in 3 was concluded to be analogous as in 2 because of their identical ^{13}C shifts at C-12 to C-18. Four out of five of the methyl ^1H NMR peaks in 3 appeared as broadened singlets due to coupling with the ^{14}N of the isocyano group (NC). The similar high-field ^{13}C (C_6D_6) shifts assigned to methyl carbons C-19 (19.9 (q)) and C-20 (20.3 (q)) indicated that both methyl groups were axial; whereas the equatorial methyl C-19 in kalihinol F (2) had a much higher value of 28.6 ppm. Given the methyl stereochemistry assigned in 3, both isocyano functions at carbons C-4 and C-10 must be equatorial. Finally, the multiplicities of axial protons, H_{ax}-2 and H_{ax}-8, respectively at 0.70 ppm (dddd, J = 13.6, 13.6, 12.4, 3.2 Hz) and 0.52 ppm (dddd, J = 13.8, 13.8, 12.8, 3.9 Hz), suggests that the *trans*-decalin skeleton of isokalihinol F (3) adopts a chair–chair conformation in solution. This is consistent with the chair–chair decalin conformation reported for crystalline kalihinol A (1),[3a] but not with that of the kalihinol F, which occupies a boat–boat conformation in the solid state.[3b]

Significant differences were observed in the kalihinol constituents of the two large collections of *A. carvenosa* obtained from Fiji (no. 86-8 and no. 87-34). As noted above, the 1986 collection (no. 86-8) yielded kalihinols A (1) (major component), F (2), X (4), and isokalihinol F (3). By contrast the 1987 collection (no. 87-34) yielded kalihinols Y (5) (major component), X (4), and Z (6). Anthelmintic (in vitro) screening conducted with pure compounds (at 50 μg/mL) against *N. brasiliensis* revealed that kalihinol Y (5) was extremely active, while kalihinols A (1), X (4), and Z (6) were very active, but isokalihinol F (3) was completely inactive. Attempts to interconvert the C-4 and C-5 substituents in 1 under acidic conditions showed that this compound was completely stable. Thus, the unusual arrangement of substituents in the A ring of 3 was not an artifact formed during workup. Biologically active diterpenoid isonitriles have also been found in *Amphimedon* sp.,[4] *Hymeniacidon amphilecta*,[5] and in *Halichondria* sp.[6] The variations in the kalihinol compositions that we and Scheuer have observed suggest that *Acanthella* is capable of rich isonitrile diterpenoid biosynthesis, and this is a subject under current investigation in our laboratory.

Experimental Section

NMR spectra were recorded on a JEOL FX-100 PFT spectrometer (99.5 MHz for ^1H and 25.0 MHz for ^{13}C) or on a GN-300 spectrometer (300 MHz for ^1H and 75 MHz for ^{13}C). High-field ^1H NMR spectra were also recorded on a Bruker 500 spectrometer (at Syntex Research Inc., Palo Alto) operating at 500 MHz. Multiplicities of ^{13}C NMR peaks were determined from APT data, and 2D COSY NMR experiments were done on the GN-300 instrument. Mass spectrometry data were obtained on a Finnigan 4000 (6000 LS7 computer system). High-performance liquid chromatography (HPLC) was done on a Waters liquid chromatograph with a Regis 10 μm ODS or 10 μm silica gel column (25 × 1.0 cm). All solvents were distilled and dried for HPLC and were spectral grade for spectroscopy. Rotations were measured on a Perkin-Elmer 141 polarimeter.

Two-Dimensional NMR Procedures. Standard pulse sequences were used for the homo COSY and the hetero COSY experiments.

Isolation Procedures. The sponge *A. carvenosa* was either extracted fresh or preserved for a short period before extraction. It was cut into small pieces and repeatedly extracted with aqueous MeOH. The extract was concentrated by distillation of the methanol under reduced pressure, and the remaining aqueous extract was solvent extracted with methylene chloride (CH_2Cl_2), which was then evaporated, yielding a dark viscous oil. The crude oil was then partitioned between aqueous MeOH and the solvent series of hexanes, CCl_4, CH_2Cl_2, and aqueous MeOH. Each partition fraction was assayed for bioactivities. The hexanes, the CCl_4, and the CH_2Cl_2 partition fractions were then separately chromatographed on flash column (Aldrich silica gel, grade 60,60A) and further purified on a normal-phase HPLC column (10 μm silical gel, 25 × 1.0 cm; hexanes/ethyl acetate solvent system) or on a reversed phase column (10 μm ODS, 25 × 1.0 cm; aqueous MeOH solvent system).

