Autoxidation of 2-*tert*-Butyl-2,3-diazabicyclo[2.2.1]heptane. Stereospecific Loss of Hydrogen from N_3 and C_5, and N_3 and C_6

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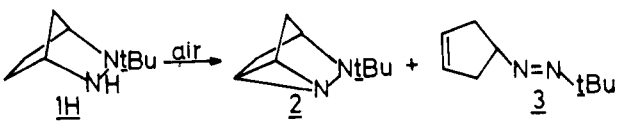
Abstract: The title compound (**1H**) is almost quantitatively converted to a 9.5:1 mixture of 3-*tert*-butyl-2,3-diazanortricyclane (**2**) and 3-cyclopentenyl-*tert*-butyldiimide (**3**) when air is bubbled through its cyclohexene solution. Autoxidation of *exo,exo*-5,6-dideuterio-**1H** gives a **2:3** ratio of about 2.2:1, and product studies show that only the exo substituents (D) at C_5 and C_6 of **1H** are removed in forming **2** and **3**, respectively. It is argued that **2** and **3** arise by hydrogen atom abstraction from **1**•.

Bubbling air through solutions of diazanorborane derivative **1H** was reported[1] to convert it to the diazanortricyclane **2**, a formal 1,3 elimination of hydrogen. After this communication, Landis discovered[2] that small amounts of a considerably more volatile isomer of **2** are also formed, and showed that this isomer is the monocyclic azo compound **3**, formally a 1,4



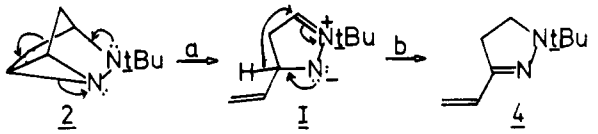
1H 2 3

hydrogen elimination product of **1**. We report here a more thorough study of this most unusual autoxidation reaction.

Results

The major autoxidation product **2** only shows three types of carbon in addition to a *tert*-butyl group in its ^{13}C NMR, making it difficult to formulate another structure. Additional support for structure **2** is provided by its thermal decomposition product. When **2** is heated to about 150 °C in solution, or injected into a hot injector port of a VPC, it is converted to dihydropyrazole **4**. The structure of **4** was verified by its independent preparation from *tert*-butylhydrazine and β-methoxyethyl ethyl ketone, the literature preparation of 3-vinyl-4,5-dihydropyrazoles.[3] **4** might be formed by retro-[4 + 2] cycloaddition of **2** (or protonated **2**), generating I (or IH^+), shown in step a of Scheme I. There is considerable

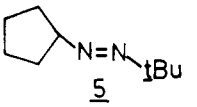
Scheme I



2 I 4

precedent for intramolecular cycloaddition of azomethinimines to olefins;[4] the retro reaction in this case relieves considerable strain. Although it is difficult to tell whether or not step a is proceeding on protonated **2**, NMR experiments indicate that solution of **2** in trifluoroacetic acid results in protonation, but the protonated form does not cleave at room temperature, even in several days. We attempted to demonstrate the presence of I by trapping it with external olefins, but were able to observe no intermolecular trapping product with either cyclohexene or dimethyl acetylenedicarboxylate. The hydrogen transfer shown in step b of Scheme I is an allowed reaction, and might be quite rapid.

The structure of **3** was verified by degradation. Catalytic hydrogenation of **3** followed by silver oxide oxidation gave *tert*-butylcyclopentyldiimide (**5**), which was identical with that prepared by reductive alkylation of *tert*-butylhydrazine with



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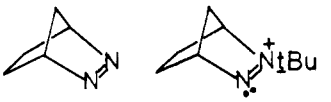
cyclopentanone using sodium cyanoborohydride,[5] followed by oxidation to the azo compound.

The yields of **2** and **3** in the autoxidation of **1H** were quantitated by VPC measurements, employing *tert*-butylbenzene as an internal standard and using response factors measured from known mixtures of VPC-purified **1H, 2, 3,** and standard. The yield of **2** + **3** is essentially quantitative when air is slowly bubbled through a solution of **1H** in cyclohexene for 12 h (Table I). Our earlier work[1,2] employed the crude concentrate from the ammonium chloride quenched addition of *tert*-butyllithium to 2,3-diazanorbornene **6** as **1H**, and a considerable residue shown to be mostly 1^+ salts (counterion undetermined)



6 1+

was found after autoxidation.[1,2] When the **1H** sample is purified by Kugelrohr distillation, the nonvolatile residue is essentially eliminated in nonpolar solvents. In polar solvents such as acetonitrile (similar results were observed in methanol and ether) formation of **2** + **3** becomes a minor process, and the major product is nonvolatile, and indicated by NMR to be 1^+ salts. We attempted to use quinones as oxidants for **1H,** but for benzoquinone in cyclohexene and for benzoquinone, chloranil, and dichlorodicyanoquinone in acetonitrile the major product was 1^+ (with quinone-derived counterion) again, and only 8–15% yields of **2** and even smaller amounts of **3** were formed. Even the use of pure oxygen instead of air leads to noticeably darker reaction mixtures and lower yields of volatile material.

