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STEREOSELECTIVE SYNTHESIS OF THREO-3-HYDROXYCARBOXYLIC ACIDS. STEREOCHEMISTRY OF AN ALDOLTYPE ADDITION UNDER KINETIC AND THERMODYNAMIC CONTROL.

Johann Mulzer*, Johann Segner and Gisela Brüntrup

Institut für Organische Chemie der Universität,
Karlstrasse 23, D 8000 München 2.

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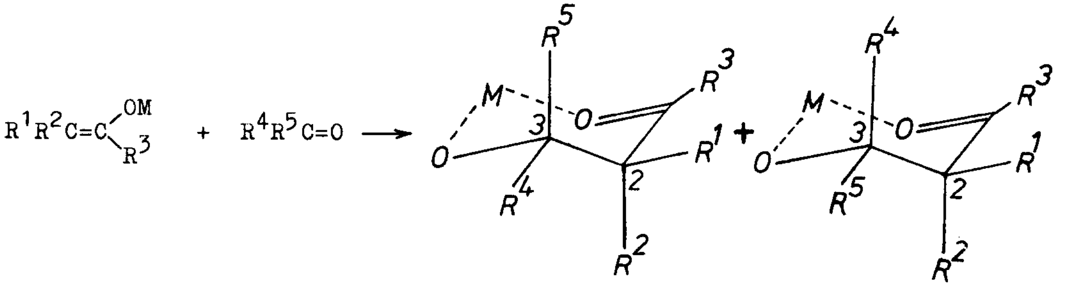
The addition of preformed enolates 1 to carbonyl compounds 2 results in the formation of metal chelates, which, having stereocenters at C-2 and C-3, are generally formed as mixtures of the *threo*- and *erythro*-isomers 3 and 4[1].



1 2 3 4

I: R^1,R^2,R^3,R^4,R^5 = H,alkyl,aryl. M = $Mg_{1/2}$,$Zn_{1/2}$,Li,Na,K.

II: R^1,R^2,R^4,R^5 = H,alkyl,aryl. R^3 = Oalkyl. M = $Zn_{1/2}$.

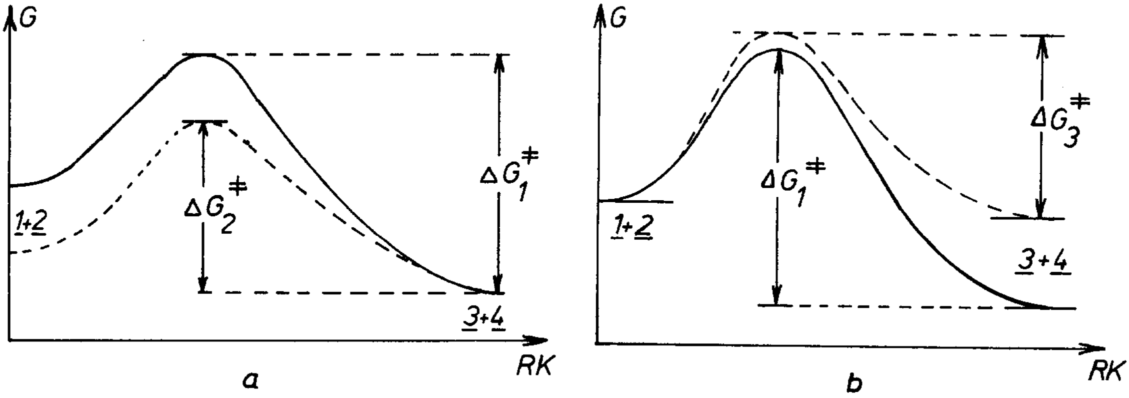
III: R^1,R^4 = alkyl,aryl. R^2 = R^5 = H. R^3 = OLi. M = Li.

For compounds of type I it has been shown by different research groups that the ratio of 3:4 largely depends on the substituents, metal ions and reaction conditions[2]. Type II corresponds to the familiar Reformatsky reaction[3]. In connection with our work on the chemistry of 3-hydroxycarboxylic acids[4] we studied some additions of type III. In this case the enolates 1 are carboxylate dianions which are readily prepared by a twofold deprotonation of the corresponding carboxylic acids 5 with lithium diisopropylamide (LDA)[5]. Our objective was to see how the ratio of 3:4 changed for various R^1 and R^4 if III was run under conditions of clearly defined kinetic or thermodynamic control.

Experimental. 0.06 moles of 5 in 80 ml THF were converted into 1 with 0.12 moles of LDA (generated in situ from the amine and n-butyllithium) in 120 ml THF/hexane (v/v 1:2) at -50°. After having stirred the mixture at 25° for 1 hr and the solvents then removed at 1 torr, the residue was dissolved in

80 ml THF, cooled to -50° and treated with 0.06 moles of 2. Then conditions A or B were applied alternatively. A: The mixture was stirred at -50° for 10 min. B: The mixture was stirred at 25° for 3 days. In each case the resulting mixtures of 3 and 4 were hydrolyzed to the corresponding hydroxyacids 6 (threo) and 7 (erythro). By independent control experiments we excluded any change of configuration at C-2 and C-3 during the conversion of 3/4 into 6/7.

