with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4), and evaporated in vacuo to give 130 mg of an oil. ^{13}C NMR revealed only six signals below δ 100, indicating that only one isomer was formed. Chromatography of the crude product on silica gel (ether) gave 68 mg (51%) of **4a** as a crystalline solid. An analytical sample was prepared by recrystallization from pentane–ether: mp 84.5–85.5 °C; NMR ($CDCl_3$) δ 6.65–7.4 (m, 9),3.94 (d, 1, J = 10 Hz), 3.35–3.9 (m, 4), 2.85 (m, 2), 1.7–2.2 (m, 2); ^{13}C NMR ($CDCl_3$) δ 66.0, 62.4, 48.4, 48.0 39.6, 33.5; IR (KBr) 3270, 2900, 1077, 1064, 1031, 968, 756, 713 cm^{-1}. Anal. Calcd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.35; H, 7.76.

Cyclization of (*E*)-6a (90% *E*, 48 mg, 0.23 mmol) as described above gave 67 mg of crude product. Chromatography of this on silica gel (ether) gave 5 mg (41%) of pure **4a** identical with that obtained from (*Z*)-**6a**.

Acknowledgment. Support of this work by the National Institutes of Health is gratefully acknowledged.

Registry No. **4a**, 85185-48-4; (*Z*)-**6**, 1142-21-8; (*E*)-**6**, 1142-22-9; (*Z*)-**7a**, 70388-65-7; (*E*)-**7a**, 27066-35-9; (*Z*)-**7b**, 85185-27-9; (*E*)-**7b**, 85185-28-0; (*Z*)-**7c**, 85185-29-1; (*E*)-**7c**, 85185-30-4; (*Z*)-**7d**, 85185-31-5; (*E*)-**7d**, 85185-32-6; (*Z*)-**7e**, 85185-33-7; (*E*)-**7e**, 85185-34-8; (*Z*)-**7f**, 85185-35-9; (*E*)-**7f**, 85185-36-0; *trans*-**9a**, 85185-37-1; *cis*-**9a**, 85185-38-2; *trans*-**9b**, 85185-39-3; *cis*-**9b**, 85185-40-6; *trans*-**9c**, 85185-41-7; *trans*-**9d**, 85185-42-8; *cis*-**9d**, 85185-43-9; *trans*-**9e**, 85185-44-0; *cis*-**9e**, 85185-45-1; *trans*-**9f**, 85185-46-2; *cis*-**9f**, 85185-47-3; 3-[3,4-(methylenedioxy)phenyl]-propyl bromide, 28437-31-2; 3-[3,4-(methylenedioxy)phenyl]-propanol, 7031-03-0; 3-(3,4-dimethoxyphenyl)propyl bromide, 3945-85-5; (3-phenylpropyl)triphenylphosphonium bromide, 7484-37-9; benzaldehyde, 100-52-7; 3,4-dimethoxybenzaldehyde, 120-14-9; 3,4,5-trimethoxybenzaldehyde, 86-81-7; piperonal, 120-57-0; [3-[3,4-(methylenedioxy)phenyl]propyl]triphenyl-phosphonium bromide, 28437-34-5; [3-(3,4-dimethoxyphenyl)-propyl]triphenylphosphonium bromide, 57293-20-6; phenyl-acetaldehyde, 122-78-1.

Metal–Ammonia Reduction of Cycloalkanones. A Revised Mechanism

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Reduction of 9-oxo-α-agarofuran (**2**) with lithium, sodium, or potassium in liquid ammonia in the presence of excess ethanol affords as the almost exclusive product the equatorial 9α-ol (**3**). In the absence of an added proton donor, lithium–ammonia reduction of ketone **2** gives a 1.4 ratio of equatorial to axial alcohol. With sodium the ratio is 0.3 and with potassium 0.2. On the basis of the relative rates of chromate oxidation of alcohol **3** and its axial epimer (**4**), the equatorial alcohol is the more stable isomer. Reduction of 8,8-dideuterio ketone **2** with sodium–ammonia–*tert*-butyl alcohol affords an equatorial–axial ratio of 2.6, compared to 1.2 with the undeuterated substrate. None of the 9α-ol (**3**) produced from the deuterated ketone has deuterium at the carbinol position, while the 9β-ol (**4**) contains 43% deuterium incorporation at this position. On the basis of these data and a survey of the results obtained in the reduction of other cycloalkanones, a revised mechanism is proposed for these reactions.

The mechanism of the metal–ammonia reduction of cycloalkanones and the stereochemical consequences thereof have attracted considerable attention since Barton first suggested that these reductions invariably afford the more stable of a pair of epimeric alcohols via a vicinal dianion.[1] Subsequently it was found that in many instances these reactions afford mixtures rich in the less stable epimeric alcohol, and a stepwise mechanism which has been generally accepted was proposed by House.[2] Recently, however, Rautenstrauch has found that reductions of (+)-[3,3-$^2H_2$]camphor[3] or 2,2-dimethyl[6,6-$^2H_2$]-cyclohexanone[4] by alkali metals in ammonia *in the presence of alcohols* afford products in which substantial amounts of the reduced alcohol contain deuterium at the carbinol carbon, and in the absence of an added proton donor, deuterium transfer is the major reaction path.[3,5]