In an attempt to discover if structural changes could be made in the trialkylhydrazine and still keep the autoxidation chemistry resembling that of **1H,** we investigated three additional compounds, **7H, 8H,** and **9H.** As expected from the trivial structural change, the major products observed from **7H** were **10** and **11,** the spirocyclopropyl analogues of **2** and **3**. Two quantitative autoxidation runs for **7H** gave 66% **10,** 15% **11** and 73% **10,** 14% **11,** respectively (assuming the same VPC sensitivities relative to *tert*-butylbenzene as for **2** and **3**). In contrast, neither **8H** nor **9H** gave the formation of any significant amounts of 1,3 or 1,4 hydrogen elimination products. Parallel runs of **1H** and **8H,** monitored by VPC for starting material disappearance, indicated that **8H** disappeared about one-fourth as rapidly as **1H,** but a complex mixture of products

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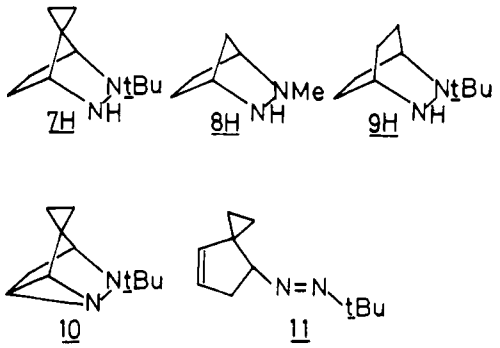


was indicated by VPC. This result seems reasonable. In contrast to **1H** and **7H, 8H** has sterically accessible, easily abstracted hydrogens on a carbon adjacent to nitrogen, and loss of these hydrogens is presumably rapid relative to loss of nonadjacent hydrogens. Although **9H** lacks such labile hydrogens, it gave no volatile products upon autoxidation, but instead an intractable, dark, tarry material we did not investigate. Thus, even going from a [2.2.1] to a [2.2.2] bicyclic system prevents the interesting 1,3 and 1,4 hydrogen elimination products from being formed. We have restricted our present studies to autoxidation of **1H** and **7H** in cyclohexene, where the yield of the unusual products is maximized.

Stoichiometry implies that, if O_2 and **1H** give **2** + **3**, H_2O_2 should be formed. Iodide titration for H_2O_2 after complete disappearance of **1H** in cyclohexene is completely negative; any H_2O_2 initially formed under the reaction conditions is consumed. Neither **2** nor **3** reacts rapidly with H_2O_2 at room temperature, but **1H** does react. Addition of 90% H_2O_2 to a cyclohexene solution of **1H** does result in formation of **2** and **3**. Although their yield is not very high, the fact that the H_2O_2 in this experiment is in a second, aqueous layer and that the autoxidation itself does not give much **2** and **3** in polar solvents makes this a reasonable result. The conditions are rather different for this reaction than for forming H_2O_2 dispersed in cyclohexene, as presumably is the case in the autoxidation. Autoxidation of **1H** in acetonitrile, where the major product is $\mathbf{1}^+$, does produce easily detectable amounts of H_2O_2. Iodide titration gives about 10% of the stoichiometric amount of H_2O_2 after **1H** is completely consumed. This result is completely consistent with the qualitative report of Snyder and co-workers[6] that H_2O_2 is formed in the autoxidation of 2-(2′-cyano-2′-propyl)-2,3-diazabicyclo[2.2.2]octane in acetonitrile. Although we have not adequately solved the analytical problem of scavenging all of the water from the reaction vessel, at least 25% of the theoretical amount of water in the autoxidation of **1** in acetonitrile was shown to be produced by VPC measurements.

Conversion of **1H** to **2** and **3** requires CH bond cleavages at C_5 and C_6, respectively. We chose deuterium labeling for a study of the stereochemistry of these cleavages. Following the procedure of Roth and Martin,[7] a sample of *exo,exo*-5,6-dideuterio-**6** (**6**-d_2) was prepared which analyzed by ^{13}C NMR spectroscopy for 96 ± 2% d_2, 4 ± 2% d_1.[8] We were concerned that *tert*-butyllithium might be a strong enough base to remove deuterium from C_5, C_6 of **6** during the addition reaction, and cause either deuterium loss or exo,endo D scrambling in the **1H**-d_2 sample produced. Unfortunately, the considerable air sensitivity of **1H** made it difficult to store our small samples until the mass spectral analysis could be run (determined empirically, by losing three samples in a row and wasting a month), so we analyzed for integrity of the deuterium label by quenching the *tert*-butyllithium addition reaction with methyl iodide instead of ammonium chloride, generating the easily handled **1Me**-d_2. The **1Me**-d_2 obtained analyzed by mass spectroscopy at 94 ± 2% d_2, 6 ± 2% d_1, so little, if any, deuterium loss occurred during the *tert*-butyllithium addition reaction. We analyzed for positional integrity of the deuterium in our samples by ^2H NMR, using broad-band proton decoupling to eliminate hyperfine structure. Even the 15.36-MHz spectra allowed by our XL-100 instrumentation should give good enough data to tell exo from endo deuterium, for we clearly could see the two peaks for C_5D and C_6D of **1H**-d_2 (resolution 25% to the base line) which differ in chemical shift by only 0.09 ppm. The ^2H NMR data are summarized in Table II.

Table I. Yields of **2** and **3** in the Air Oxidation of **1H**

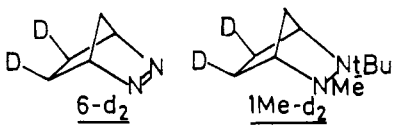
run	solvent	recovered **1H**[a]	**2**[a]	**3**[a]	(**1H** + **2** + **3**)
1	cyclohexene	0	90	10	100
2	cyclohexene	0	92	8	100
3	cyclohexene	0	92	9	101
4	cyclohexene	0	89	12	101
5	hexane	40	51	3	94
6	acetonitrile	4	15	3	22
7[b]	cyclohexene	0	60	24	84
8[b]	cyclohexene	0	64	30	94
9[b]	cyclohexene	0	59	27	86

[a] Mole percent, determined by VPC using *tert*-butylbenzene as internal standard. [b] **1H**-d_2 runs.

