TABLE I

SEPARATION OF AXIAL AND EQUATORIAL PROTON RESONANCE ABSORPTIONS IN CYCLOHEXANE AT LOW TEMPERATURES[a,b]

Temp., °C.	$C-H_a$[c]	$C-H_e$[c]	Average $C-H_a$, $C-H_e$[d]	$(C-H_a) - (C-H_e)$[e]
−72.1	−75.7	−95.3	−85.5	19.6
−73.2	−74.6	−96.2	−85.4	21.6
−82.0	−72.4	−97.9	−85.1	25.5
−85.2	−72.0	−99.5	−85.7	27.5
−86.3	−72.2	−98.9	−85.5	26.7
−95.8	−72.2	−99.9	−86.0	27.7
−106 ± 3	−69.8	−97.4	−83.6	27.6

[a] The solution was 3 *M* cyclohexane in carbon disulfide and contained 0.04 ml. of tetramethylsilane/ml. of solution. [b] The signal occurring at higher field was assumed to be due to the axial hydrogen. [c] Apparent shift of peak maximum from tetramethylsilane in c./s. [d] c./s. from tetramethylsilane. [e] c./s.

the data at very low temperatures, this difference is 27.3 cycles per second.

It is thus possible to calculate a rate constant,[3] $k_1 = 121$ sec.$^{-1}$ (at −66.5°) for the chair–chair interconversion and to provide a good estimate of the energy barrier. Assuming an unstable intermediate with an equal probability of returning to either conformation, correcting for the resulting statistical factor of two, and applying the Eyring equation, $\Delta F^* = 9700$ cal./mole for this process. Since ΔS^* is probably small, this also represents a close approximation for ΔH^*.

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(3) J. A. Pople, W. G. Schneider and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Company, New York, N. Y., 1959, p. 223.

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RECEIVED JANUARY 18, 1960

THE PARTIAL SYNTHESIS OF 3β-HYDROXY-17-KETOSTEROIDS. A NOVEL APPROACH

Sir:

We wish to report a novel approach to the semimicro synthesis of certain 3β-hydroxy-17-ketosteroids. Previous preparation of 3β-hydroxy-17-ketosteroids from the corresponding diols required numerous steps,[1,2,3] and mixtures often resulted. By protecting the 3β-hydroxyl through digitonide formation, the unprotected hydroxyl can be oxidized selectively.

5α-Androstane-3β,17β-diol (10 mg.) was dissolved in 2.5 ml. of 90% ethanol and treated with 2.5 ml. of digitonin solution (20 mg./ml. 90% ethanol) for 20 hours at room temperature. The resulting digitonide was centrifuged, washed with cold 90% ethanol and then ether to remove any free steroid. The dried digitonide was dissolved in 2.0 ml. of glacial acetic acid and 2.0 ml. of 1.2% CrO_3 in 60% acetic acid was added and stirred for about 30 minutes. The reaction could be followed by measuring the rapid increase in absorption at 568 mμ. Excess CrO_3 was destroyed with a few drops of saturated $NaHSO_3$ solution and the oxidized digitonide precipitated with 50 ml. of water. The precipitate was centrifuged, washed with water and dried by repeated additions of absolute ethanol and evaporation in a stream of nitrogen. The infrared spectrum showed a band near 5.75 μ identical to that of the digitonide of 3β-hydroxy-5α-androstan-17-one.

The digitonide was dissolved in a minimal volume of pyridine and let stand for 20 hours. Ether (50 ml.) was added and the digitonin was centrifuged and washed twice with ether. The combined ether washings and supernatant were washed with 0.2 *N* HCl, 0.1 *N* NaOH and with water till neutral, dried over sodium sulfate and evaporated to dryness. The infrared spectrum and melting point of the isolated material were identical to those of an authentic sample of epiandrosterone. The yield of 17-ketosteroid based on the amount of digitonide oxidized was approximately 50%. Oxidation under similar conditions of epiandrosterone digitonide resulted in no oxidation, indicating complete protection of the 3β-hydroxyl.

