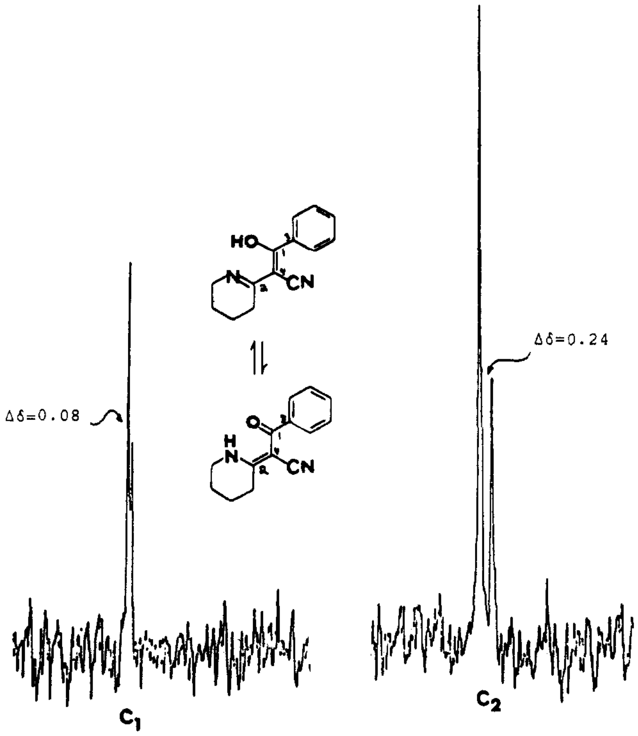

Figure 1. Low-field region for the deuterium-induced isotope shifted ^{13}C spectrum for 3.

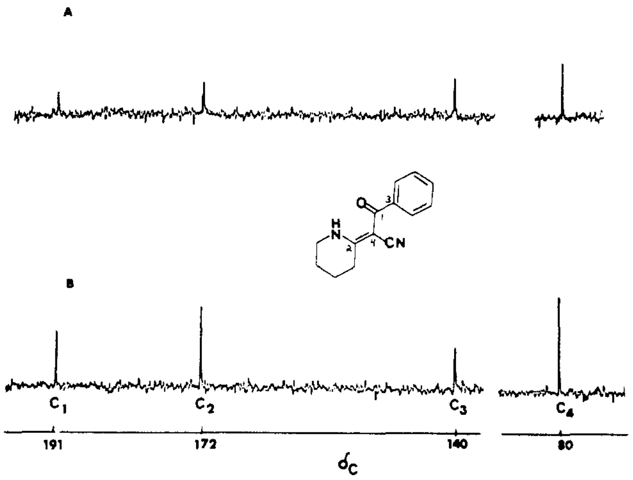

Figure 2. Deuterium-induced relaxation spectrum for 3: (A) in Me_2SO with D_2O added; (B) in Me_2SO with H_2O added.

conclusion is consistent with that recently drawn for some β-diketone derivatives[6] and with those expected from the early work of Brown;[7] namely, the double bond prefers to be exo to a five-membered-ring system.

The utility of deuterium isotope effects and the method presented here are presently being applied to other tautomeric systems.

Experimental Section

All compounds used gave satisfactory elemental analyses and were characterized by mass spectral and infrared data as well as their NMR spectral properties. Details of the synthesis will be described elsewhere.

Natural-abundance ^{13}C NMR spectra were obtained at 25.2 MHz on a Varian XL-100-12 spectrometer system, equipped with a 620/L 16K computer in the Fourier transform mode with complete proton decoupling. General spectral and instrumental parameters were internal deuterium lock to the solvent, a pulse width of 45° and a repetition time of 1.8 s. Deuterium isotope effect spectra were performed in a manner similar to that described by Pfeffer.[3] Sample concentrations were ca. 0.5 M in dimethyl-d_6 sulfoxide, using a slight excess of D_2O to ensure exchanging the H_2O also contained in the solvent. For the isotope-shifted spectra spectral widths of 1000 Hz were used (0.25-Hz spectral resolution) and a coaxial NMR tube was employed. For the reduced-intensity spectra, spectral widths of 5000 Hz, 8K data points, were used and each portion of the material from the coaxial tube was run independently, using exactly the same conditions.

Registry No. 2, 76429-88-4; 3, 76429-89-5; 4 (R = H), 76429-90-8.