Table II. ^2H NMR Spectral Data[a]

compd	δ[b] (half-width[c])
6-d_2	1.55 (1.1)
1Me-d_2	1.49 (1.8), 1.10 (1.5)[d]
1H-d_2	1.65, 1.56[e]
2 (from **1H**-d_2)	1.12 (1.5)
3 (from **1H**-d_2)	2.55 (1.0)

[a] Solvent C_6F_5, ^{19}F lock, Varian XL-100 instrumentation. [b] Reported in parts per million downfield from Me_4Si. [c] In hertz. [d] Peaks split 90% to the base line. [e] Peaks split 25% to the base line.



Air oxidation of **1H**-d_2 under the same conditions as for the undeuterated compound gave slightly lower yields of **2** + **3**, but still in the range of 84–94% (runs 7–9, Table I). The deuterium content of the **2** produced from **1H**-d_2 was found to be 93% d_1, 7% d_0, no d_2 observed, by mass spectroscopy. Only the exo substituent (D) was removed from C_5, despite a primary isotope effect favoring endo (H) removal.

The stereochemistry of the loss of hydrogen/deuterium at C_6 in the formation of **3** is also exclusively exo (deuterium) loss within the limits of NMR detection, because no vinyl deuterium could be observed by ^2H NMR of the **3** formed. Our attempts at mass spectral analysis of deuterium content of **3** were unsatisfactory, because the parent $\mathbf{3}^{+\bullet}$ cation peak in the mass spectrum was too small for direct measurement. Analysis of deuterium content in the daughter ions gave 52% **3**-d_1 and 40% **3**-d_0, but we suspect that these numbers are not correct. We can think of no reasonable way to wash deuterium out of **3** but not **2** during formation of these products, and scrambling in the spectrometer in formation of daughter fragments from **3** seems more likely to us than such scrambling in the autoxidation itself, given the ^2H NMR result.

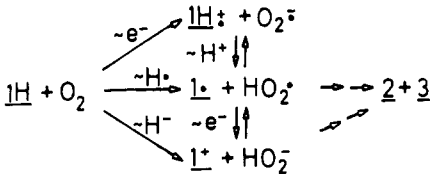
The most striking thing about **1H**-d_2 autoxidation compared to the undeuterated case is the large increase in the relative amount of **3** observed; the **2**/**3** ratio drops from 9.5 for **1H** to 2.2 for **1H**-d_2 (runs 1–4 and 7–5 of Table I). A preferential formation of product with deuterium at C_5 relative to C_6 in the monodeuterio material present in **1**-d_2 cannot be the expla-

nation. We do not believe that there is enough monodeuterio material present, but, even if there were, preferential deuterium substitution at C_5 is neither reasonable for the catalytic hydrogenation used to introduce deuterium nor permitted by the ^2H NMR spectrum of a deuterated **1H** sample which analyzed by mass spectroscopy to have about 65% of two deuteriums incorporated, so that the random distribution of deuterium C_5 and C_6 would be 42% d_2, 46% d_1, 12% d_0. Qualitatively equal heights for the partially resolved C_5,C_6 deuterium peaks at 1.65 and 1.56 were observed, showing that preferential deuteration at C_5 has not occurred.

Discussion

The initial interaction of oxygen with **1H** might give various species, as indicated in Scheme II. One could reasonably pos-

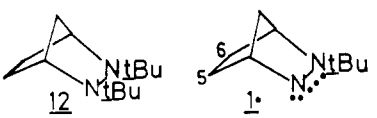
Scheme II



tulate electron, hydrogen atom, or hydride transfer from **1H** to O_2. It is difficult in principle to determine what this initial process is, because rapid electron and proton transfers might well equilibrate $\mathbf{1H^{+}\cdot}$, **1·**, and $\mathbf{1^+}$ and their oxygen-derived counterparts, possibly more rapidly than the CH bond-breaking reactions which give the observed products.

Direct electron transfer to give $\mathbf{1H^{+}\cdot}$ and $O_2^{-}\cdot$ is certainly endothermic in polar solvents. Tetraalkylhydrazines of similar structure have formal oxidation potentials in the range 0.0–0.2 V vs. SCE,[9] considerably positive of the O_2,$O_2^{-}\cdot$ wave in acetonitrile (about −0.82[10]). It seems unreasonable to postulate direct loss of two protons and an electron from $\mathbf{1H^{+}\cdot}$ and go directly to **2** and **3**, and $\mathbf{1H^{+}\cdot}$ is known to deprotonate to **1·** exceedingly rapidly in both acetonitrile and in water from electrochemical[11] and conductivity[11d] studies. We do not believe, therefore, that $\mathbf{1H^{+}\cdot}$ is a reasonable direct precursor of **2** and **3**.

Because $E^{\circ\prime}$ for $\mathbf{1\cdot,1^+}$ is about 1 V negative of the expected $E^{\circ\prime}$ for $\mathbf{1H,1H^{+}\cdot}$ in acetonitrile[11] (in other words, it is over 20 kcal/mol easier to remove an electron from **1·** than it is from **1H** in acetonitrile), $\mathbf{1^+}$ must definitely be considered as a possible precursor of **2** and **3**; it could arise from them simply by deprotonation. We have not, however, been able to achieve deprotonation of $\mathbf{1^+}$. It is far too long lived in polar solvents, where it is soluble, to be an intermediate in **1H** autoxidation. The salt $\mathbf{1^+BF_4^-}$ is easily isolable[11] and is not deprotonated by tertiary amines, even after days. Addition of sodium methoxide to $\mathbf{1^{+}\cdot BF_4^-}$ in DMSO results in the rapid formation of **1H**, presumably by hydride transfer. Addition of the stronger base *tert*-butyllithium to a suspension of $\mathbf{1^+BF_4^-}$ in THF results in dissolution of the solid and a good yield of the very strained product **12**, but no deprotonation products were detected. We

