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A REEXAMINATION OF UNSATURATED CARBOXYLATE DIANION REACTIONS. EVIDENCE FOR α- AND γ- SUBSTITUTIONS IN ALKENOIC ACIDS[1]

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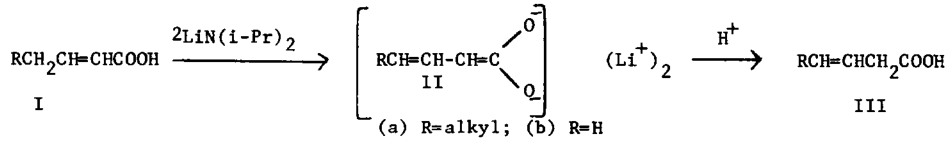
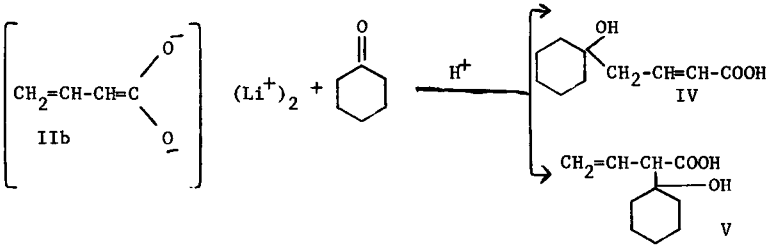
In our previous studies[2] on the preparation and reactions of dianions (Equation 1), we reported the quantitative conversion of α, β- unsaturated carboxylic acids (I) to their β, γ- isomers (III) through formation of the stable intermediate dianion (II). The dianions were prepared by reaction of the appropriate carboxylic acid with lithium diisopropylamide (butyl lithium-diisopropylamine) in tetrahydrofuran (THF). The positional and geometric transformations of each geometric isomer of 2- and 3-hexenoic acids were elucidated by examination of the dianion reactions of each isomer with methyl iodide and with deuterium oxide. Each isomer formed only the 2-substituted-3-hexenoic acids. We had also observed the quantitative formation of 3-butenoic acid from crotonic acid by neutralization of the dianion produced from the latter acid. On the basis of these studies, we assumed without further examination that the substitution reactions of the crotonate dianion would similarly produce only α-substituted products of 3-butenoic acid.



(a) R=alkyl; (b) R=H

(1)

In contrast to the foregoing evidences supporting formation of α-substituted-3-butenoic acid from crotonic acid, two recent publications report the exclusive isolation of a γ-substituted-2-butenoic acid (IV) from the base controlled addition of cyclohexanone to crotonic[3] and 3-butenoic[4] acids. These results appear to question the validity of our former conclusions concerning the mode of substitution in the butenoate isomers. After consideration of these conflicting sets of observations, we were encouraged to reexamine each of the reported dianion reactions[3,4] for confirmation



(2)

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and clarification of their mode of substitution.

In view of Watanabe and co-workers'[3] isolation of γ-(1-hydroxyl-1-cyclohexyl)-crotonic acid (IV) (64% yield) as the sole product of cyclohexanone addition to crotonate dianion, we reexamined this reaction in accordance with their procedure[5], which employs lithium diethylamide as the hydrogen-abstracting base. The product acids (60% yield) proved to be a mixture comprising 40% α-isomer (V) and 60% γ-isomer (IV) (Equation 2). Repetition of the reaction with crotonic acid using lithium diisopropylamide as base gave similar results (Table).

The structures of the two isomers were established as follows:

Acid IV, m.p. 132-133, was separated from the mixture by crystallization from acetonitrile (empirical formula $C_{10}H_{16}O_3$ confirmed by elemental analysis). Treatment of IV with diazomethane yielded the corresponding methyl ester of the γ- isomer (IVa) for which the empirical formula ($C_{11}H_{18}O_3$) was confirmed by elemental analysis and the i.r. and n.m.r. spectral data were in agreement with the report of Watanabe et al.[3]