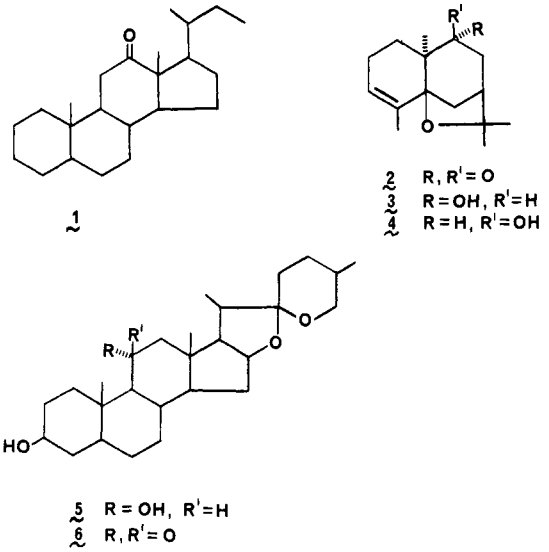
Rautenstrauch has suggested that these reductions occur via a metal ketyl dimer by transfer of a hydrogen atom from the α-position of one ketyl to the carbinol position of the other within the dimer.[3,4] He also suggests, on the basis of experimental pK_a data for ketyls,[6] that neither alcohols nor ammonia is sufficiently acidic to protonate the radical anion and that the path proposed by House competes ineffectively with the hydrogen-transfer process even in reductions carried out in the presence of alcohols.[3] Also, reduction of (+)-[3,3-$^2H_2$]camphor by alkali metals in ammonia in the presence of ammonium chloride affords little reduction product with deuterium at the carbinol carbon, and Rautenstrauch suggests that the previously accepted House mechanism is operative in this case, and reductions by alkali metals in ammonia carried out in the presence of ammonium chloride will give the thermodynamically more stable of a pair of epimeric alcohols as the major product.[3]

However, in contrast to these generalizations, reduction of norcamphor by alkali metals in liquid ammonia in the presence of ammonium chloride has been reported to afford the less stable endo alcohol as the predominent product,[7] and lithium–ammonia reduction of 2,2-dimethyl[6,6-$^2H_2$]cyclohexanone in the presence of ethanol

(1) Barton, D. H. R.; Robinson, C. H. *J. Chem. Soc.* **1954**, 3045.
(2) (a) House, H. O. "Modern Synthetic Reactions", 2nd ed.; W. A. Benjamin: Menlo Park, CA, 1972; pp 152–158. This work includes not only the evidence for this mechanism but a summary of the work in this area prior to about 1970. (b) Huffman, J. W.; McWhorter, W. W. *J. Org. Chem.* **1979**, *44*, 594. These authors presented a slightly revised version of this mechanism.
(3) Rautenstrauch, V.; Willhalm, B.; Thommen, W.; Burger, U. *Helv. Chim. Acta* **1981**, *64*, 2109. We thank Dr. Rautenstrauch for a copy of this paper prior to its publication.
(4) Rautenstrauch, V.; Geoffroy, M. *J. Am. Chem. Soc.* **1977**, *99*, 6280.
(5) Pradhan, S. K.; Kadam, S. R.; Kolhe, J. N. *J. Org. Chem.* **1981**, *46*, 2633. These authors have observed similar results with some steroidal ketones.
(6) Laroff, G. P.; Fessenden, R. W. *J. Phys. Chem.* **1973**, *77*, 1283.
(7) Huffman, J. W.; Charles, J. T. *J. Am. Chem. Soc.* **1968**, *90*, 6386. Repetition of the reduction of norcamphor with lithium–ammonia–ammonium chloride under the conditions described in ref 3, but at −33 °C rather than −78 °C, affords a mixture consisting of 11% recovered ketone, 76% *endo*-norborneol, the less stable epimeric alcohol, and 13% *exo*-norborneol, in substantial agreement with the results obtained previously.
(8) Murphy, W. S.; Sullivan, D. F. *J. Chem. Soc., Perkin Trans. 1* **1972**, 999.

0022-3263/83/1948-1474$01.50/0

Chart I



gives a reduction product containing only 19% deuterium at the carbinol position. The same reduction carried out in the presence of *tert*-butyl alcohol gives a somewhat higher precentage of deuteration on using sodium as the reducing agent.[4] In the lithium ammonia reduction of [2,2-^{2}H]-(+)-camphor with ethanol–water as a proton source a total of 24% of the product alcohols arise by deuterium transfer, and with ammonium chloride, the amount of deuterium transfer does not exceed 3%, while in the absence of an added proton donor, 72% of the product alcohols arise by deuterium transfer.[3] In previous work reported from these laboratories we have shown that various 12-keto steroids afford primarily the less stable 12α (axial) alcohol with lithium in ammonia when the reduction is carried out in the presence of methanol and that the more stable 12β-ol predominates when methanol is absent.[9] The reduction of 24-nor-5β-cholan-12-one (1, Chart I) in the presence of *tert*-butyl alcohol affords an intermediate product ratio.[9a]

The somewhat contradictory and frequently confusing body of data concerning these reductions and the mechanistic interpretations associated with them have been further complicated the recent resurrection of the Barton dianion mechanism by Pradhan et al.[5,10] In addition, the deuterium-transfer data of Rautenstrauch[3,4] are clearly incompatible with the House mechanism as usually stated,[2] while the formation of a preponderance of an unstable epimer in reductions in the presence of ammonium chloride is inconsistent with Rautenstrauch's interpretation of these reactions.[3] It is also very difficult to explain the changes in product ratios observed in the reductions of 12-keto steroids in the presence and absence of various alcohols[9] in terms of the Rautenstrauch mechanism.