Isokalihinol F (3): colorless long needles; crystallized from diethyl ether, mp 180–182 °C, changed to brown liquid; $[\alpha]^{20}_D$ +13.6° (c 0.018, $CDCl_3$); molecular weight 383.257 calculated for $C_{23}H_{33}N_3O_2$; LREIMS, m/z (percent) 383 (trace, M^+), 357 (1, M^+ – NC), 330 (1, M^+ – NC – HCN), 303 (10, M^+ – NC – 2HCN), 285 (5, M^+ – NC – 2HCN – H_2O), 152 (38), 125 (10), 84 (100); LRCIMS (isobutane), m/z (percent) 384 (2, M^+ + H), 357 (30, M^+ – NC), 330 (45, M^+ – NC – HCN), 303 (100, M^+ – NC – 2HCN), 285 (19, M^+ – NC – 2HCN – H_2O), 152 (10); NMR shifts in ppm from Me_4Si, assignments based on assessing the number of attached protons and COSY data [[atom number] ^{13}C (C_6D_6) δ's at 75 MHz, ^1H (C_6D_6) δ's (multiplicites, J's (Hz), integration) at 500 MHz] [1] 47.0 (d), 0.90 (m, 1 H); [2] 21.4 (t), 1.63 (m, H_{eq}) and 0.70 (dddd, J = 13.6, 13.6, 12.4, 3.2, H_{ax}); [3] 37.0 (t), 1.50 (m, 2 H); [4] 61.5 (br t, distorted due to NC, $J \approx 5$ Hz); [5] 76.7 (d), 3.44 (dd, J = 8.4, 3.3, 1 H); [6] 43.0 (d), 0.95 (m, 1 H); [7] 53.8 (d), 1.20 (m, 1 H); [8] 26.3 (t), 1.02 (m, H_{eq}) and 0.52 (dddd, J = 13.8, 13.8, 12.8, 3.9, H_{ax}); [9] 40.6 (t), 1.52 (m, 2 H); [10] 59.8 (br t, distorted due to NC, $J \approx 5$ Hz); [11] 87.5 (s); [12] 39.0 (t), 1.18 and 1.48 (m, 2 H); [13] 25.0 (t), 1.50 (m, 2 H); [14] 82.4 (d), 3.07 (dd, J = 6.0, 2.2, 1 H); [15] 59.6 (br t, distorted due to NC, $J \approx 5$ Hz); [16] 25.4 (q), 1.12 (br s, 3 H); [17] 25.8 (q), 0.75 (br s, 3 H); [18] 18.2 (q), 0.87 (s, 3 H); [19] 19.9 (q), 1.27 (br s, 3 H); [20] 20.3 (q), 0.80 (br s, 3 H) (NC ^{13}C δ's at 158.2, 157.0, and 155.3 were weak signals).

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Registry No. 1, 91294-83-6; 2, 93426-91-6; 3, 117229-41-1; 4, 109979-17-1; 5, 109979-18-2; 6, 110043-50-0.