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Reduction of Alkyl Halides by Sodium Naphthalene: Proton Sources

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Alkyl anions, generated by reduction of alkyl halides by sodium naphthalene (1),[2] are reported to abstract protons from ethereal solvents.[3] When we tried to determine the extent of this process, however, we found it to be quite low. In fact, preliminary experiments with lauryl chloride detected no deuterium incorporation in *n*-hendecane when the solvent was tetrahydrofuran-d_4 (THF-d_4), specifically deuterated in either the α or β position.[4] We report here the results of further studies using 5-hexenyl fluoride, chosen specifically because it has been the subject of extensive study, and its behavior is presumed to be well understood.[2] The intermediate 5-hexenyl radical may cyclize to methylcyclopentyl radical, and both are reduced further by 1 to anions before forming 1-hexene and methylcyclopentane. Other products are also formed, but we have restricted our attention to the C_6 hydrocarbons and the proton sources leading to them.

Results and Discussion

Five combinations of deuterated and undeuterated reagents were investigated. The products were analyzed for deuterium content by combined GC/MS. Table I shows the reagents, the relative yields, and the percentage of deuterium incorporation in the C_6 products for each set of conditions.

Not only are 2-hexenes formed, but they appear to be the predominant reduction products, presumably formed by protonation of the 1-propylallyl anion (2). Generation of 2 by reaction of 3-chloro-1-hexene with sodium metal in THF is reported to afford 95% 2-hexenes and 5% 1-hexene.[5]

The hexenes were shown to be stable in the presence of 1-d_0 and 1-fluorohexane in THF-d_8 as that halide was reduced to form hexane (7% deuterium incorporation). In particular, no 2-hexenes were formed from 1-hexene. Thus, intermolecular proton abstraction by hexyl anion is not

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Table I. Relative Yields and Deuterium Incorporation of C_6 Products

run	THF[a]	N	MCP PP	MCP PD	1-H PP	1-H PD	t-2-H PP	t-2-H PD	c-2-H PP	c-2-H PD	3 PP	3 PD	4 PP	4 PD
1	d_8	d_0	20[b]	6	≤12	17	13	8	29	8	14	NA	12	(0)
2	d_0	d_8	14	21	21	24	16	39	39	48	2	(0)	8	NA
3	d_8	d_8	19	30	18	43	11	46	31	54	7	(0)	14	NA
4	α-d_4	d_0	17	(3)	30	(2)	9	(1)	24	(17)	1	NA	18	NA
5	β-d_4	d_0	13	(3)	35	15	17	(1)	18	(2)	1	NA	18	NA

[a] THF = tetrahydrofuran; N = naphthalene; MCP = methylcyclopentane; 1-H = 1-hexene; t-2-H = *trans*-2-hexene; c-2-H = *cis*-2-hexene; PP = percentage of C_6 product; PD = percentage of compound which is monodeuterated; NA = not available. [b] Values without parentheses are considered reliable to ±5% (absolute), with parentheses, ±15%.

significant. Formation of **2** in our experiments, then, must proceed from an intramolecular hydrogen abstraction in the 5-hexenyl anion, as has been reported for that anion in the presence of K or Cs in THF.[6]

trans- and *cis*-2-hexenes were found not to equilibrate under the reaction conditions. The excess of the cis isomer shown in Table I is consistent with other examples of kinetically controlled protonation of allylic anions.[5,7]

Two other C_6 products, **3** and **4**, have not been positively identified. Neither has the same retention time as that of cyclohexene or any of the hexadienes. Compound **3** has the same retention time and mass spectrum as those of bicyclo[3.1.0]hexane. Since no S_N2 or E2 products have been observed in this system,[8] and since this compound would presumably arise by a much less probable α-elimination to a carbenoid species, we regard this structure assignment as highly doubtful. Compound **4** has the same retention time and mass spectrum as those of methylenecyclopentane.

Proton Sources. As Table I shows, only a relatively small percentage of the products is formed by proton abstraction from the solvent.[9] Previous workers have assumed this to be the sole process, based on observations[8,10] that methyl vinyl ether is formed when anions are generated in 1,2-dimethoxyethane.

Given the relatively small amount of proton donation by solvent, runs 4 and 5 show that hydrogen is abstracted from both the α and the β positions of THF. Unfortunately, the numerical isotope data are not as reliable for these runs (except for 1-hexene in run 5) as for the others; however, the involvement of the β hydrogens in the formation of 1-hexene contrasts with other reports, which found evidence only for α-position participation in THF when alkyl halides were reduced directly by alkali metals.[3]

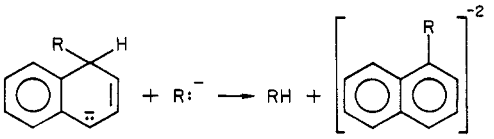
A more important source of protons is the naphthalene or, more likely, the anionic intermediate (**5**) formed by alkylation of **1** by alkyl radical.[2] (Previous results with lauryl chloride indicated the same behavior.[4]) It is difficult to arrive at a completely satisfactory path for this process which is consistent with the following observations.