During work directed toward the synthesis of some naturally occurring polyhydroxyagarofurans,[11] we made the serendipitous observation that 9-oxo-α-agarofuran (2) was a particularly sensitive substrate for the study of the mechanism and stereochemistry of the metal–ammonia reduction of cycloalkanones. In the course of this study, we have carried out the reduction of ketone 2 using various alkali metals in liquid ammonia, both in the presence and absence of alcohols, and have also carried out the reduction of deuterated ketone 2. On the basis of these data we suggest a revised mechanism for these reductions, which is consistent both with Rautenstrauch's data and with those of other workers.

Table I. Metal-Ammonia Reductions of 9-Oxo-α-agrofuran (2)

metal (equiv)	alcohol	rel % of products: 9α-ol 3	9β-ol 4	2	9α/9β ratio
Li (1.2)	ethanol[a]	91	trace	9	>99
Li (1.3)	none	59	41	none	1.4
Na (0.78)	ethanol[a]	73	trace	27	>99
Na (0.61)	ethanol[b]	25	50	25	0.5
Na (0.62)	*tert*-butyl alcohol[a]	31	27	42	1.2
Na (0.52)[c]	*tert*-butyl alcohol[a]	31	12	68	2.6
Na (0.61)	none	14	42	44	0.3
K (0.69)	ethanol[a]	44	trace	56	>99
K (0.92)	none	15	71	14	0.2

[a] Solvent is a 1:1 mixture of alcohol and ether. [b] One equivalent. [c] Ketone 2: 75% 8,8-$^2H_2$; 25% 8-^{2}H.

Results

9-Oxo-α-agarofuran (2) is a hindered cycloalkanone in which the carbonyl group occupies a steric environment somewhat similar to that of the carbonyl group in camphor. Reduction of ketone 2 with sodium, lithium, or potassium in ammonia in the presence of excess ethanol affords the equatorial 9α-ol 3 as the predominant reduction product (Table I). In the absence of added alcohol there is an increase in the relative amount of axial 9β-ol 4 as one goes from lithium to potassium (Table I). If the reduction is carried out with sodium in the presence of *tert*-butyl alcohol, or with a limited amount of ethanol, product ratios intermediate between these obtained with excess ethanol and no alcohol are observed (Table I).

The basic principles of conformational analysis predict that equatorial alcohol 3 should be more stable than its axial epimer (4), particularly in view of the two axial–axial interactions present in alcohol 4, combined with a severe steric interaction involving one of the *gem*-dimethyls. In addition, alcohol 4 is completely resistant to esterification under normal conditions and is not derivatized with *tert*-butyldimethylsilyl chloride and imidazole.[12] However, the NMR spectrum of this alcohol shows that it is strongly intramolecularly hydrogen bonded (see Experimental Section) which could conceivably enhance its stability relative to the equatorial epimer. In order to clarify this point, an attempt was made to effect the equilibration of alcohols 3 and 4 by using a variation of the alkoxide–benzophenone system employed some years ago by House.[13]

Under these conditions, even with prolonged heating, the 9α-ol 3 was recovered unchanged, while the axial 9β-ol 4 underwent oxidation to ketone 2, which is then stable to the reaction conditions. Consideration of the steric factors present in ketone 2 and alcohols 3 and 4, combined with the generally accepted mechanism of this equilibration procedure,[13] provides a ready explanation for these results. Examination of models of alcohol 3 indicates that the 9β-hydrogen is quite inaccessible due to shielding by one of the *gem*-dimethyls, while, in contrast, the equatorial 9α-hydrogen in alcohol 4 is relatively unhindered and may readily undergo transfer to benzophenone, affording ketone

(9) (a) Huffman, J. W.; Copley, D. J. *J. Org. Chem.* **1977**, *42*, 3811. (b) Huffman, J. W.; Alabran, D. M.; Bethea, T. W.; Ruggles, A. C. *Ibid.* **1964**, *29*, 2963.
(10) Pradhan, S. J.; Sohani, S. V. *Tetrahedron Lett.* **1981**, *22*, 4133.
(11) (a) Huffman, J. W.; Hillenbrand, G. F. *Tetrahedron, Suppl.* **1981**, *No. 9*, 269. (b) Huffman, J. W.; Desai, R. C. *J. Org. Chem.* **1982**, *47*, 3254.
(12) Hillenbrand, G. F. Ph.D. Disseration, Clemson University, 1982.
(13) House, H. O.; Muller, H. C.; Pitt, C. G.; Wickham, P. P. *J. Org. Chem.* **1963**, *28*, 2407.

2. The reduction of ketone **2** by hydride transfer would proceed via a transition state either in which there are the incipient steric repulsions present in the alkoxide derived from axial alcohol **4** or in which the hydride must be transfered to the extremely congested β face of the molecule to give alcohol **3**.