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Aromatization and Disproportionation of 1,3- and 1,4-Cyclohexadienes by Potassium 3-Aminopropylamide[1]

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Recently, we reported the isomerization and aromatization of the 1,3-di-*tert*-butylcyclohexadienes in several strongly basic media including potassium 3-aminopropylamide (KAPA)[2] in 1,3-diaminopropane (DAP).[3]

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Table I. Reactions of 1,3-Cyclohexadiene (1) and 1,4-Cyclohexadiene (2) with KAPA/DAP at 25 °C:[a] The Composition of Water-Quenched Samples

		products, mol %[d]			
[diene][b,c]/[KAPA]	time, min	1	2	3	4
0.05/0.04[b]	3.0			9	91[e]
0.30/0.05[b]	1.3	34	8	28	30
	4.3	5	3	39	53
	15.0			42	58[e]
0.13/0.08[a,b]	1.5	19	29	23	28
	3.5	4	13	32	50
	8.5		6	35	59
	17.0			37	63[e]
0.09/0.09[c]	4.0			11	89[e]
0.30/0.09[c]	2.0		4	22	74
	6.0			24	76[e]

[a] The third listed experiment was done at 0 °C. [b] The ratio of molar concentrations of 1,3-cyclohexadiene (1) to KAPA. [c] The ratio of 1,4-cyclohexadiene (2) to KAPA. [d] The absence of entries indicates less than 0.5% of the particular compound was observed. [e] When reaction in the above listed experiments was complete, the calculated percent aromatization was 82, 16, 26, 78, and 52%.

The effect of the base system upon the competitive reactions of cyclohexadienyl anions was interpreted in terms of the differing interactions of the carbanionic salts with the medium that may affect the distribution between contact and solvent separated ion pairs. The influence of ion pairing on the reactions of cyclohexadienyl intermediates has been considered for the 6-methyl-6-phenylcyclohexadienyl anion[4] and peralkylcyclohexadienyllithium compounds.[5] The concept was used in explanations of the efffect of counterion and solvent polarity on the isomerization, disproportionation, and aromatization of 1,3- and 1,4-cyclohexadienes using alkali metal naphthalides as catalysts.[6] To better understand the action of KAPA on 1,3- and 1,4-cyclohexadienes, we have examined their reactions in solutions containing concentrations of KAPA comparable to the concentrations of diene.

Aromatization of 1,3- or 1,4-cyclohexadiene, **1** or **2**, to benzene occurs in competition with disproportionation to cyclohexene, **3**, and benzene, **4**, and the interconversion of the dienes.[7] An intense red solution is obtained upon addition of 1,3-cyclohexadiene to a freshly generated solution of KAPA in DAP, and the reaction is accompanied by hydrogen evolution. Table I shows that aromatization is the major reaction when the initial concentration of the base is nearly equal to or greater than the concentration of the diene while there is an increase in the relative rate of disproportionation of the diene when the concentration of the diene is increased relative to that of the amide base (entries 1 and 2, Table I). Similar behavior is exhibited by 1,4-cyclohexadiene (entries 4 and 5, Table I). This is to be expected since the rate-determining step in the disproportionation of the cyclohexadiene probably involves the transfer of a hydride ion from the cyclohexadienyl anion to a molecule of 1,3-cyclohexadiene, which accounts for the second-order dependence on the diene concentration.[7,8] The reactions are illustrated in Scheme I.

Scheme I

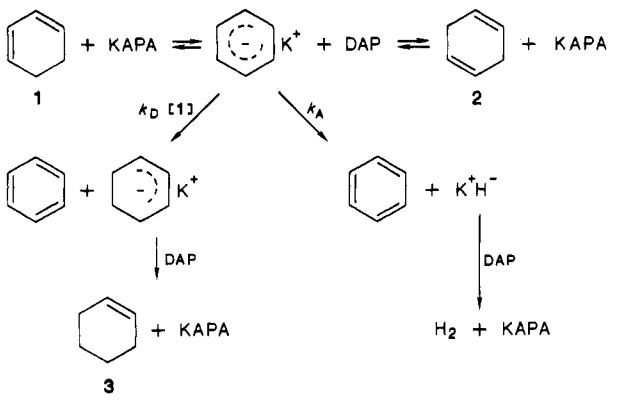

Table II. Reaction of 1,3-Cyclohexadiene (1) with KAPA/DAP in the Presence of 18-Crown-6 at 0 °C:[a] The Composition of Water-Quenched Samples

	products, mol %[b]			
time, min	1	2	3	4
4.0	73	16	7	4[c]
15.0	52	12	20	16
30.0	33	11	29	27
60.0	20	8	37	35
120.0	13	6	42	39

[a] The initial molar concentrations of 1, KAPA, and 18-crown-6 were 0.13, 0.09, and 0.09 M, respectively. [b] No hydrogen was evolved. [c] The excess of cyclohexene over the 1:1 ratio to benzene was observed only in the presence of the crown ether.

