-1,3-butadiene (5 mL, 0.044 mol) with vinyl acetate (Aldrich, 20.5 mL, 0.22 mol).[13] The product was distilled (bp 105-109 °C (25 mm Hg)) and determined to be a 3.7/1 mixture of two products, the desired acetate and the dimer of 2,3-dimethyl-1,3-butadiene, 1,2,4-trimethyl-4-(2-propenyl)cyclohex-1-ene. The two materials were separated by preparative VPC (25% DEGS on Chromosorb W, 8 ft × $^3/_4$ in., 135 °C, He flow 70 mL/min). The acetate had ^{1}H NMR ($CDCl_3$) δ 4.95 (m, 1, methine), 2.03 (s, 3, $OCOCH_3$), 1.60 (s, 6, C1, C2 methyls), 1.50-2.30 (br m, 6, C3, C5, C6 methylenes).

4-(Trimethylsilyloxy)-1,2-dimethylcyclohex-1-ene. A solution of 1,2-dimethylcyclohexen-4-ol (1.0 g, 8.0 mmol) in dry pyridine (3 mL) was placed in a 25-mL round-bottomed flask. The flask was secured to the receiving end of a distillation apparatus, and trimethylsilyl chloride (approximately 2 mL, 16.0 mmol) was distilled from pyridine directly into the stirred reaction mixture under N_2. Pentane (25 mL) and H_2O (25 mL) were added, and the contents were transferred to a separatory funnel. The organic layer was separated and washed with saturated $CuSO_4$ (2 × 50 mL) and H_2O (50 mL). The pentane solution was dried (Na_2SO_4) and filtered, and the pentane was distilled. The colorless, oily residue was purified by preparative VPC (10% Carbowax on Chromosorb W 60/80, 8 ft × $^1/_2$ in., 120 °C, He flow 80 mL/min): ^{1}H NMR ($CDCl_3$) δ 3.78 (m, 1, methine), 1.56 (s, 6, C1, C2 methyls), 1.65-2.10 (br m, 6, C3, C5, C6 methylenes), 0.10 (s, 9, $OSi(CH_3)_3$); ^{13}C NMR ($CDCl_3$) δ 125.0, 123.4 (sp^2), 68.5 (C4), 41.3 (allylic C3), 35.8, 32.5 (C5, C6), 19.1 (C1, C2 methyls).

4-Cyano-1,2-dimethylcyclohex-1-ene was prepared by the Diels-Alder reaction of 2,3-dimethyl-1,3-butadiene (5 mL, 3.63 g, 0.044 mol) with acrylonitrile (Aldrich, 3.0 mL, 0.046 mol):[13] 5.5 g (92%), bp 45 °C (0.06 mm Hg) (lit.[19] bp 217-222 °C (760 mm Hg)); ^{1}H NMR ($CDCl_3$) δ 2.80 (m, 1, methine), 1.62 (s, 6, C1, C2 methyls), 1.80-2.25 (br m, 6, C3, C5, C6 methylenes); ^{13}C NMR ($CDCl_3$) δ 125.8 (C≡N), 122.7, 122.3 (sp^2 carbons), 34.2 (C4), 29.3 (C3 allylic), 26.0, 25.5 (C5, C6), 18.9, 18.8 (C1, C2 methyls).

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Metmyoglobin and Methemoglobin as Efficient Traps for Nitrosyl Hydride (Nitroxyl) in Neutral Aqueous Solution

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Abstract: The reactions of metmyoglobin (Mb^+, ferric myoglobin) and methemoglobin (Hb^+, ferric hemoglobin) with trioxodinitrate monoanion ($HN_2O_3^-$) in neutral aqueous solution have been studied at 25 °C under anaerobic conditions. The sole heme product of the reaction is nitrosylmyoglobin (MbNO) or nitrosylhemoglobin (HbNO). The reactions are approximately first-order in [$HN_2O_3^-$] and zero-order in ferric heme protein concentration, and the rate of formation of the nitrosyl (ferrous) heme protein product is always less than that of $HN_2O_3^-$ decomposition. The $HN_2O_3^-$/ferric heme protein mole ratio required for quantitative conversion to the nitrosyl heme protein is about 1.4 by titration and, in the case of Mb^+, 1.25 by kinetic analysis. Product analyses show that nitrosyl heme protein formation occurs at the expense of N_2O production, but not of nitrite production. The results are consistent with the view that $HN_2O_3^-$ decomposes in the rate-determining step into nitrosyl hydride (nitroxyl, HNO) plus nitrite and that HNO then partitions in fast reactions between dimerization/dehydration to form N_2O and reaction with ferric heme protein to form nitrosyl heme protein. Hb^+ shows kinetic evidence for cooperativity in the latter reaction. In an alternative possibility, $HN_2O_3^-$ may decompose into NO and $(HONO)^-$ (Doyle, M. P.; Mahapatro, S. N. *J. Am. Chem. Soc.* **1984**, *106*, 3678-3679). Subsequently $(HONO)^-$ reduces Mb^+ or Hb^+ to Mb or Hb, and the latter captures NO to form MbNO or HbNO. This pathway is held to be unlikely on chemical grounds.

Nitrosyl hydride (HNO), commonly referred to as nitroxyl, is a reactive N^{1+} species that can be produced by pulse radiolysis of NO in aqueous solutions[1] and by photolysis of H_2/NO and other systems in the gas phase.[2] Nitroxyl is subject to matrix isolation.[3] In the gas phase, nitroxyl rapidly dimerizes and dehydrates to form N_2O;[2] in aqueous solutions, NO^- reacts rapidly with NO to form $N_2O_2^-$, $N_3O_3^-$, and their conjugate acids.[1] $N_3O_3^-$ and HN_3O_3 decay rapidly into N_2O and nitrite.[1] The decomposition of sodium trioxodinitrate (Angeli's salt, $Na_2N_2O_3$) in aqueous solution has been the subject of several reports.[5-10] Under neutral or mildly alkaline conditions, the monoanion, $HN_2O_3^-$, spontaneously de-

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