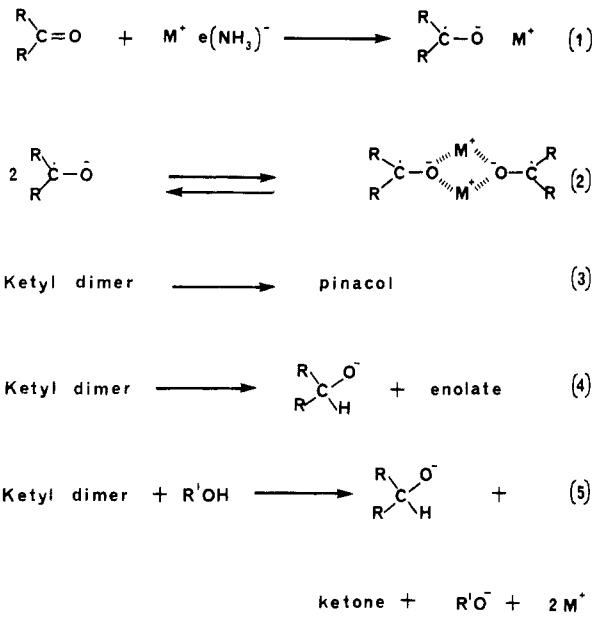
An alternative approach to the determination of the relative stabilities of a pair of epimeric cycloalkanols is a comparison of their relative rates of oxidation by chromic acid.[14] However, preliminary qualitative experiments indicated that 9β-ol **4** was oxidized extremely rapidly by Jones reagent, and consequently the relative rates of oxidation of these alcohols were determined by carrying out a competitive reaction by using a limited amount of oxidant. Under these conditions the rate of oxidation of the axial alcohol was 3.2 times that of the equatorial isomer. These data clearly show that the equatorial isomer is at least 0.6 kcal/mol more stable than its axial epimer;[14] however, this figure is subject to considerable uncertainty. It is known that in most cases the chromic acid oxidation of alcohols proceeds by a two-step mechanism: rapid, reversible, acid-catalyzed formation of a chromate ester, followed by a slow, rate-limiting decomposition to the ketone.[15] However, it is also known that if an alcohol is extremely hindered, the rate of formation of the chromate ester is decreased, affording an abnormally low rate of consumption of oxidant.[15] In view of the extreme difficulty encountered in preparing esters of alcohol **4**, the observed rate of its oxiation may well be anomalously low due to a similar effect.

In order to further probe the course of the metal–ammonia reduction of ketone **2**, we prepared the 8,8-dideuterio derivative by prolonged heating with NaOD/D_2O[16] which resulted in material which contained 75% D_2 and 25% D_1[17] species. Deuterated ketone **2** was then subjected to reduction with sodium–ammonia–*tert*-butyl alcohol, a system which affords approximately equal amounts of alcohols **3** and **4** on using undeuterated ketone **2** (9α/9β ratio of 1.2); however, the deuterated ketone affords a considerably larger 9α/9β ratio (2.6). Analysis of these products for both total deuterium content[17] and the location of the deuterium[18] showed that the 9α-ol **3** from this reaction consisted of 38% D_2, 46% D_1, and 16% D_0 species, with *no detectable deuterium at the carbinol position* (C-9). The 9β-ol **4** contained 19% D_3, 31% D_2, 27% D_1 and 13% D_0,[17] species, with 43% of the material deuterated at C-9.[18] The recovered ketone was, as expected, a mixture of mono-, di-, and undeuterated material (61% D_1, 12% D_2, and 27% D_0).

An attempt was made to reduce 20-nor-5β-cholan-12-one (**1**) with lithium–ammonia–ammonia chloride under conditions alleged to lead to the formation of a preponderance of the stable alcohol.[3] However, this reduction failed, probably due to a lack of solubility of the steroidal substrate in the polar reaction medium. In the presence of ethanol, by using conditions similar to those of Rautenstrauch,[3] the mixture of product alcohols contained 90% of the axial 12-α-ol, a result comparable to that obtained in the presence of methanol.[9a]

A classical example of the metal–ammonia reduction of a hindered ketone which affords the thermodynamically stable alcohol is the preparation of 5α,22α-spirostane-3β,11α-diol (**5**) by reduction of the corresponding 11-one (**6**).[19] Repetition of the reduction of ketone **6** with lithium–ammonia by using the same conditions employed for the reduction of ketone **2** afforded the equatorial 11α-ol as the only detectable reduction product, both in the presence and absence of ethanol.

Scheme I



Discussion

The distribution of deuterium found in the sodium–ammonia–*tert*-butyl alcohol reduction of 8,8-dideuterio-9-oxo-α-agarofuran (**2**) clearly shows that *the House mechanism* (or some variation thereof)[2] *and the Rautenstrauch mechanism*[3] *are competitive reaction paths.* The absence of deuterium incorporation at the carbinol position in equatorial alcohol **3** indicates that it must arise by the reaction of some intermediate with an exogenous proton source, almost certainly *tert*-butyl alcohol.[20] The rather high incorporation of deuterium at the carbinol position of the axial 9β-ol **4** indicates that a significant portion of this compound must arise by the Rautenstrauch hydrogen-transfer path. The marked change in product ratio observed in carrying out this reduction of deuterated vs. nondeuterated ketone **2** (Table I) also indicates competitive reaction paths, and the only reasonable explanation for the decrease in the amount of 9β-ol relative to 9α-ol is the intervention of a deuterium isotope effect in the reaction path leading to the 9β-ol. This isotope effect is absent (or considerably less) in the path leading to the 9α-ol.[21]