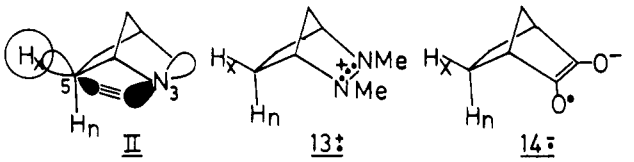


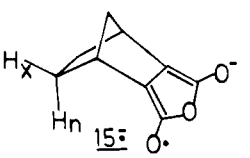
therefore suggest that a radical pair [**1·**,·OOH] seems to be the mostly likely precursor of **2** and **3** under autoxidation conditions. Abstraction of a hydrogen atom from C_5 of **1·** to give **2** is an example of a bimolecular 1,3 radical displacement reaction,[12] or, in the jargon of ESR spectroscopy, a hydrogen atom γ to the spin-bearing center has been abstracted. Loss of a halogen 1,3 to a radical center to generate a cyclopropane ring is well precedented,[12] but γ-hydrogen loss to give a cyclopropane is rare. Radical combination and 1,2 abstraction (hydrogen atom transfer disproportionation) are diffusion controlled for most alkyl radicals, and the far slower 1,3 abstraction does not complete effectively. Berson and co-workers[13] observed small amounts of tricyclic product from the high-temperature generation of bornyl radicals, providing some precedent for 1,3 elimination in a carbon-centered bicyclo[2.2.1]hept-2-yl system. We think that is reasonable that this process could become the dominating reaction for **1·**, where the equilibrium for dimerization lies far on the side of the radical[11] and 1,2 abstraction is blocked by the bicyclic structure (a Bredt's rule effect;[14] the 1,2 abstraction product is highly strained and hence is not formed rapidly).

In support of a radical-pair precursor to **2** and **3**, other free-radical conditions produce these products. Photolysis of **1H**–di-*tert*-butyl peroxide mixtures and letting degassed solutions of **1·** (produced by electrolytic reduction of $\mathbf{1^+}$) stand at room temperature both produce **2** and **3**. It must be pointed out, however, that [**1·**,**X·**] radical pairs might well undergo electron transfer to yield $[\mathbf{1^+},\mathbf{X^-}]$ ion pairs before CH bond cleavage occurred (see Scheme II). We know of no operational distinction between such ion and radical pair mechanisms.

The high yields of **2** and **3** in the autoxidation of **1H** are particularly striking when one considers that **1·** is being formed in the presence of oxygen, but oxygen is not incorporated into the products under these conditions. In contrast to the much-studied triarylhydrazyl diphenylpicrylhydrazyl (DPPH),[15] trialkylhydrazyl **1·** is known to react with oxygen. Electrolytically prepared **1·** samples rapidly lose their **1·** ESR spectrum upon exposure to air, and the ESR spectrum of the hydrazyl oxide is produced,[11] followed by that of its decomposition product, a nitroxide. We believe that the reaction of **1·** with O_2 must be slower than the hydrogen abstraction reactions which produce **2** and **3** under autoxidation conditions, because we would not expect NO bond cleavage to easily occur in the hydrazyl oxide. For **9·**, in which the tricyclic analogue of **2** is considerably more strained, reaction with O_2 might successfully compete with CH abstractions, and divert the product mixture to different pathways: **1H** and **9H** do give entirely different types of autoxidation products, as noted above.

Only the exo substituent (D) was removed from C_5 in forming **2**, despite a primary isotope effect favoring endo (H) loss. Although the exo face of the bicycloheptyl system is less sterically hindered than the endo face, free-radical abstractions by 2-norbornyl radicals give mixtures of exo and endo products,[16] and we suggest that electronic factors must be important in determining the observed result of complete stereospecificity of attack at C_5. For **1·** there is a homohyperconjugative[17] or "W-plan" interaction of the $H_{5x}C_5$ band with the N_3 p orbital, as shown diagrammatically in II. The $H_{5n}C_5$ bond



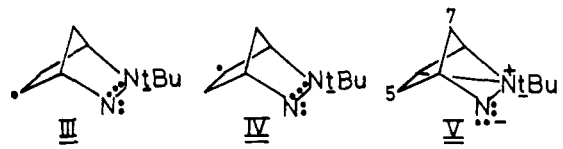


is not lined up properly for interaction. The presence of such interactions is indicated spectrally by the enhanced ESR splittings for γ hydrogens held in proper geometry with respect to a spin-bearing orbital, which has received considerable study by the groups of Russell, Stock, Nelsen, and others.[17] Choosing cases as geometrically similar to **1·** as possible, hydrazine

radical cation $13^{+\bullet}$ exhibits an $a(H_x)/a(H_n)$ ratio of 6, that for semidione $14^{-\bullet}$ is too large to measure because $a(H_n)$ is unobservably small, and semifuraquinone $15^{-\bullet}$ has an $a(H_x)/a(H_n)$ ratio of 7.6.[17] Because $i(H)$ is a measure of the odd-electron density in the hydrogen 1s orbital, a weaker CH bond ought to accompany a large $a(H)$. Although we are not aware of extensive correlations of $a(H)$ with hydrogen abstraction rate,[18] it is clearly true that β hydrogens which are forced to lie near the nodal plane of the spin-bearing orbital exhibit both small $a(H)$ and low abstraction rates. It has also been shown that the larger $a(H)$ axial hydrogen atom is preferentially abstracted from cyclohexyl radicals which are forced to occupy predominantly one chair form by substituents.[19] The exo stereochemistry observed does not, however, help to distinguish between a radical-pair and ion-pair transition state for **1**• + X• → **2**. Bicyclo[2.2.1]heptan-2-one derivative homoenolization studies have demonstrated that the exo hydrogen is preferentially removed by strong base.[20] II is as valid a picture for the ion pair as the radical pair.

