third factor is important. However, from the point of view of catalysis, which is concerned primarily with rates and not the component activation parameters, the lesson from Table II and the work of others[22,23] is clear. Nonreactive additives have a disappointing rate effect on the water reactions of carboxylic acid derivatives.[24] Our data suggest that hydrolytic enzymes do not achieve appreciable rate accelerations by perturbing the microscopic environment at the active sites.[25]

Acknowledgment. This work was supported by a grant from the National Science Foundation (GP-42919X) and from the National Institutes of Health (GM-20336 and GM-21457).

Registry No.—I, 5070-13-3; water, 7732-18-5.

References and Notes

(1) Recipient of a Camille and Henry Dreyfus Foundation Teacher–Scholar Grant and a National Institutes of Health Research Career Development Award.
(2) S. L. Johnson, *Adv. Phys. Org. Chem.*, **5**, 237 (1967).
(3) R. E. Robertson, *Prog. Phys. Org. Chem.*, **4**, 213 (1967).
(4) C. A. Bunton, N. A. Fuller, S. G. Perry, and V. J. Shiner, *J. Chem. Soc.*, 2918 (1963); A. R. Butler and V. Gold, *ibid.*, 2305 (1961).
(5) W. P. Jencks and J. Carriuolo, *J. Biol. Chem.*, **234**, 1280 (1959).
(6) M. L. Bender and H. d'A. Heck, *J. Am. Chem. Soc.*, **89**, 1211 (1967).
(7) T. C. Bruice and J. J. Bruno, *J. Am. Chem. Soc.*, **84**, 2128 (1962).
(8) The most thorough mechanistic investigation of a water reaction has been carried out by J. L. Kurz and J. M. Farrar, *J. Am. Chem. Soc.*, **97**, 2250 (1975); J. L. Kurz and D. N. Wexler, *ibid.*, **97**, 2255 (1975); J. L. Kurz and G. J. Ehrhardt, *ibid.*, **97**, 2259 (1975).
(9) J. F. J. Engbersen and J. B. F. N. Engberts, *J. Am. Chem. Soc.*, **97**, 1563 (1975).
(10) A. J. Kresge, *Pure Appl. Chem.*, **8**, 243 (1964).
(11) R. L. Schowen, *Prog. Phys. Org. Chem.*, **9**, 275 (1972).
(12) T. H. Fife and D. M. McMahon, *J. Am. Chem. Soc.*, **91**, 7481 (1969); *J. Org. Chem.*, **35**, 3699 (1970).
(13) C. A. Lane, M. F. Cheung, and G. F. Dorsey, *J. Am. Chem. Soc.*, **90**, 6492 (1968).
(14) R. P. Bell, "The Proton in Chemistry", Cornell University Press, Ithaca, N.Y., 1973, p 186.
(15) S. S. Minor and R. L. Schowen, *J. Am. Chem. Soc.*, **95**, 2279 (1973); C. R. Hopper, R. L. Schowen, K. S. Venkatasubban, and H. Jayaraman, *ibid.*, **95**, 3280 (1973).
(16) Analysis of the data in Table I by means of a polynomial regression program indicates that quadratic and higher terms in eq 3 are insignificant. We thank Professor R. L. Schowen and Mr. Daniel P. Quinn for carrying out these calculations.
(17) This result contrasts with that of B. D. Batts and V. Gold, *J. Chem. Soc. A*, 984 (1969), who found a slight curvature in the k_n vs. n plot for the water reaction of acetic anhydride at 25.0 °C. Since our runs were carried out at 50.0 °C, direct comparison of the two systems is difficult.
(18) This conclusion agrees with that of Fife and McMahon[12] who determined a Bronsted coefficient of 0.3 for the general-base-catalyzed hydrolysis of I.
(19) M. J. Blandamar, *Q. Rev., Chem. Soc.*, **24**, 169 (1970); S. Lindenbaum, *J. Phys. Chem.*, **74**, 3027 (1970).
(20) J. A. Rupley, *J. Phys. Chem.*, **68**, 2002 (1964).
(21) A. Ben-Naim and M. Yaacobi, *J. Phys. Chem.*, **79**, 1263 (1975).
(22) S. Marburg and W. P. Jencks, *J. Am. Chem. Soc.*, **84**, 232 (1962).
(23) C. A. Bunton, N. A. Fuller, S. G. Perry, and I. H. Pitman, *J. Chem. Soc.*, 4478 (1962).
(24) Urea and other additives also have minute effects on the water solubility of naphthalene, uric acid, and peptides: M. Roseman and W. P. Jencks, *J. Am. Chem. Soc.*, **97**, 631 (1975).
(25) E. M. Kosower, "Molecular Biochemistry", McGraw-Hill, New York, N.Y., 1962, p 273.