(14) Muller, P.; Perlberger, J. C. *J. Am. Chem. Soc.* **1976**, *98*, 8407 and references therein.
(15) Rocek, J.; Westheimer, J. H.; Eschenmoser, A.; Moldovanyi, L.; Schreiber, J. *Helv. Chim. Acta* **1962**, *45*, 2554.
(16) The use of DCl/D_2O at 60 °C leads to extensive decomposition of the substrate.
(17) Analysis for total deuterium content by mass spectrometry.
(18) Analysis by NMR.
(19) Sondheimer, F.; Mancera, O.; Rosenkranz, G.; Djerassi, C. *J. Am. Chem. Soc.* **1953**, *75*, 1282.
(20) The NMR spectrum of this material shows the carbinol protons as a very broad singlet with a small overlaid doublet (J = 10 Hz) arising from coupling with the axial H-8 in the D_1 material present in the sample.
(21) It is not possible to quantitatively derive the relative amount of the 9β-ol which arises by this path due to the following facts. (1) The starting ketone contained 25% D_1 species. (2) The enolate product of the hydrogen transfer is converted back to ketone under the reaction conditions giving D_1 or D_0 species. (3) The magnitude of the deuterium isotope effect is not known, but it may be assumed to be considerable, and thus the D_1 and/or D_0 species will undergo proton transfer significantly faster than deuterium transfer from a D_2 species. Given, however, the more than twofold change in the 9α/9β product ratio for deuterated vs nondeuterated substrate, combined with the 43% incorporation of deuterium in the 9β-ol, it may be tentatively concluded that most of the 9β-ol arises via the hydrogen-transfer path.

On the basis of these data, those summarized in Table I, and the body of experimental evidence already present in the literature, we suggest in Scheme I a modified path for these reactions which appears to be compatible with *all* of the available data.

It has been established that the first step in these reductions is the formation of a metal ketyl (step 1)[22] which is converted reversibly to bridged dimeric or polymeric species (step 2).[23] These ketyls have been demonstrated experimentally to undergo a number of different reactions, the nature of which varies as a function of the structure of the ketone, the nature of the metal, and the presence or absence of an exogenous proton donor. In the absence of an added proton donor the lithium ketyl dimer derived from a nonenolizable ketone (2,2,6,6-tetramethylcyclohexanone) is stable in tetrahydrofuran in the presence of excess lithium below −75 °C.[24] It has been established experimentally that the ketyl dimers derived from enolizable ketones, in the absence of a proton source, undergo two competitive reactions: dimerization to pinacols (step 3)[2b,3,7,8,9b,23] or disproportionation to alkoxide and enolate (step 4).[3,4]

The most convincing evidence that intramolecular hydrogen transfer occurs in the ketyl dimer is that presented very recently by Rautenstrauch,[25] who found that reductions of (+)-camphor and (±)-camphor with potassium in ammonia afford different ratios of epimeric alcohols. These results can only be explained in terms of a stereochemically homogeneous intermediate ketyl dimer in the reduction of the (+)-enantiomer and a mixture of diastereomeric intermediates in the case of the racemate.[25] This work also explains, after a number of years, the consistent differences in product ratios for this reduction found in our laboratory[2b,7] and those of several other groups.[2a,8,26]

The extent of pinacol formation is maximum for lithium ketyls and usually negligible for potassium with sodium intermediate and is quite sensitive to steric effects in the ketyl.[2b,3,8] It is also known that the ratios of epimeric alcohols may vary as a function of the metal in the absence of an added proton donor (Table I).[3,10,26]

In the presence of various proton donors (water, alcohols, ammonium chloride, etc.) ketyl dimers have been shown previously to undergo two reactions: with alcohols some of these intermediates form relatively stable solvates,[27] and the addition of water to the ketyl dimer derived from 2,2,6,6-tetramethylcyclohexanone results in an exceedingly rapid disproportionation to an equimolar mixtrue of alcohol and regenerated ketone.[24]

Although Rautenstrauch has suggested, on the basis of pK_a data,[3,6] that alcohols are not sufficiently acidic to protonate a ketyl, the reduction of deuterated ketone **2** discussed above convincingly demonstrates that an alcohol may serve as a proton donor in these reactions. In addition, it is very difficult to explain the differences in product ratios observed in these reductions as a function of the presence, concentration, and relative acidity of an added alcohol (Table I)[9] unless the alcohol *is* playing a vital role in these reductions. While it is true that the *equilibrium* between a ketyl and an alcohol does not favor protonation of the ketyl, the *rate* of this protonation has been shown to be exceedingly rapid.[6] Assuming that subsequent transformations of the protonated ketyls are irreversible, these pK_a considerations then become unimportant.[28]

Thus, it is apparent that in the presence of an alcohol there is a third reaction path open to the ketyl dimer, protonation to give an intermediate which is subsequently converted to the product alcohol. Although a number of paths are formally possible for this conversion, analogy with the reaction of water and the ketyl of 2,2,6,6-dimethylcyclohexanone indicates that this protonation should occur very rapidly within a dimeric species to afford ultimately one molecule of alcohol, as the alkoxide, and regenerate a molecule of ketone (Scheme I, step 5).[24] Alternatively, protonation of a monomeric ketyl could occur, particularly in the presence of a strongly acidic proton donor.