1. All products contain appreciable amounts of deuterium in run 2. This requires a process other than an S_N2-like hydride transfer from **5** to alkyl fluoride.

2. The percentage of deuterium incorporation in run 3, in each product, is approximately equal to the sum of those found in runs 1 and 2. If abstraction from solvent were to compete effectively with abstraction from **5**, any isotope effect would produce a much higher percentage of deuterium in run 3, in which both hydrogen sources are deuterated, than in run 1 or 2, in which one of them contains protium. This implies either that there is no isotope effect or that **5** donates its proton in overwhelming preference to donation by solvent. With the latter as a basis, the percentage of deuterium incorporation in run 2 allows calculation of the total amount of alkylation as 36–55% of the reaction,[9] comparable to the 42% reported by Garst, Barbas, and Barton.[11]

3. The delocalized ion **2** abstracts a higher percentage of its proton **5** than does either primary alkyl ion. This contrasts with the comparable amounts of deuterium found in all hexenes in run 1, in which only the solvent contained deuterium. That is, hydrogen abstraction from solvent is equally important for all anions, but the process involving **5** apparently has a feature favoring reaction with a more stable species in preference to a less stable one.

This feature indicates that it is reaction of **5** with anions, rather than with radicals, which is occurring. Although the latter is more attractive on electrostatic grounds, it would be expected that primary alkyl radicals would be more reactive than the delocalized 1-propylallyl radical. On the other hand, for an anion–anion reaction, the more delocalized anion **2** would have less electrostatic repulsion than the localized ones.



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In run 3, in which both solvent and naphthalene were perdeuterated, a substantial amount of the reduction products obtained hydrogen from some other source. Since great care was taken to ensure the removal of any spurious protic substances, the alkyl fluoride or some of the products must account for a substantial part of the protonation. Unfortunately, we have no other information to bear on this point.

Experimental Section

5-Hexenyl fluoride was obtained from Professor J. F. Garst and stored over 3-Å molecular sieves prior to use. It was then distilled on the vacuum line into breakseal tubes which had been prerinsed

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(6) J. F. Garst, J. A. Pacifici, C. C. Felix, and A. Nigam, *J. Am. Chem. Soc.*, **100**, 5974 (1978).

(7) D. J. Cram, "Fundamentals of Carbanion Chemistry", Academic Press, New York, 1965, pp 194–196.

(8) J. F. Garst and F. E. Barton, II, *J. Am. Chem. Soc.*, **96**, 523 (1974).

(9) The amount of total hydrogen abstraction, P, from a substrate, SH or SD, is related to the observed deuterium content of the product, PD, by

$$\frac{P}{PD} = 1 + \frac{k_H[SH]}{k_D[SD]}$$

Professor G. Dann Sargent privately informed a reviewer that he had observed $k_H/k_D \simeq 10$ in reactions of sodium naphthalene with halides in deuterated THF. Allowing for as much as 5% undeuterated substrate, P is likely to be from 1.1 to 1.5 times PD.

(10) G. D. Sargent, J. N. Cron, and S. Bank, *J. Am. Chem. Soc.*, **88**, 5363 (1966).

(11) J. F. Garst, J. T. Barbas, and F. E. Barton, II, *J. Am. Chem. Soc.*, **90**, 7159 (1968).

with a solution of sodium naphthalene in THF and then baked under vacuum at 220 °C for 48 h.[12] About 0.2 g of alkyl fluoride was distilled into each tube.

Approximately 0.5-g samples of commercial sublimed naphthalene were vacuum sublimed into breakseal tubes pretreated as above.

Tetrahydrofuran was stored on the vacuum line over benzophenone ketyl and distilled directly into pretreated reaction vessels. Perdeuterated THF (Merck) and the two THF-d_4 compounds[13] were stored on the vacuum line over Na/K alloy before distillation into the reaction vessels. Isotopic purity was found by NMR spectroscopy to be 95% for THF-α-d_4 and at least 99% for all other deuterated compounds.

All-glass reaction vessels, fabricated without stopcocks, were pretreated as above and then filled with solvent and sealed. A breakseal was crushed and naphthalene was introduced by dissolving it in THF. The solution was allowed to react with a sodium metal mirror and then stirred as the alkyl fluoride was allowed to slowly distill through another crushed breakseal. Stirring was continued for about 7 h at room temperature. Approximately half the fluoride reacts in this time. Reaction was quenched by opening the vessel to dry air. The product solutions were analyzed by GC/MS,[14] using 10% Na_2SO_4 on Al_2O_3 as the stationary phase.[15] Mass spectral data were converted to percentage deuterium content by using the computer program HEAVY.[16]

Acknowledgment. This work was supported in part by funds from the Foundation of the University of North Carolina at Charlotte and from the State of North Carolina.