Removal of hydrogen from C_6 to ultimately give **3** was also observed to be completely exo. For **1**•, $a(N_2)$ and $a(N_3)$ only differ by 7%,[11] and bending at N_2, which would make the relative sizes of $a(N)$ a poor indication of relative spin density, is unlikely both on structural grounds and from the sum of the two $a(N)$ values; the odd electron at each nitrogen is in a nearly pure p orbital. The amount of homohyperconjugative bond weakening for C_5H_x and C_6H_x should thus be very similar, yet the **2**/**3** ratio is about 9.5 for **1H** autoxidation. Obviously, it is transition-state energies, not CH bond strengths in the **1**• ground state, which governs the **2**/**3** product ratio.

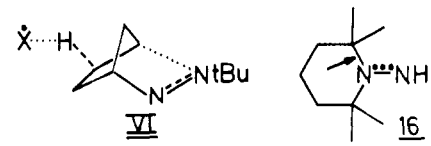
An intermediate between $\mathbf{1}^{\bullet}/\mathbf{1}^{+}$ and **2** seems highly unlikely. There is weak N_3,C_5 interaction even in the ground state. Breaking the H_x-C_5 bond and forming the N_3C_5 bond should be able to proceed simultaneously—diradical III need not ever



III IV V

be formed. Two bonds must be cleaved to convert $\mathbf{1}^{\bullet}/\mathbf{1}^{+}$ to **3**, the H_x-C_6 and C_1-N_2 bonds. We first considered the possibility that H_x-C_6 bond breakage occurs independently of C_1-N_2 breakage. By the same argument as above, one should not produce diradical IV but zwitterion V, although it must be admitted that we do not know how to properly determine the energy gap between these structure, especially in nonpolar solvents. It might be argued that IV and V are resonance structures for $\mathbf{1}^{\bullet}/\mathbf{1}^{+}$ with H_x removed from C_6. Although each might be expected to cleave to **3** rapidly, both are, we believe, rather clearly destabilized relative to **2**, and formation of a high-energy intermediate such as IV/V might provide a rationalization for the high **2**:**3** ratios observed for **1H** autoxidation, despite the similar CH bond strengths expected at C_5 and C_6 of **1**•. We have consistently observed a slightly lower **2**/**3** ratio in polar solvents, but the fact that formation of these products is only a minor process in polar solvents makes us reluctant to conclude that the transition state for **3** formation is more polar, as V would suggest.

If removal of H_{6x} did not lead immediately to **3** but instead gave an intermediate (IV/V?), one might conceivably trap this intermediate by hydrogen abstraction, returning to **1**•. Excellent hydrogen donors (such as **1H**) are present in the reaction mixture. If V were present either as an intermediate or a transition state, C_5 and C_7 would be required to scramble in the return to **1**•, for they are identical in V. Landis had reported observing such a carbon-scrambled product in the autoxidation of **7H**.[2] We have looked repeatedly for evidence for such positional scrambling in the decomposition of both **1H**-d_2 and **7H**, with entirely negative results at a variety of hydrazine concentrations and also in the presence of added N_2H_4 as an additional hydrogen donor. We see no deuterium at position 7 of recovered **1H** in the **1H**-d_2 autoxidation, nor can we observe any rearranged material in the **7H** autoxidation. To the best of our ability to tell, then, once H_{6x} removal occurs under our autoxidation conditions, **3** is formed irreversibly, not a surprising result. The dramatic drop in the **2**/**3** ratio in **1H**-d_2 autoxidation requires either that **2** and **3** do not both arise from $\mathbf{1}^{\bullet}/\mathbf{1}^{+}$ (and we have been unable to think of no reasonable alternative mechanism) or that the deuterium isotope effect is far larger for H_{5x} removal (giving **2**) than for H_{6x} removal (giving **3**). We shall assume the latter. For example, if k_H/k_D for H_{5x} removal were 6, a fairly large primary isotope effect, the observed change in the **2**/**3** ratio (undeuterated 9.5 ratio; 94% d_2, 6% d_1 mixture, 2.3 ratio) would require that k_H/k_D for H_{6x} removal be only 1.17. Apparently, either very much or very little C_6H_{6x} bond breaking is occurring at the transition state. One possible argument would be a Hammond's postulate one, that the product from H_{6x} removal, IV/V, is considerably higher in energy than the product from H_{5x} removal, **2**, so the transition state occurs earlier for the H_{6x} abstraction. Nevertheless, we would find it quite surprising that processes as similar as H_{5x} removal to give **2** and H_{6x} removal to give IV/V would have such different deuterium isotope effects. There is, of course, no experimental evidence at all that IV/V is an intermediate. What might be expected if H_{6x} removal from $\mathbf{1}^{\bullet}/\mathbf{1}^{+}$ gave **3** in a single step? Both the $H_{6x}C_6$ and C_1N_2 bonds would have to cleave. It seems quite conceivable to us that C_1N_2 bond breaking might be considerably more important than $H_{6x}C_6$ bond breaking at the transition state, as we have tried to indicate in structure VI. The trialkylhydrazyl **16** is known[21] to



VI 16

decompose thermally by homolytic cleavage of the CN bond indicated with an arrow in structure **16**; this bond is structurally analogous to the longest bond (C_1N_2) in the proposed transition state VI. There can be no thought of actually breaking the C_1N_2 bond of $\mathbf{1}^{\bullet}/\mathbf{1}^{+}$ without at least beginning to break the $H_{6x}C_6$ bond, because of the observed stereospecificity (no vinyl deuterium is observed in **3** from **1H**-d_2) and regiospecificity (none of the product of hydrogen abstraction from C_7, 2-cyclopentenyl-*tert*-butyldimide, is observed, and the **2** + **3** yield is so high that little could be formed and somehow not observed). Although we cannot claim any evidence at all for transition state VI, we suggest that it at least provides a rationalization for the puzzling observation of very different k_H/k_D values for bond cleavages which appear as geometrically similar to those of $H_{5x}C_5$ and $H_{6x}C_6$. Unfortunately, an experimental test of this hypothesis has not be devised.