A consideration of the available experimental data concerning these reductions shows that reactions of the ketyl dimers (steps 3–5) occur competitively and that their rates must be of the same order of magnitude. Increasing the overall acidity of the reaction medium (i.e., the addition of an alcohol or ammonium chloride) increases the rate of step 5 relative to steps 3 and 4.[29] In reactions carried out in the absence of an added proton donor the rate of step 5 with ammonia as a proton donor will be greatly diminished.

The stereochemical consequences of these reductions are dictated by steps 4 and 5. In the absence of an added proton donor, assuming that the hydride-transfer mechanism is operative (step 4), the stereochemistry of the products will be determined by the detailed geometry of the ketyl dimer as exemplified most grapically by the differences in product ratios obtained in the reduction of (+)- and (±)-camphor.[25] The structures of the ketyl dimers are, in turn, a function of the structure of the substrate ketone and the length of the metal–oxygen bonds.

Although there is no direct evidence for the nature of the intermediates in step 5, the reduction of camphor and norcamphor by sodium dithionate affords product ratios similar to those obtained with alkali metals in ammonia,[30] and it has been shown that these reductions proceed via carbanions, but not radical anions.[31] These data suggest that carbanions are intermediates in step 5, as proposed in the House mechanism,[2] and it is known that carbanions generated by means other than proton removal undergo inversion faster than they capture a proton.[32] Therefore, regardless of the detailed nature of the steps in which this carbanion is protonated, the stereochemical distribution of the products will be dictated by the relative rates of equatorial vs. axial protonation, combined with the configurational preference of the anion.

Finally, there is *absolutely no evidence to support the intervention of dianions in the metal–ammonia reduction of cycloalkanones.*[5,8,10] Although this mechanism is of some historical importance,[2a,7] it was refuted on sound mechanistic grounds by House.[2a] The stability of the ketyl derived from 2,2,6,6-tetramethylcyclohexanone in the pres-

(22) Hirota, N.; Weissman, S. O. *J. Am. Chem. Soc.* **1964**, *86*, 2538 and earlier papers in this series.
(23) Hirota, N. *J. Am. Chem. Soc.* **1967**, *89*, 32.
(24) Rautenstrauch, V.; Geoffroy, M. *J. Am. Chem. Soc.* **1976**, *98*, 5035.
(25) Rautenstrauch, V. *Helv. Chim. Acta* **1982**, *65*, 402. We thank Dr. Rautenstrauch for a copy of this paper prior to its publication.
(26) Coulombeau, A.; Rassat, A. *Chem. Commun.* **1968**, 1857.
(27) (a) Nakamura, K.; Wong, B. G.; Hirota, N. *J. Am. Chem. Soc.* **1973**, *95*, 6919. (b) Chen, K. S.; Mao, S. W.; Nakamura, K.; Hirota, N. *Ibid.* **1972**, *94*, 4419.
(28) This is analogous to the classical acetoacetic ester condensation in which ethyl acetate is a number of powers of ten less acidic than ethanol; however, the reaction proceeds due to a subsequent irreversible step.
(29) The addition of a relatively weakly acidic proton donor such as *tert*-butyl alcohol would result in a smaller increase in rate than addition of a stronger acid such as methanol or ethanol.
(30) (a) Krapcho, A. P.; Seidman, D. A. *Tetrahedron Lett.* **1981**, *22*, 179. (b) deVries, J. G.; Kellogg, R. M. *J. Org. Chem.* **1980**, *45*, 4126.
(31) Chung, J. K. *J. Org. Chem.* **1981**, *46*, 5467.
(32) (a) Hoz, S.; Aurbach, D. *J. Am. Chem. Soc.* **1980**, *102*, 2340. (b) Stille, J. K.; Sannes, K. N. *Ibid.* **1972**, *94*, 8489.

ence of excess lithium[24] and the observation that fenchone[2b] and various steroidal ketones[5] give ratios of alcohols to recovered ketone which are less than 1 in the presence of excess metal and the absence of a proton donor precludes the formation of vinical dianions as intermediates in these reductions. The *only* experimental data which appear to support a dianion path are those of Pradhan,[5] in which the ratio of cyclization vs. reductions of steroidal ketones containing unsaturation proximate to the carbonyl group is found to vary with metal concentration. These effects are readily explained in terms of the mechanism outlined in Scheme I on the basis of the fact that cyclization is a unimolecular reaction whic may proceed in the undimerized ketyl, while reduction in the absence of a proton donor is a bimolecular process (step 2).

The mechanism outlined in Scheme I explains the stereochemical course of *all* the metal–ammonia reductions of cyclic ketones reported to date and is based on a body of sound experimental evidence. Since the diverse and frequently confusing results obtained when these reductions are carried out in the absence of an added proton donor are a consequence of the geometry of specific ketyl dimers, assuming the hydrogen-transfer mechanism is operative, it must be concluded at this time that the course of a given reduction under these conditions is essentially unpredictable.