Metalation of Cumene with *n*-Pentylsodium in the Presence of *N,N,N′,N′*-Tetramethylethylenediamine. Preparation of α-Cumylsodium

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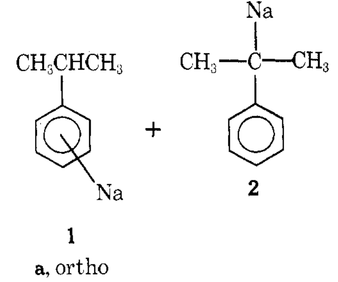
Received September 15, 1975

The metalation of cumene with *n*-pentylsodium was reinvestigated to assess the effect of *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) on this reaction. It was found that in the presence of TMEDA, cumene was metalated by *n*-pentylsodium giving a 65% yield of α-cumylsodium with an isomeric purity of 95% after a 24-h reaction period. In the initial stages of the reaction, a kinetically controlled metalation occurred giving principally *o*-, *m*-, and *p*-isopropylphenylsodium. At longer reaction times, these compounds isomerized to α-cumylsodium in a thermodynamically controlled process.

In 1963 Professor Benkeser and co-workers[2] reported that cumene was metalated by *n*-pentylsodium in a kinetically controlled process to give a mixture of *m*- and *p*-isopropylphenylsodium (**1b** and **1c**) and trace amounts of α-cumylsodium (**2**). In the presence of excess cumene, the ring sodium compounds **1b** and **1c** slowly converted to the α compound **2** in a thermodynamically controlled process. The α-sodium compound was shown to be unstable and decomposed to α-methylstyrene and sodium hydride.[3]



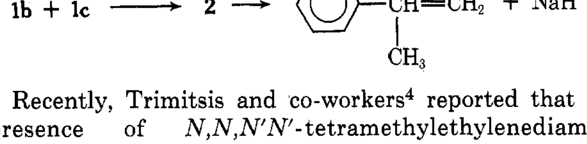
1

a, ortho

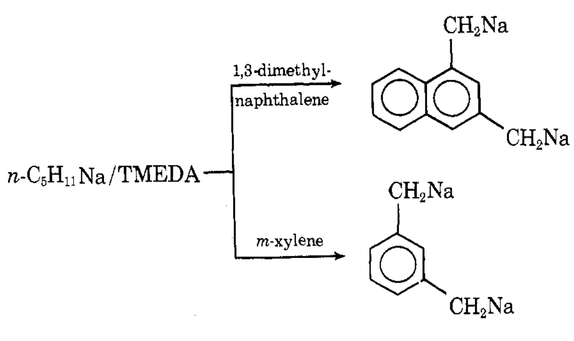
b, meta

c, para

2



Recently, Trimitsis and co-workers[4] reported that the presence of *N,N,N′N′*-tetramethylethylenediamine (TMEDA) greatly altered the reactivity of *n*-pentylsodium in metalation reactions. Thus, 1,3-dimethylnaphthalene and

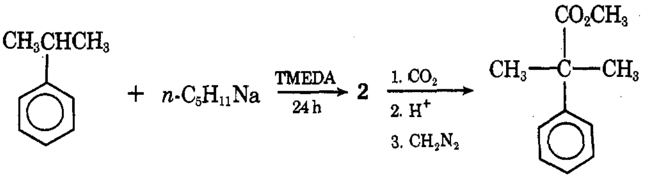


m-xylene were quantitatively dimetalated by *n*-pentylsodium in the presence of TMEDA. In the absence of TMEDA, monometalation occurred in low yield. This observation is in general agreement with several other laboratories who reported that TMEDA greatly activated organolithium reagents in metalation reactions.[5]

In view of the rather dramatic effect which TMEDA had on the metalation of 1,3-dimethylnaphthalene and *m*-xylene, we were prompted to reinvestigate the metalation of cumene by *n*-pentylsodium in the presence of TMEDA. The general objectives of this research were to assess the effect of TMEDA on the stability of α-cumylsodium and the kinetic vs. thermodynamic factors operating in the presence of this reagent.