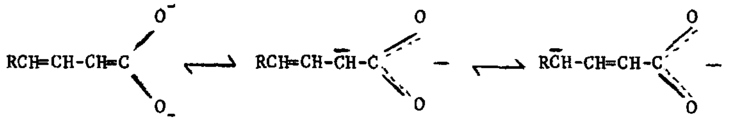
A second product (V), a viscous oil, was isolated from the filtrate. This product was converted to its methyl ester Va with diazomethane and the ester purified by distillation (b.p. 101-102, 3mm). Catalytic hydrogenation of Va over PtO_2 produced a saturated product that exhibited a mass spectrum with a molecular ion at m/e 200 in agreement with the empirical formula ($C_{11}H_{20}O_3$).[6] The i.r. absorption spectrum (CCl_4) for methyl ester Va showed the characteristic intramolecularly hydrogen bonded hydroxyl absorption (3530 cm^{-1}, position independent of concentration), terminal ethylene (3080 cm^{-1}), two characteristic non-conjugated carbonyl stretch frequencies (free C=O at 1735 cm^{-1} and hydrogen-bonded C=O at 1720 cm^{-1}), and the terminal C=C stretch (1635 cm^{-1}). The n.m.r. spectrum of Va consisted of a broad singlet centered at 1.5 δ in correspondence with the 10 protons of the cyclohexane ring, a doublet at 3.0 δ for the single α-hydrogen (J=10.5 H_z), a singlet for the hydroxyl proton (2.9 δ), a singlet corresponding to 3 protons for the methoxy group (3.75 δ), and resonance peaks for the three olefinic protons centered at 5.10 δ, 5.35 δ and 6.0 δ.

In the course of preparing and analyzing the methyl esters, Watanabe et al.[3] failed to detect the α- isomer Va. In their work-up procedure the acid products were not isolated but instead were characterized as the methyl esters, which they obtained "in the usual manner" by esterification of the total reaction mixture. Assuming that their "usual manner" of esterification implied the classical acid catalysis in alcohol, we reexamined the esterification rates of both γ (IV) and α (V) isomers under these conditions. Esterification of the α- isomer V in refluxing methanol with p-toluene sulfonic acid or H_2SO_4 as catalyst is very slow (presumably due to α-branching and intermolecular hydrogen-bonding) as this method produced only 17% conversion to methyl ester in 20 hours. By contrast, the γ- isomer IV is quantitatively esterified in three hours. The low level of esterification of V by the classical method thereby suggests that the previous workers may have extracted and separated acid V from ester IVa in the course of their work-up and purification stages.[7] Analysis of the methyl esters IVa and Va was simply performed by glpc (6 ft. column, 25% DEGA containing 3% phosphoric acid, 200° isothermal). Under these conditions, the γ- isomer IVa had the longer retention time (17 min.) compared to the α- isomer Va (6 min.). The latter's shorter retention time may be attributed to the effect of the intramolecular hydrogen bond.

In the study by Angelo[4] lithium-naphthalene was employed as base for the deprotonation of 3-butenoic acid prior to reaction with cyclohexanone. Here, too, only the single product IV was reported. The efficacy of the reaction was not indicated and could not be assessed owing to exclusion of analytical and yield data. Our repetition of Angelo's procedure with 3-butenoic acid produced both IV and V as minor products (24% overall yield) in a ratio of 3:1 with an 18% isolated yield of IV. The extension of the reaction to include crotonic acid for comparison with its isomer gave a more complicated mixture of products. The methyl esters (conversion via diazomethane) of this product mixture appeared to be derivatives of high molecular weight acids containing no unsaturation as evidenced by n.m.r. and i.r. analysis. This mixture exhibited no evidence of IVa or Va by glpc. It must be concluded from these results that lithium naphthalene as base does not produce a common dianion intermediate from this pair of isomeric acids.

It was further determined that methyl iodide alkylation of dianion IIb (prepared with lithium diisopropylamide) gave both α- and γ- methyl substituted products in a ratio comparable to cyclohexanone addition (Table). In contrast, the addition of cyclohexanone to <u>trans</u>-2-hexenoate dianion produced 96% α- substitution and 4% γ- substitution whereas methylation[2] resulted exclusively in α- substitution.