Conclusion

The balance of factors permitting the autoxidation of **1H** to give a high yield of the formal 1,3 hydrogen elimination product **2** is very delicate. The presence of either abstractable hydrogen on carbons next to nitrogen or enlargement of the bicyclic system to bicyclo[2.2.2]octyl completely eliminates this type of product, and even changing the oxidant from oxygen to quinone or going from a nonpolar to a polar solvent makes its formation a minor process. Abstraction of the H_{5x} hydrogen must show a rather large deuterium isotope effect, because k_H/k_D is about five times smaller for deuterium isotope effect, because k_H/k_D is about five times smaller for formation of azo compound **3**, a minor product in the autox-

idation of **1H**. Only loss of exo hydrogen in formation of both **2** and **3** was observed, which was attributed to homohyperconjugative bond weakening of the C_5H_{5x} and C_6H_{6x} bonds.

Experimental Section

2-*tert*-Butyl-2,3-diazabicyclo[2.2.1]heptane (1H). Dry tetrahydrofuran (25 mL) was distilled into a 25-mL flask fitted with a magnetic stirrer, an addition funnel, and a rubber septum. After the addition funnel was charged with 0.5 g (5.2 mmol) of azo compound **6** in 10 mL of dry THF and argon was bubbled through both solutions to remove oxygen, the flask was cooled to −78 °C and 12 mmol of commercial *tert*-butyllithium solution was injected. The solution of **6** was run in, the color of the mixture deepening to a reddish orange. After 5 min of stirring at −78 °C, the reaction mixture was transferred via a stainless steel cannula to a flask containing 10 g of ammonium chloride in 150 mL of liquid ammonia. The ammonia was allowed to evaporate under argon, and the salts were triturated with ether and rapidly filtered in air. After concentration by rotary evaporation (vacuum broken using an argon atmospere), the light green oil obtained was purified by Kugelrohr distillation, giving 0.68 g (85%) of **1H** as a clear liquid.[22] ^{1}H NMR ($CDCl_3$): δ 1.04 (s, 9 H), 1.1–2 (m, 6 H), 3.25 (br s, 1 H), 3.50 (br s, 2 H). ^{13}C NMR ($CDCl_3$): δ 26.5 (q, *t*-Bu*Me*), 31.3 and 32.5 (t, C_4 and C_5), 35.4 (t, C_7), 56.5 and 57.4 (d, C_1 and C_4), 58.0 (s, *C*Me$_3$). IR (CCl_4): 3400 cm^{-1}, NH. **1H-*d*$_2$** was prepared by the same method from **6-*d*$_2$**.[14,15]

Autoxidation of 1H. Solutions of **1H** in 50 mL of cyclohexene (freshly distilled from sodium) containing a weighed amount of *tert*-butylbenzene were stirred while dry air was bubbled through an 18-gauge needle for 12 h. VPC analysis was carried out on 12 ft × $\frac{1}{8}$ or $\frac{3}{8}$ in. 15% XF-1150 on Chromosorb W (60–80 mesh) columns, using a Varian-Aerograph A90-P3 or Hewlett-Packard 5710A VPC. After **3** was eluted at 50 °C, the column temperature was increased to 80 °C for elution of **2**, *tert*-butylbenzene, and **1H**. Sensitivities were calculated from weighed mixtures of **2**, **3**, **1H**, and *tert*-butylbenzene. Peak areas were measured using a Hewlett-Packard Model 3380A electronic integrator.

3-*tert*-Butyl-2,3-diazatricyclo[2.2.1.0^{2,6}]heptane (2) was separated by preparative VPC from the autoxidation mixture of **1H** as a clear oil.[22] ^{1}H NMR ($CDCl_3$): δ 1.14 (s, 9 H), 1.25, 1.53 (br d, *J* = 9 Hz, 2 H), 2.30 (br d, *J* = 2 Hz, 2 H), 3.48 (br s, 1 H). ^{13}C NMR ($CDCl_3$): δ 28.6 (q, *C*Me_3), 32.4 (d, $C_{1,6}$), 32.8 (t, $C_{5,7}$), 49.5 (d, C_4), 54.1 (s, *C*Me$_3$). IR (CCl_4): no NH stretch.

***tert*-Butyl-3-cyclopentenyldiimide (3)** was separated by preparative VPC from the autoxidation mixture of **1H** as a clear oil.[23] ^{1}H NMR ($CDCl_3$): δ 1.1 (s, 9 H), 2.6 (m, 4 H), 4.2 (m, 1 H), 5.8 (br s, 2 H). ^{13}C NMR ($CDCl_3$): δ 26.8 (q, *C*Me_3), 37.7 (t, *C*H$_2$), 65.0 (s, *C*Me$_3$), 75.0 (d, *C*H), 129.1 (d, =*C*H). IR: no NH, 2980, 2900 cm^{-1}.