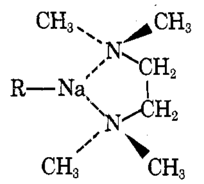
Results and Discussion

When cumene was metalated with *n*-pentylsodium in the presence of TMEDA for 24 h, *α-cumylsodium* (**2**) *was produced in a 65% yield and with an isomeric purity of 95%* as adjudged by the formation of methyl 2-methyl-2-phenylpropanoate (**3**) upon carbonation and esterification of the reaction. The identity of **3** was proven by comparing its VPC retention time and NMR and ir spectra with those of an authentic sample of this compound. Small quantities of *m*-isopropylphenylsodium (**1b**, 3%) and *p*-isopropylphenylsodium (**1c**, 2%) were also formed based on VPC analysis of the methyl esters obtained upon carbonation and esterification. Practically all of the *n*-pentylsodium was consumed in the metalation reaction as adjudged by the relatively small quantity of methyl hexanoate observed in the gas chromatogram.[6] In addition, VPC analysis revealed that only trace amounts of α-methylstyrene were produced during the course of the reaction indicating that the α-cumylsodium was not decomposing to any significant degree. When this reaction was run in the absence of TMEDA, only a 40% yield of metalation products was obtained consisting of 55% of the meta compound **1b**, 45% of the para compound **1c**, and none of the α compound **2**. Additionally, a large quantity of *n*-pentylsodium remained unreacted.



3

The stability of the α-cumylsodium and the increased reactivity of the *n*-pentylsodium observed under our reaction conditions apparently result from complex formation between TMEDA and the organosodium compounds. In the case of α-cumylsodium one could speculate that this complex is responsible for increasing the ionic character of the benzylic carbon–sodium bond, thus permitting benzylic resonance to play a more significant role in stabilizing the α-cumyl carbanion. In a similar manner, complex formation between TMEDA and *n*-pentylsodium may increase the ionic character and thus the basicity of the *n*-pentylsodium. This would be reflected in a more reactive metalating reagent and hence higher yields of product. Alternately, it could be argued that the TMEDA breaks down the highly associated *n*-pentylsodium into smaller, more reactive aggregates. These arguments parallel those used by Trimitsis[4] and Benkeser[7] in explaining their observations in the organosodium reactions which they studied.



R = *n*-pentyl or α-cumyl

Table I. Metalation of Cumene by *n*-Pentylsodium in the Presence of TMEDA as a Function of Time[a]

Time, h	**1a**, %	**1b**, %	**1c**, %	**2**, %
1	3 (3)[b]	57 (57)	33 (34)	7 (6)
2	3	42	26	29
4	0	11	9	80
6	0 (0)	2 (5)	2 (5)	96 (90)
12	0 (0)	2 (2)	1 (2)	97 (96)
18	(0)	(1.5)	(0.5)	(98)
24	0 (0)	2 (1)	1 (1)	97 (98)

[a] The values reported in this table were obtained by removing aliquots from the reaction at the stated times. Aliquots were not removed from the first experiment at 18 h and from the second experiment at 2 and 4 h. [b] Numbers in parentheses represent the results of a second experiment.

The metalation of cumene by *n*-pentylsodium in the presence of TMEDA was also studied as a function of time by removing aliquots from the reaction. Table I shows that after a 1-h reaction period, metalation occurred principally on the ring giving the ortho, meta, and para sodium compounds **1a**, **1b**, and **1c**.[8] In addition analysis of the 1-h aliquot showed that practically all of the *n*-pentylsodium was consumed based on the small quantity of methyl hexanoate observed in the gas chromatogram. At longer reaction times, the α-sodium compound **2** predominated. Since practically all of the *n*-pentylsodium was consumed in the early stages of this reaction metalation must have occurred initially on the aromatic ring of cumene in a kinetically controlled process. In the presence of TMEDA, the ring compounds **1a**, **1b**, and **1c** rapidly reverted to the more thermodynamically stable α-cumylsodium (**2**) presumably via a transmetalation sequence involving excess cumene.

These results are in sharp contrast to those of Broaddus,[9] who did not observe the ring to side chain isomerization in the metalation of a series of alkylbenzenes including cumene with *n*-butyllithium in the presence of TMEDA. The lack of isomerization in these reactions is most likely due to the lower reactivity of organolithium reagents compared to the corresponding sodium compounds. It is also of interest to note that the kinetically controlled product distribution which was observed in our metalation reaction after 1 h was very close to the kinetically controlled product distribution observed by Broaddus.