A typical reaction that begins with a small excess of 1,3-cyclohexadiene at 0 °C is reported as the third experiment in Table I. The GC analysis of the water-quenched samples shows the presence of 1,4-cyclohexadiene as the major diene. Apparently, the strong amide base converts a large fraction of the diene to the cyclohexadienyl salt, which upon protonation with water forms mainly the unconjugated isomer.[9] The carbanion undergoes aromatization to benzene while being involved in the disproportionation reaction with the remaining diene. At complete conversion to cyclohexene and benzene, the excess of benzene over the 1:1 ratio for disproportionation agrees with the percent dehydrogenation calculated from the evolution of hydrogen during the reaction. Clearly a small excess of KAPA is able to convert 1,3- or 1,4-cyclohexadiene almost completely to its conjugate base much as it does the 1,3- or 1,4-pentadienes.[10]

Aromatization was totally inhibited when the diene was added to a solution of KAPA/DAP containing 18-crown-6 in amounts equivalent to the base at 0 °C (Table II). After correcting for the 2–3% excess cyclohexene in the sampled reaction mixtures, cyclohexene, **3**, and benzene, **4**, were formed in equimolar proportions, indicating that disproportionation proceeded isn the presence of the cation complexing agent. The small excess of cyclohexene may result from the addition to the diene of the hydride ion, which is brought into solution by the added crown ether. The latter appeared to solubilize the last remaining particles of potassium hydride during the initial period of reaction.[11] In time, the ratio of the 1,3- and 1,4-cyclohexadienes in water-quenched samples of the reaction mixture approached the ratio of 2.0, a value close to the

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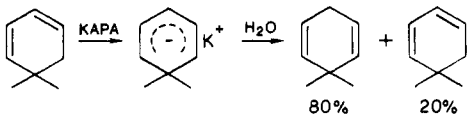
equilibrium distribution,[12] which indicates that only a very small fraction of the diene is present as the carbanionic salt. The result is like the report that in the presence of the macrobicyclic diamino polyether[2.2.2], a cation encapsulating agent,[13] allylic carbanions exhibit increased reactivity toward the solvent, which results in the recovery of some unreacted starting material in addition to the expected reaction products.[14]

Addition of 18-crown-6 seems to have an effect on the apparent acidity of cyclohexadiene. The deep red color of the carbanion is rapidly generated upon addition of the diene to KAPA in DAP; however, the color did not develop in solutions of KAPA/DAP containing an equivalent of 18-crown-6 though the latter solutions were found to convert both triphenylmethane (pK_a = 31.4)[15] and diphenylmethane (pK_a = 33.4)[15] to their colored conjugate bases when the amide solutions were titrated with neopentyl alcohol in xylene (see the Experimental Section). The apparent decrease in acidity may indicate that the crown ether lowers the interaction between the potassiusm cation and the cyclohexadienyl anion more than it affects the interaction between the cation and the amide ion. Such an effect could be due to the ability of the localized charge of the latter to penetrate the molecular framework of the crown ether that surrounds the cation.[16] Olmstead and Bordwell have discussed the effect of added [2.2.2]-cryptand[13] and the anion's structure on ion pair dissocation constants in dimethyl sulfoxide.[17]

The reaction of 5,5-dimethyl-1,3-cyclohexadiene with excess KAPA (0.05 M diene, 0.13 M KAPA) at 25 °C yields a deep red solution. Water-quenched samples contain a mixture of 1,4- and 1,3-dienes in the ratio of nearly 4:1, which indicates that the excess KAPA has deprotonated the diene,[9,10] the reprotonation of the U-shaped pentadienyl carbanion resulting in the formation of the 1,4-diene as the principal isomer.[10] 6,6-Dimethylcyclohexadienyl anion, which has been reported to be stable even at room temperature,[18] was found to undergo protonation preferentially at the central carbon atom by Bates, Gosselink, and Kaczynski.[19] In our experiment, toluene was not detected in the GC analysis, which indicates the absence of aromatization.