In the presence of a relatively acidic proton donor (methanol, ethanol, ammonium chloride) the stereochemical course of the reduction will be governed by the direction of protonation of the carbanion generated during step 5 (Scheme I). For those ketones in which there is a large energy difference between the epimers of the reduced alcohols (e.g., ketones **2** and **6**), there should be little carbanion corresponding to the axial alcohol at equilibrium, and the reduction will afford predominently the stable alcohol. In those cases in whch the energy differences are relatively small such as 12-keto steroids,[9] bicycloheptanones,[2b,7,8,26] several decalones related to vernolepin,[33] and certain 16-keto steroids[10] there may be a significant amount of the unstable epimer of the carbanion at equlibrium, and the product ratio will then be determined by the relative rate of protonation of the epimer carbanions.[34] There is also, in any system, the possibility of competition between steps 3–5 (Scheme I). Reduction via step 5 will be enhanced by using a metal other than lithium and the most acidic possible proton donor.

Experimental Section

Microanalyses were performed by Atlantic Microlab, Atlanta, GA. Infrared spectra, reported in reciprocal centimeters, were measured for solutions in chloroform on a Perkin-Elmer Model 137 spectrophotometer. Proton magnetic resonance spectra were recorded in deuteriochloroform at 90 MHz by using a JEOL FX-90Q spectrometer or at 60 MHz by using a Hitachi Perkin-Elmer R-24 spectrometer. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane as an internal standard. Mass spectral measurements were performed on a Hewlett-Packard 5985 GC/MS system with a 0.6 m × 3.3 mm column of 2% OV-101 on 100–120-mesh Chromosorb WHP. Electron ionization was used in all cases for mass spectral determinations. Melting points, which are uncorrected, were obtained by using a Kofler hot-stage apparatus.

Reagents. 9-Oxo-α-agarofuran (**2**) was prepared by the route described in ref 11. 3β-Hydroxy-5α,22α-spirostan-11-one was a commercial sample, and the norcamphor was a sample purified by McWhorter.[2b] 24-Nor-5β-cholan-12-one was a sample remaining from earlier work.[9a] The alkali metals were commercial products used without further purification, and all solvents were either commercially available anhydrous materials or were purified before use. The ammonia was freshly distilled through potassium hydroxide pellets.

General Reduction Procedure. A solution of 0.090–0.100 g of substrate ketone in 10 mL of dry ether, in 5 mL of ether and 5 mL of *tert*-butyl or ethyl alcohol, as appropriate, was added to 30–40 mL of liquid ammonia. To this stirred solution at −33 °C was added 0.48–1.3 equiv of the metal, and the reaction mixture was stirred for 30 min. The ammonia was evaporated in a stream of dry nitrogen, and the products were isolated by extraction with ether. The product mixtures were analyzed by isolation and separation by chromatography for ketones **1**, **2**, and **5** and by GLC and NMR for norcamphor.[35]

In the reductions of 9-oxo-α-agarofuran (**2**), the crude product mixture was taken up in hexanes–ether (3:1) and chromatographed on Woelm silica gel. Elution with the same solvent mixture afforded first unreduced ketone followed by **9β-hydroxy-α-agarofuran (4)** which crystallized from hexanes: mp 77–78 °C;[36] IR 3695; NMR δ 0.90 (s, 3 H, CH_3), 1.30, 1.55 (s, 3 H each, $(CH_3)_2C$), 1.75 (br s, 3 H, $CH_3C{=}$), 2.83 (d, J = 11 Hz, 1 H, CHOH, disappears on shaking with D_2O), 3.39, (m, 1 H, CHOH, collapses to t, J_{app} = 6 Hz, on shaking with D_2O), 5.58 (m, 1 H, =CH). Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.23. Found: C, 76.17; H, 10.25.

Elution with hexanes–ether (2:1) gave 9α-hydroxy-α-agarofuran (**3**), which crystallizes from hexanes: mp 99–100 °C; NMR δ 0.81 (s, 3 H, CH_3), 1.20, 1.32 (s, 3 H each, $(CH_3)_2C$), 1.69 (br s, 3 H, $CH_3C{=}$), 3.82 (dd, J = 6, 10 Hz, CHOH), 5.5 (m, 1 H, =CH). Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.23. Found: C, 76.25; H, 10.25.

8,8-Dideuterio-9-oxo-α-agarofuran. To a solution of NaOD (prepared by adding 1.75 g of sodium to a mixture of 30 mL of dry dioxane and 50 mL of D_2O) with stirring under N_2 was added 0.516 g of ketone **2**. The reaction mixture was stirred at 65 °C under N_2 for 73 h, and the aqueous layer was drawn off and extracted with ether. The organic phases were dried and the solvents removed at reduced pressure to afford 0.525 g of deuterated ketone. The NMR showed approximately 25% residual ^1H at C-8 (disappearance of multiplet at δ 2.55). The mass spectrum showed 75% D_2, 25% D_1, and no detectable D_0.