In summary, we have found that *cumene is metalated by n-pentylsodium in the presence of TMEDA to give α-cumylsodium in high yield and isomeric purity.* This metalation occurred initially in a kinetically controlled process on the aromatic ring of cumene followed by an isomerization of the sodium to the benzylic position of cumene in a thermodynamically controlled process.

Experimental Section

Organosodium reactions were run under a positive nitrogen pressure in a Morton flask fitted with a Stir-O-Vac (La Pine Scientific Co.) high-speed stirring apparatus. All glassware employed in these reactions was dried in an oven at 110 °C and flushed with nitrogen before use. Octane, 1-chloropentane, and cumene were purified by standard techniques and shown to be VPC pure. TMEDA was distilled from BaO or CaH_2 immediately before use.[10] NMR spectra were obtained on a Hitachi Perkin-Elmer R20-A spectrometer and ir spectra on a Perkin-Elmer 457 spectrometer.

Reference Compounds. Methyl *p*-isopropylbenzoate and methyl 2-methyl-2-phenylpropanoate were obtained by esterifying *p*-isopropylbenzoic acid (Eastman Kodak Co.) and α,α-dimethyl-α-phenylacetic acid (K and K Laboratories, Inc.) with diazomethane.[11] Methyl *o*- and *m*-isopropylbenzoate were prepared by treating *o*- and *m*-bromocumene with magnesium followed by carbonation and esterification with diazomethane. The *o*- and *m*-bromocumene compounds were prepared by adaptations of standard literature methods.[12]

Analytical Method. Metalation reactions were analyzed by carbonating the reaction mixtures and esterifying the resulting carboxylic acids with diazomethane.[13] The resulting methyl esters were analyzed on a F and M Model 720 gas chromatograph equipped with a 6-ft 15% diisodecyl phthalate column at 170 °C with a helium flow rate of 60 ml/min. The validity of this technique was demonstrated by the analysis of an authentic sample as follows:

Ester	Synthetic mixture, %	VPC analysis, %
α	31	31
o-	9	8
m-	30	31
p-	30	30

The yield of cumene methyl esters was obtained employing quantitative VPC analysis using ethyl benzoate as an internal standard. Analysis of a synthetic mixture of the four isomeric cumene methyl esters showed this technique to be reliable to within 5%.

***n*-Pentylsodium.** To a vigorously stirred 9.2-g (0.40 mol) sodium dispersion[14] in 125 ml of octane maintained at −10 to −20 °C was added 16 g (0.15 mol) of 1-chloropentane in 25 ml of octane over 1.5 h. After the addition of the 1-chloropentane, the mixture was stirred for an additional 0.5 h at −10 to −20 °C to ensure complete reaction.

Metalation of Cumene with *n*-Pentylsodium in the Presence of TMEDA. To a *n*-pentylsodium sample in 150 ml of octane was added 36 g (0.30 mol) of cumene and 13.9 g (0.12 mol) of TMEDA. The mixture was vigorously stirred for 24 h before being poured onto a dry ice–ether slurry. After the mixture warmed to room temperature, hydrolysis was effected[15] followed by separation of the organic and aqueous layers. The organic layer was washed three times with water and these washings were added to the aqueous layer. The combined aqueous layer was extracted three times with ether and these extracts combined with the original organic layer. The combined organic layer containing the neutral compounds was dried over Drierite before solvent was removed on a rotary evaporator. Analysis of the residue on a silicone gum rubber column at 100 °C revealed that only a trace of α-methylstyrene was produced. The combined aqueous layer was acidified with concentrated HCl and the resulting mixture was extracted five times with ether. The combined ether extracts which contained the acidic compounds were esterified with diazomethane and dried over Drierite, and solvent was removed on a rotary evaporator. VPC analysis of the resulting methyl esters showed that a 65% yield[16] of cumene methyl esters was obtained consisting of 95% methyl 2-methyl-2-phenylpropanoate (**3**), 3% methyl *m*-isopropyl benzoate (**1b**), and 2% methyl *p*-isopropylbenzoate (**1c**). Additionally, VPC analysis showed that only a small quantity of methyl hexanoate was present. Distillation of the methyl esters gave a sample of methyl 2-methyl-2-phenylpropanoate boiling at 92–94 °C (8 mm) which had an ir and NMR spectra superimposable with the ir and NMR spectra of an authentic sample of this compound.

Metalation of Cumene with *n*-Pentylsodium in the Absence of TMEDA. Cumene was metalated by *n*-pentylsodium in the absence of TMEDA using the above procedure. VPC analysis of the methyl esters showed that a 40% yield of cumene methyl esters was obtained consisting of 55% methyl *m*-isopropylbenzoate (**1b**) and 45% methyl *p*-isopropylbenzoate (**1c**). VPC analysis also revealed that large quantities of methyl hexanoate were present.