Registry No. 1, 3481-12-7; 5-hexenyl fluoride, 373-15-9; methylcyclopentane, 96-37-7; 1-hexene, 592-41-6; *trans*-2-hexene, 4050-45-7; *cis*-2-hexene, 7688-213.

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[12] M. Szwarc, "Carbanions, Living Polymers, and Electron Transfer Processes", Interscience, New York, 1968, p 151.

[13] E. R. Bissell and M. Finger, *J. Org. Chem.*, **24**, 1259 (1959).

[14] Analyses were performed by Research Triangle Institute, Research Triangle Park, NC.

[15] Recommended by Professor J. F. Garst.

[16] D. Rosenthal, *QCPE*, **10**, 324 (1977).

New Synthesis of α-Alkylamino Ketones[1]

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α-Alkylamino ketones are important intermediates for the synthesis of adrenergic compounds (see ref 2 and 3, for example) and, in addition, have considerable potential utility in the Knorr pyrrole synthesis.[4] These substances are commonly prepared by the hydrolysis of α-(*N*-alkyl-*N*-*p*-toluenesulfonylamino) ketones,[5] by the reductive amination of α-diketones,[6] or by the alkylation of primary amines with α-halo ketones.[2,3,4a] The utilization of the last-mentioned synthesis is the most widespread, but other products are often formed[7] as a consequence, at least in part, of the strong basicity of the aliphatic amines. The yields of the desired products can be particularly poor when the halo group being displaced is on a primary carbon atom.[2,3,4a]

Imidates are much less basic[8] than the primary amines from which they are derived, but the nucleophilicity thereof is still appreciable, and N-alkylation with reactive alkyl halides occurs relatively readily.[8a,9] These observations, when considered with the well-known ease of hydrolysis of formamides should, in principle, constitute a synthesis of α-alkylamino ketones. This publication shows that this is indeed the case for methyl *N*-alkylformimidates (**2**, eq 1). Thus, diverse α-bromo ketones

$$\underset{\mathbf{1}}{\mathrm{R^1COCHBrR^2}} + \underset{\mathbf{2}}{\mathrm{R^3N{=}CHOCH_3}} \rightarrow \underset{\mathbf{3}}{[\mathrm{R^1COCHR^2NR^3{=}CHOCH_3}]^+\mathrm{Br^-}} \rightarrow \underset{\mathbf{4}}{\mathrm{R^1COCHR^2NR^3CHO}} + \mathrm{CH_3Br}\ 4 + \mathrm{HBr} \rightarrow \underset{\mathbf{5}}{\mathrm{R^1COCHR^2NHR^3{\cdot}HBr}} \quad (1)$$

reacted with excess methyl *N*-methylformimidate[10] (**2**, $R^3 = CH_3$) in dimethoxyethane–toluene solution at 70–80 °C to give fair to good yields (Table I) of the expected *N*-methylformamides (**4**, $R^3 = CH_3$). Methyl *N*-(2-phenylethyl)formimidate (**2**, $R^3 = C_6H_5CH_2CH_2$) reacted, under similar conditions, with a variety of α-bromo ketones to give uniformly excellent yields (Table I) of the anticipated formamides. In the case of 3,4,-bis(benzyloxy)-α-bromopropiophenone (entry 10), however, a large excess of the imidate as well as a protracted reaction period was required to achieve a good yield of the formamide. Both of these parameters could be greatly decreased, without loss in product yield, when acetonitrile was used as the reaction medium (entry 11). The use of this solvent also made it possible to reduce the imidate–bromo ketone ratio by 50% for phenacyl bromide with only a modest reduction in the yield of the formamide (entry 8). This latter result is of particular significance for those instances where the use of a rare or expensive imidate is contemplated. In the above alkylation reactions, it was not determined whether the methyl bromide, formed as a result of the decomposition of the salt **3**, reacted with the excess imidate (to produce the corresponding *N*,*N*-dialkylformamide) or merely escaped from the reaction mixture.

The above formamides showed the expected physical properties (Table II), including, in several instances, the phenomenon of restricted rotation about the NCO bond. For example, the NMR spectrum of *N*-methyl-*N*-phenacylformamide (**4**; $R^1 = C_6H_5$, $R^2 = H$, $R^3 = CH_3$) showed two sets of absorptions (ca. 1:3 ratio) for the methyl, methylene, and formyl protons, each of which coalesced into a singlet at about 140 °C ($\Delta G^{\neq} \approx 23$ kcal/mol). This barrier to rotation is somewhat higher than has been re-

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[1] Contribution No. 558 from the Syntex Institute of Organic Chemistry.

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