Experimental Section

Reagents. 1,3- and 1,4-Cyclohexadienes were purified by distillation from calcium hydride under nitrogen. Cyclooctane was distilled prior to use. 1,3-Diaminopropane (DAP) was distilled from calcium oxide and stored over 3A molecular sieves. 18-Crown-6 was purified by means of its acetonitrile complex,[20] mp 37–38.5 °C. 5,5-Dimethyl-1,3-cyclohexadiene was synthesized according to the literature.[21] *n*-Pentane was distilled from sodium under nitrogen. Neopentyl alcohol was distilled over calcium hydride under nitrogen, and the white crystalline solid (mp 52 °C) was dissolved in dry xylene to titrate the base. Xylene was purified by distillation from sodium benzophenone ketyl and stored over $LiAlH_4$ under nitrogen. Triphenylmethane was recrystallized from absolute ethanol and dried in air.

Reactions of Cyclohexadienes with KAPA. KAPA in DAP was prepared from potassium hydride and DAP in a cylindrical tube (50 mL) fitted with two stopcocks, a connector to permit the attachment of a solids addition tube, and a male ST 24/40 joint, which could be closed with a rubber septum. The transfer to the reaction vessel of 4–5 drops of a 35 wt % potassium hydride suspension in mineral oil (Aldrich Chemical Co.) was done in a dry nitrogen swept glovebag. The reaction tube was then closed with a tight-fitting septum and connected to the source of dry nitrogen and to an automatic gas burette. The mineral oil was removed under a stream of nitrogen by washing with several portions of dry pentane introduced and removed by syringe. The excess pentane was removed in the nitrogen stream. Dry 1,3-diaminopropane (10 mL) was added to the dry powder, and the volume of evolved hydrogen was noted. The concentration of the amide formed was calculated from the volume of gas generated. The solution remaining after the removal of samples for GC analysis was titrated with a solution of neopentyl alcohol in xylene (triphenylmethane indicator) to determine the concentration of strong base present.[2] After equilibrating the base solution at a selected temperature, 1,3- or 1,4-cyclohexadiene was introduced via a gas-tight syringe. Cyclooctane was added as internal standard in amounts half that of the total diene concentration. At selected intervals, 0.30-mL aliquots of the reaction mixture were withdrawn by means of a gas-tight syringe, quenched in 1 mL of ice-cold water, and after extracting with 0.20 mL of *n*-pentane, the organic layer was analyzed by using a Varian Model 940 GC connected to a Laboratory Data Control Model 308 computing integrator. A 25 ft × $^1/_8$ in. column containing 10% Carbowax 750 on 60–80 mesh Chromosorb P was operated at 55 °C with nitrogen as carrier gas.

Experiments Using 18-Crown-6. When desired, 18-crown-6 was added to the KAPA solution before the introduction of the diene by using the solid-addition tube. A solution of KAPA, which was calculated to be 0.103 M from the measurement of the gas evolved in its preparation from potassium hydride and 1,3-diaminopropane, was found to be 0.095 M by titration with neopentyl alcohol in xylene after the addition of 1 equiv of 18-crown-6 ether. This solution converted both triphenylmethane and diphenylmethane to their conjugate bases as judged by the immediate generation of the color of these carbanions. The addition of 1,3-cyclohexadiene to solutions of KAPA generates a deep red color; however, this does not occur in solutions that contain the crown ether.

Registry No. 1, 592-57-4; 2, 628-41-1; 3, 110-83-8; KAPA, 56038-00-7; benzene, 71-43-2; 5,5-dimethyl-1,3-cyclohexadiene, 33482-80-3; 3,3-dimethyl-1,4-cyclohexadiene, 35934-83-9.

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Ph_4SbI-Catalyzed Selective Formation of γ- and δ-Lactones from Oxiranes or Oxetanes with Ketenes

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Five- and six-membered lactones are very common in nature and are important targets in organic synthesis.[1] As

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