Metalation of Cumene with *n*-Pentylsodium in the Presence of TMEDA as a Function of Time. To a *n*-pentylsodium sample in 150 ml of octane was added 36 g (0.30 mol) of cumene and 13.9 g (0.12 mol) of TMEDA. Aliquots (20 ml) were removed and carbonated at various time intervals (see Table I) and after 24 h the reaction was carbonated. Workup, esterification, and analysis of the samples were performed in the usual manner. The results appear in Table I. Additionally, only trace amounts of methyl hexanoate were observed in the gas chromatogram in the 1-h aliquot.

Registry No.—2, 15544-84-0; TMEDA, 110-18-9; cumene, 98-82-8; *n*-pentylsodium, 1822-71-5.

References and Notes

(1) (a) Author to whom inquiries should be sent. (b) The authors wish to express their appreciation to the University of Wisconsin—Oshkosh for financial support through a Chancellor's Grant and a CAS Grant.

(2) R. A. Benkeser, J. Hooz, T. V. Liston, and A. E. Trevillyan, *J. Am. Chem. Soc.*, **85**, 3984 (1963).

(3) It should also be pointed out that previous attempts by T.F.C. to prepare α-cumylsodium by cleaving α-cumyl methyl ether with sodium failed even though α-cumylpotassium could readily be prepared by this method. See T. F. Crimmins, M.S. Thesis, Purdue University, West Lafayette, Ind., 1963.

(4) G. B. Trimitsis, A. Tuncay, R. D. Beyer, and K. J. Ketterman, *J. Org. Chem.*, **38**, 1491 (1973).

(5) See, for instance, (a) R. E. Ludt and C. R. Hauser, *J. Org. Chem.*, **36**, 1607 (1971); (b) R. E. Ludt, G. P. Crowther, and C. R. Hauser, *ibid.*, **35**, 1281 (1970); (c) D. W. Slocum, G. Book, and C. A. Jennings, *Tetrahedron Lett.*, **39**, 3443 (1970); (d) D. A. Shirly and C. F. Cheng, *J. Organomet. Chem.*, **20**, 251 (1969); (e) R. West and P. C. Jones, *J. Am. Chem. Soc.*, **90**, 2656 (1968).

(6) Carbonation and esterification of *n*-pentylsodium gives methyl hexanoate under these experimental conditions.

(7) R. A. Benkeser, T. F. Crimmins, and W. Tong, *J. Am. Chem. Soc.*, **90**, 4366 (1968).

(8) It is of interest to note the small yet significant amount of the ortho compound **1a** which was observed in the early stages of the reaction. Previous investigators studying the metalation of various alkylbenzenes with *n*-pentylsodium in the absence of TMEDA did not observe ortho metalation. See, for instance, (a) ref 2 and 7 and (b) R. A. Benkeser, A. E. Trevillyan, and J. Hooz, *J. Am. Chem. Soc.*, **84**, 4971 (1962).

(9) C. D. Broaddus, *J. Org. Chem.*, **35**, 10 (1970).

(10) In our hands it was observed that the activating effect of the TMEDA was greatly diminished if the TMEDA was not distilled from BaO or CaH_2 prior to use.

(11) J. A. Moore and D. E. Reed, *Org. Synth.*, **41**, 16 (1961).

(12) H. Gilman and A. H. Blatt, "Organic Syntheses", Collect. Vol. I, Wiley, New York, N.Y., 1941, pp 111, 133, and 135.

(13) Previous research has demonstrated that this carbonation and esterification technique is an accurate method to "tag" the location of the sodium in these highly reactive and air-sensitive organosodium compounds. See ref 2, 7, and 8b.

(14) M. Schlosser in "Newer Methods of Preparative Organic Chemistry", Vol. 5, W. Foerst, Ed., Verlag Chemie, Weinheim/Bergstr., Germany, and Academic Press, New York, N.Y., 1968, p 299.

(15) Prior to hydrolysis, a piece of dry ice was added to the breaker to produce a carbon dioxide atmosphere. This prevented fires resulting from the reaction of excess sodium with water.

(16) *n*-Pentylsodium was the limiting reagent in these reactions. Percentage yields of cumene esters were based on an assumed 70% (0.1 mol) yield of *n*-pentylsodium.