***tert*-Butylcyclopentyldiimide (5).** A mixture of 70 mL of acetonitrile, 1.08 g of *tert*-butylhydrazine hydrochloride, 0.72 g of cyclopentanone, and 0.54 g of sodium cyanoborohydride was treated with 2 mL of 15% NaOH and 2 mL of acetic acid. After the mixture was stirred overnight, 70 mL of 15% NaOH was added and the mixture extracted with pentane. After drying with Na_2SO_4, the pentane extract was stirred with 1.08 g of Ag_2O for 4 h, filtered, and concentrated. **5** was isolated by VPC.[22] ^{1}H NMR ($CDCl_3$): δ 1.1 (s, 9 H), 1.25–2.0 (m, 8 H) 3.8 (m, 1 H). ^{13}C NMR ($CDCl_3$): δ 25.3 (t), 26.8 (q), 31.2 (t), 6.58 (s), 77.7 (d). UV (hexane): λ_{max} 362 nm, ε 14.8. The same compound as determined by VPC retention time and ^{1}H NMR spectrum was found when **3** was hydrogenated over Pd/C at 40 psi in MeOH, followed by filtration, stirring with Ag_2O, and concentration, with final purification by VPC.

7-Spirocyclopropyl-2-*tert*-butyl-2,3-diazabicyclo[2.2.1]heptane (7H). Using the same procedure as for **1H**, 11 mL of 1.1 M *tert*-butyllithium are added to 1.22 g of 7-spirocyclopropyl-2,3-diazabicyclo-2-norbornene,[24] and the oil obtained purified by VPC.[22] ^{1}H NMR (CD_3CN): δ 0.3–0.7 (m, 2 H), 0.81–1.1 (m, 2 H), 1.0 (s, 9 H), 1.4–2.0 (m, 4 H), 2.65 (br s, 1 H), 2.9 (br s, 1 H). (N*H* was observed as a broad singlet at δ 3.5 in $CDCl_3$). ^{13}C NMR (CD_3CN): δ 4.93, 10.94 (m, cyclopropyl C), 27.92 (q, *C*Me_3), 33.27, 33.38 (t, C_5 and C_6), 56.33 (s, *C*Me$_3$), 60.98 and 62.48 (d, C_1 and C_4). IR (CCl_4): 3400 (NH) cm^{-1}.

7-Spirocyclopropyl-2,3-diazabicyclo[2.2.1.0^{2,6}]heptane (10). This compound was separated by VPC for the autoxidation of **7H**.[22] ^{1}H NMR ($CDCl_3$): δ 0.5–1.0 (m, 4 H), 1.25 (s, 9 H), 1.75 (br s, 2 H), 1.95 (d, *J* = 4 Hz, 1 H), 2.55 (br d, *J* = 4 Hz, 1 H), 3.00 (br s, 1 H). ^{13}C NMR ($CDCl_3$): δ 2.44 and 8.85 (m, cyclopropyl C), 28.60 (q, *C*Me_3), 29.43, 33.49, 39.279 (d, C_1, C_4, C_5), 34.71 (t, C_6), 57.20 (s, *C*Me$_3$). IR (CCl_4): no NH.

2-Spirocyclopropyl-3-cyclopentenyl-*tert*-butyldiimide (11). This compound was isolated by preparative VPC for the autoxidation of **8H**.[23] ^{1}H NMR ($CDCl_3$): δ 0.7 (br s, 4 H), 1.2 (s, 9 H), 2.5–3.0 (m, 2 H), 3.65 (d of d, *J* = 8, 4 Hz, 1 H), 5.18 (m, 1 H), 5.8 (m, 1 H). ^{13}C NMR ($CDCl_3$): δ 7.57, 11.58 (t, two cyclopropyl CH$_2$), 27.09 (q, *C*Me_3), 37.65 (t, CH$_2$), 79.79 (d, CH), 126.78, 136.65 (d, two vinyl C) (quaternary carbons not observed). IR (CCl_4): no NH, 3060, 2980, 1360 cm^{-1}.

2-Methyl-2,3-diazabicyclo[2.2.1]heptane (8H). This compound was prepared using the same procedure as for **1H**, on 0.5 g of **6** and 2.6 mL of commercial methyllithium solution. A clear oil was obtained in 70% yield and purified by VPC.[22] ^{1}H NMR (CD_3CN): δ 1.1–2.0 (m, 6 H), 2.2 (s, 3 H), 3.0 (broad, 1 H), 3.15 (br s, 1 H), 3.37 (br s, 1 H). ^{13}C NMR (CD_3CN): δ 28.98 (m, C_5), 32.32 (m, C_7), 33.97 (m, C_6), 46.29 (q, Me), 58.18 and 63.68 (d, C_4 and C_1). IR (CCl_4): 3400 (NH) cm^{-1}.

2-*tert*-Butyl-2,3-diazabicyclo[2.2.2]octane (9H). The same method as for preparation of **1H** was used, starting with 2,3-diazabicyclo[2.2.2]octane,[21] giving **9H**[22] in 90% yield as a clear oil. ^{1}H NMR: δ 1.15 (s, 9 H), 1.5–2.1 (m, 8 H), 3.0 (very broad s, 2 H). IR (CCl_4): 3400 (NH), 2980 (CH) cm^{-1}.

2,3-Di-*tert*-butyl-2,3-diazabicyclo[2.2.1]heptane (12). A slurry of 0.24 g of **1**$^+$**BF**$_4^-$ [8] in 20 mL of dry THF was stirred at −78 °C, while 0.91 mL of 1.1 M *tert*-butyllithium was added dropwise by syringe slowly, so that the yellow color of the alkyllithium did not build up. The salt dissolved as it reacted, and the solution was faint yellow after the addition. The reaction mixture was quenched by addition of 0.1 g of solid ammonium chloride, warmed to room temperature, filtered, and concentrated to dryness, giving **12**[22] as an oil which was purified by VPC (as high flow rate as possible, column temperature 80 °C, injector and detector temperatures 110 °C). ^{1}H NMR ($CDCl_3$): δ 1.0–2.1 (complex, 2 H), 1.14 (s, 9 H), 1.25 (s, 9 H), 3.65 (br s, 1 H), 3.7 (br s, 1 H). ^{13}C NMR ($CDCl_3$): δ 29.0 and 29.3 (t, C_4 and C_5), 30.5 and 31.0 (q, two *C*Me_3), 37.8 (t, C_7), 56.3, 57.7 (s, two *C*Me$_3$), 60.6 and 61.9 (d, C_1 and C_4). IR (CCl_4): 2980, 1480, 1390, 1340, 1210 cm^{-1}.