Results and Mechanistic Interpretation. The stereochemical results obtained under conditions A and B are summarized in Table 1. It may be safely assumed that A leads to kinetically controlled product mixtures for all systems. As 1 undoubtedly is a highly reactive and hence little selective carbanion, the ratios of 3:4 may be expected to differ relatively little even if the sizes of R^1 and R^4 are varied over a wide range. Considering the results of condition B the systems in Table 1 fall into two groups 1 and 2. The systems in group 1 remain under kinetic control; so nearly the same ratios of 3:4 are observed as for condition A. The systems in group 2, however, now react reversibly and, therefore, are thermodynamically controlled: the formation of the more stable chelate 3 with equatorial substituents only is favored over 4, which has to cope with an axial R^1 or R^4. The reason why the activation barrier of the retrograde addition is much lower for the systems in group 2 than for those in group 1 may be attributed to the following two substituent effects: a. The energy of 1 is lowered by additional conjugation (R^1= C_6H_5, systems h-q, Fig. 1a). b. 3 and 4 are destabilized by the steric congestion of bulky R^1 and R^4 (systems e,f,g,n, Fig. 1b). A cooperation of both effects accelerates equilibration substantially; so the equilibrium composition is reached at 25° after 6 hrs for system n (effect a+b), and after 72 hrs for system g (effect b only) !



a

b

Fig. 1. Energy profiles of III for systems of group 1 (solid curves) and of group 2 (dashed curves) illustrating effects a and b. For simplicity it has been assumed that there is no energy difference between 3 and 4 of one and the same system.

Table 1. Ratios of 3:4 and total yields under conditions A and B.

System	R^1	R^4	ratios of 6:7 1) (= 3:4) and % total yields of 6+7 under conditions		
			A	B	
a	CH_3	$C(CH_3)_3$	1.0/70	1.0/68	group 1
b	CH_3	C_6H_5	1.2/75	1.2/75	
c	C_2H_5	"	1.1/73	1.2/75	
d	$CH(CH_3)_2$	"	1.2/80	1.4/73	
e	$C(CH_3)_3$	$CH(CH_3)_2$	3.8/78	9.0/75 2)	group 2
f	"	$C(CH_3)_3$	4.0/85	49.0/83 2)	
g	"	C_6H_5	1.5/73	7.3/70	
h	C_6H_5	"	2.5/88	11.5/80	
i	"	1-naphthyl	2.7/85	12.0/78	
j	"	2-thienyl	2.3/75	10.5/68	
k	"	2-furyl	2.4/68	11.0/60	
l	"	$C_6H_5CH=CH$	2.4/88	11.0/75	
m	"	$3\text{-}Cl\text{-}C_6H_4$	-	11.5/85	
n	"	$C(CH_3)_3$	1.9/95	49.0/85	
o	"	$CH(CH_3)_2$	1.9/83	4.0/72	
p	"	C_2H_5	1.4/70	1.8/60	
q	"	CH_3	1.4/65	1.8/50	

1) The assignments of *threo*- and *erythro*-configurations are well established and will be published in due course. For the determination of the ratios of 6:7 the ^{1}H-NMR-signals of the carbinol protons have been used.

2) Equilibrium was reached at 45° after 3 days.

Additional evidence for the reversibility of the group-2-systems was gained by the following experiments. 1. 6n was converted into 3n with 2 equivalents of LDA. Then an excess of 3-chlorobenzaldehyde was added whereupon 3m and 4m were formed in a ratio of 92:8 (total yield 85%) after 2 days at 25°. 2. Analogously, 6h,6n,6p and 6q were transformed into 3h,3n,3p and 3q and kept at 25° for 3 days; phenylacetate could be isolated from the reactions in yields up to 10%. 3. Alternatively, a 60:40-mixture of 6g:7g was treated with 2 equivalents of LDA; after 3 days at 25° the ratio of 6g:7g had changed to 9:1. Repetition of these experiments with systems of group 1 failed.

Conclusion. Aldol additions of type I are generally regarded as reversible[2], whereas type-II-additions have been demonstrated to be irreversible[3], at least for $R^5 = H$. In contrast to these results we have shown that additions of type III may proceed both reversibly and irreversibly, depending on the nature of the substituents R^1 and R^4.

Preparative Utility. All the threo-acids listed in Table 1 have been obtained in practically pure form, either by choosing condition B or by crystallizing the threo-erythro-mixtures from ether/pentane or from chloroform/pentane. With appropriate reagents these threo-acids can be converted into threo-esters (which, for the group-2-systems, constitutes a highly stereoselective version of the Reformatsky reaction), cis-olefins and trans-ß-lactones stereospecifically[6].

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