Attempted Equilibrium of 9α- and 9β-Hydroxyagarofuran. A solution of 0.068 g of 9β-hydroxy-α-agarofuran (**4**) in 2 mL of dry toluene was added to a suspension of sodium butoxide (from 0.03 g of NaH and 0.5 mL of 1-butanol) in 1 mL of toluene containing 0.028 g of benzophenone. The reaction mixture was heated at reflux for 68 h, poured into D_2O, and extracted with ether. The ethereal extract was dried and the solvent removed at reduced pressure to give 0.091 g of viscous oil. This residue was dissolved in hexanes–ether (3:1) and chromatographed on Woelm silica gel. Elution with the same solvent system afforded first 0.011 g of benzhydrol and then 0.031 g of 9-oxo-α-agarofuran (**2**). Analysis of the crude reaction mixture by both TLC and NMR showed no trace of alcohol **3** or **4**. When the same reaction was carried out with 0.062 g of 9-α-hydroxy-α-agarofuran (**3**), examination of the crude product mixture by both TLC and NMR showed the presence of only starting alcohol and benzhydrol.

Competitive Oxidation of 9α- and 9β-Hydroxy-α-agarofuran. To a solution of 0.071 g (0.30 mmol) of 9β-ol **4** and 0.062 g (0.26 mmol) of 9α-ol **3** in 5 mL of purified acetone was added dropwise, with stirring, 0.086 mL (0.30 equiv) of Jones reagent. The reaction mixture was stirred at 25 °C for 30 min, and the precipitated solids were filtered off and washed with acetone. The solvent was removed at reduced pressure to leave a residue which was taken up in ether, washed with water, and dried, and the solvent was removed to leave 0.112 g of an oil. Qualitative analysis by TLC indicated three components, and quantitative analysis by NMR showed that the mixture contained 31% 9-oxo-α-agarofuran (**2**), 39% 9α-ol **3**, and 30% 9β-ol **4**, corresponding to

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(34) Qualitatively this will lead to product ratios somewhat similar to those observed in the borohydride reductions of similar systems. For a more detailed discussion see ref 2b and references therein.

(35) In those reactions carried out with more than 0.100 g of ketone, the quantities of solvents, metal, and ammonia were increased proportionally.

(36) This compound was originally prepared by $LiAlH_4$ reduction of ketone 2.[12]

the consumption of 0.04 mmol of 9α-ol and 0.13 mmol of 9β-ol. Analysis of mixtures of known composition of these three compounds by NMR indicated that the results were accurate to within 1%.

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Theoretical Study on the Mechanism of the Thermal Decarboxylation of 2-Oxetanones

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The mechanism of the thermal decarboxylation of 2-oxetanone is investigated by the use of the MNDO method. The state correlation diagram shows that five heavy atoms of 2-oxetanone, three carbon and two oxygen atoms, are kept in the same plane in the decarboxylation. This is found to be a one-step reaction and to proceed via a zwitterionic transition state. The substitution effect and solvent effect on the reactivity are discussed.

The present paper deals with the mechanism of the thermal decarboxylation of 2-oxetanones, which yields olefin and carbon dioxide. The mechanisms of 2 + 2 reactions have received increasing attention during the past few years.[1] The decarboxylation of 2-oxetanones is one of them. This reaction has repeatedly been employed in the stereospecific synthesis of olefins because it proceeds with retention of geometrical configuration.[2] Recently, substitution effects on the thermal decarboxylation have been investigated, and the electronic effects of substituents attached at the C_3 or C_4 position have been clarified.[3] It is suggested that the reaction proceeds via a zwitterionic intermediate. However, it is still questionable how the bond scission takes place to give olefin and carbon dioxide. It is also not certain whether the zwitterionic species is really an intermediate or not, that is, the species is located on a local energy minimum in the reaction coordinate.

In this work, the decarboxylation path is examined by a correlation diagram[4] and then it is traced by the MNDO method[5] in order to clarify the reaction mechanism. The substitution effect and solvent effect on the obtained potential energy are investigated.

Simulation of the Reaction Path

The method of simulating the decarboxylation path is described. First, the fully optimized equilibrium geometries of 2-oxetanone and its decomposition products, ethylene and carbon dioxide, are obtained. Second, the state correlation diagram is drawn by the use of the molecular orbitals (MO's) of 2-oxetanone, ethylene, and carbon dioxide to judge whether the coplanarity formed by five heavy atoms, three carbon and two oxygen atoms, is kept or not throughout the reaction. Third, the energy-optimized path is calculated by the MNDO method.

Figure 1 shows the fully optimized geometry of 2-oxetanone obtained by the MNDO method together with the observed geometry.[6] The optimized geometry with the 4-31G basis set is also depicted.[7] In both MNDO and 4-31G calculations, bond lengths and angles are optimized within the accuracy of 0.005 Å and 0.1°, respectively. The calculated results are in fairly good agreement with the observed ones. Both experimental and computational data demonstrate that 2-oxetanone belongs to a point group of the C_s symmetry, which means that O_1, C_2, C_3, C_4, and O_5 are in the same plane.

Since 2-oxetanone is found to be planar, it is checked by a state correlation diagram as to whether the decarboxylation proceeds with retention of the planar structure. Figure 2 shows the state correlation diagram for the decarboxylation path with the C_s symmetry. The ground state of 2-oxetanone can connect with that of a product site without any avoided crossing, which is represented by a bold line in the figure. This means that the thermal decarboxylation is predicted to take place preserving the planarity of 2-oxetanone. The state correlation diagram also gives information on the photodecarboxylation. The

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