Similarly, starting with androst-5-ene-3β,17β-diol and 19-nor-5α-androstane-3β,17β-diol,[4] dehydroepiandrosterone and 3β-hydroxy-19-nor-5α-androstan-17-one (I), respectively, were prepared. The synthesis of (I) has not been described previously. Crystallization of (I) from methylene chloride and ether yielded colorless needles, m.p. 177–179°, $[\alpha]^{20}D + 108°$; $\lambda_{max.}^{KBr}$ 2.80 (OH), 5.75 μ (cyclopentyl C=O), 9.0, 9.1, 9.25, 9.45, 9.65, 9.83 9.9 μ. (I) was identical to a metabolite of 19-nortestosterone.[5] Oxidation of (I) with CrO_3 in 80% acetic acid resulted in a dione ($\lambda_{max.}$ 5.75 and 5.85 μ), identical to the oxidation product of 17β-hydroxy-19-nor-5α-androstan-3-one[6] and to 19-nor-5α-androstane-3,17-dione.[7]

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(1) E. Elisberg, H. Vanderhaeghe and T. F. Gallagher, THIS JOURNAL, **74**, 2814 (1952).

(2) M. Gut and M. Uskokovic, *J. Org. Chem.*, **24**, 673 (1959).

(3) C. Djerassi, A. J. Mason and M. Gorman, THIS JOURNAL, **77**, 4925 (1955).

(4) This compound did not form an insoluble digitonide. The entire reaction mixture was dried and the oxidation was carried out on the whole mixture.

(5) D. Kupfer and E. Forchielli, *Fed. Proc.*, Abstract forwarded for April Meetings.

(6) This compound was kindly supplied by Dr. Milan Uskokovic.

(7) This compound was kindly supplied by Dr. Mika Hayano.

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RECEIVED JANUARY 13, 1960

CHEMICAL EFFECTS ARISING FROM SELECTIVE SOLVATION: SELECTIVE SOLVATION AS A FACTOR IN THE ALKYLATION OF AMBIDENT ANIONS

Sir:

Ordinarily, the alkylation of phenolic salts in solution produces the ether (oxygen alkylation) in quantitative yields (Table I).[2] It has now been found, however, that, in certain selected solvents, solutions of phenolic salts undergo much carbon alkylation (Table I); these solvents are water, phenol and fluorinated alcohols.

It is proposed that, whereas phenoxide ions react exclusively at oxygen when dissolved in most sol-

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(1) This research was supported by the United States Air Force under Contract No. AF49(638)-324 monitored by the A. F. Office of Scientific Research of the Air Research and Development Command.

(2) N. Kornblum and A. P. Lurie, THIS JOURNAL, **81**, 2705 (1959).

TABLE I

NATURE OF REACTION OF ALLYL AND BENZYL HALIDES WITH SOLUTIONS OF SODIUM PHENOXIDE AT 27°

Solvent	% O-Alkylation[a]	% C-Alkylation[a, b]
Dimethylformamide	100	0
Dioxane	100	0
Ethanol	100	0
Ethylene glycol dimethyl ether	100	0
Methanol	100	0
1-Propanol	100	0
Tetrahydrofuran	100	0
Water	55	45
Phenol[c]	25	75
2,2,3,3-Tetrafluoropropanol-1[d]	45	55
2,2,2-Trifluoroethanol[e]	50	50

[a] Analysis by gas chromatography. In each solvent yields were verified by isolation of products from typical experiments. Completely analogous results also have been obtained using potassium phenoxide, sodium *p*-cresoxide and potassium *p*-*t*-octylphenoxide. [b] In each case both the *ortho* and *para* isomers are found. [c] At 43°. [d] We thank the Organic Chemicals Department of the du Pont Co. for a generous gift of this alcohol. [e] We thank the Pennsalt Co. for a generous gift of this alcohol.

vents, in water, phenol and fluorinated alcohols, substances which are unusually effective at forming hydrogen bonds, the oxygen of the phenoxide ion is so intensely solvated that the availability of the oxygen for nucleophilic displacement is greatly decreased; as a consequence, displacements employing the otherwise unfavored *ortho* and *para* carbon atoms compete successfully.

