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Investigations on Transition State Geometry of the Aldol Condensation in Aqueous Medium

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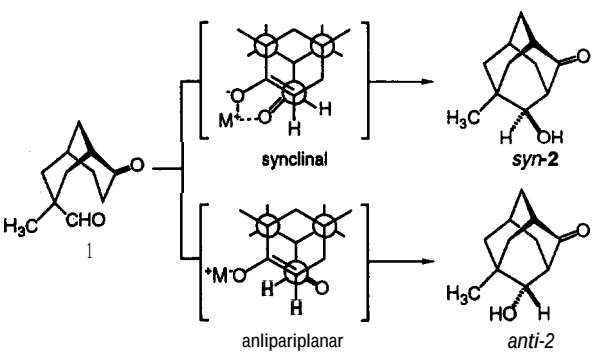
Key Words: Aldol Condensorion; Aqueous Solvent; Synclinal; Antiperiplanar; Syn- and Anti-aldol

Abstract: In aqueous medium, base-induced aldol condensations of keto aldehyde 1 show high anti-selectivity independent of metal ion and water content of the solvent. The acid-induced aldol condensations afford syn-aldol products in variable selectivity depending upon acid strength and water content of the medium.

The aldol condensation is one of the most important carbon-carbon bond-forming reactions in organic chemistry.1 and elucidation of the factors controlling the stereochemical outcome is a continuing challenge.[2] Previous reports from these laboratories have addressed the transition-state geometry in the aldol condensation in organic solvents using model system 1 (Scheme 1).[3] The intramolecular aldol reaction of metal enolates showed an increasing preference for the syn-aldol product (syn-2) with increasing coordinating ability of the cation ($K^+ < Na^+ < Li^+$ c $MgBr^+$). In the presence of strong cation-complexing agents, however, the model revealed a strong preference for reaction via an antiperiplanar orientation of the reactant giving the anti-aldol product (anti-2) with high selectivity.

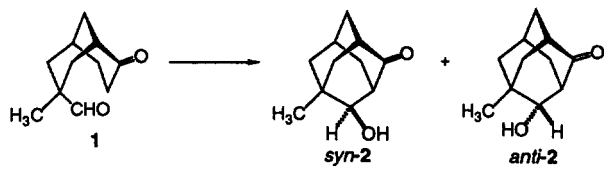
Scheme 1



In the course of our studies we became interested in investigating the stereochemical outcome in an aqueous solvent system. Although water is not a conventional solvent for the aldol condensation in

preparative organic chemistry[4], other hio-relevant aldol processes take place in aqueous media. We were particularly intrigued by Eschcnmoser's analysis of the stereochemical course of the formose reaction.5 The formation of allose-2,4,6-triphosphate and ribose-2,4-diphosphate as the dominant kinetic products in the aldomerization of glycoaldehyde phosphate in 2M sodium hydroxide was rationalized by a synclinal transition structure which minimizes 1.5interactions. Moreover, the D-*threo* specificity of rabbit muscle aldolase catalyzed reactions can also be accommodated by a similar transition structure analysis. To probe the existence of orientational preferences, we carried out a systematic investigation on the transition-state geometry of the aldol condensation in aqueous medium.

Table 1. Acid or Base Induced Cyclization of **1** in Aqueous Solvent Systems.