<u>Conclusions</u>: While the main purpose of the present investigation was directed to the clarification of these dianion reactions, the study has also provided evidence for the importance of substituent effects on the relative reactivity of the α- and γ- positions to electrophilic reactions. Butenoate dianion must differ from the longer chain homologs in distribution of the charge density at the α- and γ- positions. In the former dianion (IIb) charge density is approximately equally distributed (canonical structures II'b and II"b) whereas it is essentially localized at the α-position in the hexenoate dianion (II"a) through the effect of the electron donating alkyl group ($R = C_2H_5$). The opposite effect of an electronegative substituent is indicated in a reported



IIa or IIb II'a or II'b II"a or II"b

example of the α-anion of methyl 4-bromocrotonate (R = Br) in which substitution is directed exclusively to the γ- position.[8]

TABLE

YIELDS OF α- AND γ- SUBSTITUTED PRODUCTS FROM REACTIONS OF BUTENOATE AND HEXENOATE DIANIONS

ACID	REACTANT	BASE	YIELD, %	α-POSITION[a]	γ-POSITION[b]
crotonic	cyclohexanone	Li Diethylamide[c]	60[d]	40	60(100% *trans*)
crotonic	cyclohexanone	Li Diisopropylamide	58[d]	40	60
crotonic	methyl iodide	Li Diisopropylamide	75[e]	60	40(100% *trans*)
crotonic	cyclohexanone	Li Naphthalene	0		
3-butenoic	cyclohexanone	Li Naphthalene	24[f]	25	75
trans-2-hexenoic	cyclohexanone	Li Diisopropylamide	70[d]	96 {60% *cis* 40% *trans*}	4(100% *trans*)
trans-2-hexenoic[2]	methyl iodide	Li Diisopropylamide	86[e,g]	100 {66% *cis* 34% *trans*}	
cis-2-hexenoic[2]	methyl iodide	Li Diisopropylamide	85[e,g]	100 (100% *trans*)	

a) 2-Substituted-3-alkenoic acid; b) 4-Substituted-2-alkenoic acid; c) Lithium diethylamide prepared from lithium naphthalene and diethylamine; d) Isolated yields; e) Conversions determined by glpc; f) Isolated yield of γ- isomer, 18%; α/γ ratio determined by glpc; g) Remainder of product is 2,2-dimethyl-3-hexenoic acid

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1. Paper No. VI in the series on α-Anions of Carboxylic Acids.
2. P. E. Pfeffer and L. S. Silbert, J. Org. Chem., 1971, 36, 3290.
3. S. Watanabe, K. Suga, T. Fujita and K. Fujiyoshi, Chem, and Ind. 1972, 80.
4. B. Angelo, Bull. Soc. Chim. France, 1970, 1848; Compt. rend., Series C, 1970, 270, 1471.
5. The experimental procedure reported in Ref. 3 appeared to be incomplete since the prescribed method resulted in poor yields of product. A modified version received in a private communication from the author differed from the published version mainly by prescribing the preparation of lithium naphthalene in THF at 25° (temperature not formerly stated), addition of distilled diethylamine at 25° (instead of -30°), addition of crotonic acid to the lithium diethylamide preparation at -30° (instead of -5°), and addition of cyclohexanone to the crotonate dianion at -20° (instead of -5°). Our reexamination of this procedure is based on the modified version.
6. Reduction was necessary since the mass spectrum of IVa showed a preionization fragmentation with no evidence of a molecular ion.
7. Since the use of diazomethane is limited to analytical preparations and determinations of methyl esters, preparations of IVa and Va may be quantitatively obtained on a preparative scale by a recently reported esterification procedure involving alkylation of the potassium salt of IVa and Va with alkyl halide, [P. E. Pfeffer, T. A. Foglia, P. A. Barr, I. Schmeltz and L. S. Silbert, Tett. Letters, No. 40, 4063 (1972)]. Esters IVa and Va were thermally stable and not interconvertible under the prescribed glpc conditions.
8. G. A. Koppel, Tetrahedron Letters, 1972, 1507.