The possibility that carbon alkylation in water, phenol and fluorinated alcohols derives from a carbonium ion process[2] is rejected for several reasons: (a) extrapolated initial rates for the reaction of allyl chloride with sodium phenoxide in water at 27.5°, over a twenty-six fold change in initial phenoxide ion concentration, give a second order rate constant $9 \pm 2 \times 10^{-2}$ l. mole^{-1} min.$^{-1}$ [3] (b) The allyl and benzyl halides are almost quantitatively accounted for by considering only the products of phenoxide alkylation. Carbonium ion formation would produce major quantities of solvolytic products, *e.g.*, alcohols, and these are not found. (c) The reaction of allyl chloride with sodium hydroxide in water at 27.5°, unlike the corresponding reaction with sodium phenoxide, remains homogeneous and, when followed to 25% reaction, it yields a precise second order rate constant $3.47 \pm 0.18 \times 10^{-3}$ l. mole^{-1} min.$^{-1}$ over a twenty-fold change in initial hydroxide concentration. The fact that this reaction of hydroxide ion, a poorer nucleophile than phenoxide ion, is unmistakably first order in hydroxide and first order in allyl chloride provides further support for the view that the reaction of allyl chloride with phenoxide is an S$_N$2 process.

The full significance of these findings becomes apparent when it is recognized that the examples of carbon alkylation herein described are not unique in being second order processes; the purely oxygen alkylation reactions of sodium phenoxide with allyl bromide in methanol, and in ethanol, are also second order[4] and there can be little doubt that this is true of the other instances of purely oxygen alkylation recorded in Table I. Thus, the incorporation of different solvent molecules into an otherwise identically constituted activated complex produces a profound change in the course of a reaction. This is a result of far reaching implications and a broad study is in progress.

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[3] The reactions of allyl chloride, and allyl bromide, with sodium phenoxide in water proceed at rates clearly dependent on the phenoxide ion concentration and this is not a salt effect. But, insolubility of the products results in extraction of some of the allylic halide from the aqueous phase and, hence, precise rate data cannot be obtained in the ordinary way.

(4) K. Lauer aud H. Shingu, *Ber.*, **69**, 2731 (1936).

(5) Predoctoral fellow 1957–1960 CF-7406-C2, National Cancer Institute, Public Health Service.

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RECEIVED JANUARY 7, 1960

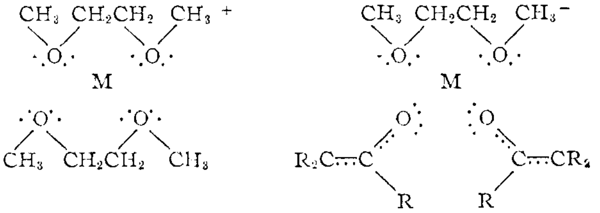
CHEMISTRY OF ENOLATES. IV. SOLVENTS FOR ENHANCED CARBANION ACTIVITY[1]

Sir:

Alkylations and acylations of carbanions commonly are carried out in inert media such as aromatic hydrocarbons or diethyl ether.[2] In these solvents, the carbanions are associated with metallic cations as aggregates which do not conduct an electric current.

We wish to report greatly increased rates of alkylation of enolate anions in the dimethyl ethers of ethylene glycol and diethylene glycol (monoglyme and diglyme). In the latter solvent at 30°, ethylation of 0.13 *M* sodiobutyrophenone by 1.6 *M* ethyl bromide is 75% complete in 152 seconds. The time for a comparable ethylation in diethyl ether is 234 hours. Halides that alkylate at inconveniently slow rates in diethyl ether may now be employed; *e.g.*, half-lives for the alkylations of 0.42 *M* potassiobutyrophenone in monoglyme by 2.0 *M* propyl and isobutyl chlorides are 6.25 and 50 hours, respectively.

The activity of the carbanion is increased by coördination of the solvent with the cation. Four- and six-coördinated solvates of several enolates have been isolated.[3] Coördination of the metal ion by the ketonic product of alkylation recently has been proposed to explain the autocatalysis of the alkylation reaction.[4] If solvates of the type shown are produced, conducting solutions would be expected. Solutions of sodio- and potassio-butyrophenone in monoglyme are indeed conductors of electricity. The molar conductivity of the sodium



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(1) This investigation was supported by a research grant (G-4475) from the National Science Foundation.

(2) C. R. Hauser, F. W. Swamer and J. T. Adams, "Organic Reactions," Vol. 8, John Wiley and Sons, Inc., New York, N. Y., 1954, p. 59; J. Conia, *et al.*, *Bull. soc. chim. France*, 493 (1959); 1064 (1957); 1040, 1392 (1956).

(3) N. V. Sidgwick and F. M. Brewer, *J. Chem. Soc.*, 2379 (1925).

(4) H. D. Zook and W. L. Gumby, THIS JOURNAL, in press.