2-*tert*-Butyl-3-methyl-2,3-diazabicyclo[2.2.1]heptane (1-Me). The same procedure was used for **1H**, but the reddish-orange solution was quenched by injection of an excess of methyl iodide, followed by removal of THF under vacuum, trituration with ether, filtration, and concentration to a 68% yield of **1-Me** as a clear oil.[22] Final purification was by preparative VPC (XF-1150 column). ^{1}H NMR ($CDCl_3$): δ 0.8–2.3 (m, 6 H), 1.05 (s, 9 H), 2.48 (s, 3 H), 3.35 (br s, 1 H), 3.40 (br s, 1 H). ^{13}C NMR ($CDCl_3$): δ 22.3 (t, C_5), 28.1 (q, *C*Me_3), 31.3 (t, C_6), 36.7 (t, C_7), 43.3 (q, N*Me*), 57.4 (s, *C*Me$_3$), 58.6 and 63.7 (D, C_1 and C_4). IR: no NH.

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Optical Rotatory Dispersion Studies. 128.[1] Octant Contributions of Methyl Groups in 4-*tert*-Butylcyclohexanones

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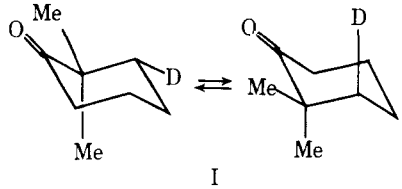
Abstract: A number of methyl-substituted 4-*tert*-butylcyclohexanones have been synthesized with high optical purity from naturally occurring chiral molecules of known absolute configuration. The circular dichroism spectra of these compounds were measured at both room temperature and 77 K in polar and nonpolar solvents, and empirical force field calculations were carried out to determine the energy difference between the chair and twist-boat conformations. Of particular interest was the discovery that the *trans*-3-methyl-4-*tert*-butylcyclohexanone (+)-**4** exists mainly in the twist-boat form. In addition, the apparent antioctant behavior of the β-axial methyl group in compound (−)-**5** at low temperature and in a polar solvent is interpreted as arising from solvation of the molecule.

Introduction

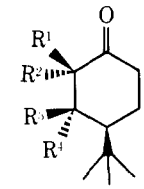
We reported in two recent communications[2,3] that variable-temperature circular dichroism measurements of monodeuterio substituted α,α-dimethylcyclohexanones (e.g., compound I) can be used to determine the energy difference



I

between the chair conformations with the deuterium in the equatorial and axial position, respectively. For the quantitative calculation of the energy difference it was necessary to make assumptions about the absolute magnitude of the rotational strengths ([*R*] values) of both conformers involved in the equilibrium. These values were obtained by adding the partial octant contributions of an α-equatorial and an α-axial methyl group as they have been reported in the literature[4,5] for a variety of model compounds, including steroids. A more direct method, which has been widely employed in the investigation of conformational equilibria by various physical methods,[6,7] is to introduce substituents into the conformationally flexible molecule so as to lock it into one or the other conformation. Ideally this conformational blocking group should have no effect on the physical property under investigation (in this study, the rotational strength). Cyclohexanones substituted with a γ-*tert*-butyl group are well suited for this type of study, since such molecules are known to function as conformationally rigid systems.[8] Also, the 4-*tert*-butyl group is located in a nodal plane in the octant diagram and should not contribute to the rotational strength.

In a previous paper,[9] we presented the synthesis of (*R*)-(+)-2,2-dimethyl-4-*tert*-butylcyclohexanone (**3**). We have now extended the methodology used in the synthesis of (+)-**3** to the synthesis of (2*R*,4*R*)-(+)-2-methyl-4-*tert*-butylcyclohexanone (**1**), (3*R*,4*R*)-(+)-3-methyl-4-*tert*-butylcyclohexanone (**4**), (3*S*,4*R*)-(−)-3-methyl-4-*tert*-butylcyclohexanone (**5**), and (*S*)-(−)-3,3-dimethyl-4-*tert*-butylcyclohexanone (**6**), and report the CD spectra of ketones **1**–**6** together with the CD



1, R^1 = Me; R^2 = R^3 = R^4 = H
2, R^2 = Me; R^1 = R^3 = R^4 = H
3, R^1 = R^2 = Me; R^3 = R^4 = H
4, R^4 = Me; R^1 = R^2 = R^3 = H
5, R^3 = Me; R^1 = R^2 = R^4 = H
6, R^3 = R^4 = Me; R^1 = R^2 = H

spectra of several of the synthetic intermediates to these compounds. Ketone (+)-**3** is closely related to the conformationally mobile cyclohexanone I and the measurement of the CD spectrum of (+)-**3** will help to evaluate the conformational effects, if any, of the α,α-dimethyl "chiral probe".[2] Ketones (+)-**1** and (+)-**2** have been prepared previously,[10] although only their optical rotatory dispersion (ORD) spectra have been reported. By measuring their CD spectra, it can be determined if the partial methyl contributions are additive (i.e., is the α,α-dimethyl group contribution simply an algebraic sum of the individual methyl group contributions?). Also, these compounds can furnish additional chiroptical reference values

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