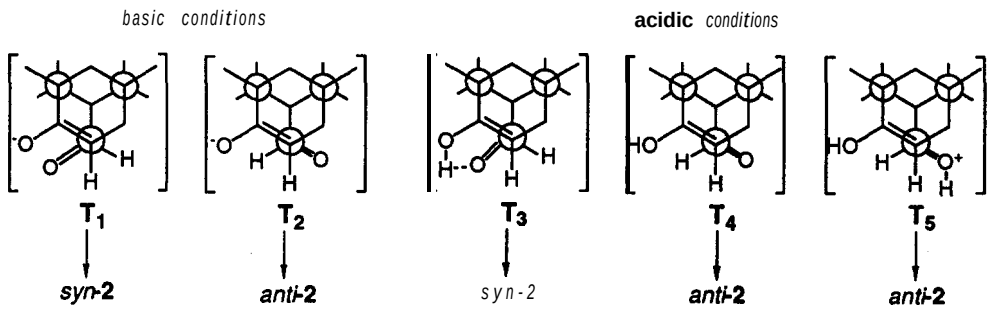
entry	acid/base[a]	temp,°C	time, h	THF/H_2O	syn/anti[b]	$\Delta\Delta G^{\ddagger}$[c]
1	LiOH	0	1	4/1	17/83	-0.86
2	LiOH	rt	1	4/1	17/83	-0.94
3	NaOH	0	1	10/1	16/84	-0.90
4	NaOH	0	1	4/1	15/85	-0.94
5	NaOH	0	1	1/1	13/87	-1.03
6	NaOH	rt	1	4/1	16/84	-0.98
7	cat. NaOH	rt	1	4/1	17/83	-0.94
8	KOH	0	1	4/1	15/85	-0.94
9	KOH	rt	1	4/1	16/84	-0.98
10	$Ca(OH)_2$	0	1	4/1	19/81	-0.79
11	$Ca(OH)_2$	rt	1	4/1	24/76	-0.68
12	CH_3COOH	rt	3	4/1	87/13	1.13
13	CF_3COOH	rt	1	4/1	72/28	0.56
14	HCl (10 equiv)	rt	1	4/1	65/35	0.37
15	HCl (1 .O equiv)	rt	1	4/1	72/28	0.56
16	HCl (0.1 equiv)	rt	1	4/1	87/13	1.13
17	HCl (0.01 equiv)	rt	1	4/1	91/9	1.37
18	1N HCl	rt	1	1/3	85/15	1.03
19	1N HCl	rt	1	10/1	54/46	0.09
20	HCl (g)	0	1	THF/Et_2O	49/5 1	0.02

a 1.1 Equiv of reagent unless otherwise specified. b From capillary GC analysis. Average of at least 3 runs with ± 3%. All reactions were shown to be under kinetic control. c Kcal/mol at reaction temperature.

The results of aqueous acid- and base-induced aldol reactions of model system 1 are collected in Table 1.[6] Under basic aqueous conditions (entries 1-11) cyclizations proceeded with modest but consistent anti selectivity. Changing the cation (LiOH, NaOH, KOH, $Ca(OH)_2$), temperature (0°C or room temperature), and amount of water in the solvent system (THF/H_2O = 10/1, 4/1, 1/1) had little effect. The anti selectivity and metal ion independence in base-induced cyclization can be explained by the strong hydration of the metal cation by the water molecules. Even with a smali amount of water, the reacting species is most likely a solvent separated enolate ion (compare entries 3-5). Since this enolate has no coordinated metal cation, (though most likely hydrogen bonded to water) it cyclizes via the open transition structure T_2 (Scheme 2). This structure minimizes the Coulombic repulsion between the enolate and aldehyde oxygens that would favor the anti product. This behavior is reminiscent of the cyclization of **1** with KHMDS in the presence of Kryptofix [2.2.2]. Here again the high anti selectivity was interpreted in terms of a metal-free (naked) enolate.3 This explanation is not inconsistent with the insensitivity of the reaction to solvent; water is always present and the local solvation of the enolate may not represent the composition of the bulk medium.

Under acidic aqueous conditions (entries 12-20) the stereochemical course reversed to a syn-selective cyclization. Unlike the reactions promoted by base, these cyclizations displayed a pronounced sensitivity to reaction conditions. For example, comparing the results in 4/1 THF/water, the syn selectivity decreased in the order $CH_3CO_2H > CF_3CO_2H \sim 1N\,HCl$ (entries 12, 13 and 15) suggesting a dependence on acid strength. This was verified by systematically varying hydrogen ion concentration while keeping the water content constant (entries 14-17). In this series, the syn/anti selectivity increased from 65/35 to 91/9 with decreasing hydrogen ion concentration. Finally, the role of water is illustrated by comparison of entries 18, 15, 19 and 20. By decreasing the water content of the medium from 75% to 20% to 9% to 0%, the syn/anti selectivity decreased from 85/15 to 72/28 to 54/46 to 49/51 resp.

Scheme 2



In acidic medium, the reactive nucleophilic species is most likely the enol form of the ketone. However, the electrophilic species can be either the free aldehyde or its Brønsted conjugate acid. Thus, the observation of net syn selectivity indicates that the cyclization proceeds through a synclinal transition structure, *but to explain the variation in syn selectivity, we propose that the two different electrophilic species react via different transition states.* Under weakly acidic conditions (acetic acid or 0.01 equiv HCl), the aldehyde is not protonated. and can be activated for addition by intramolecular hydrogen bonding via transition structure T_3. As the hydrogen ion concentration increases, the proportion of reaction via the

protonated aldehyde form increases. Reaction of this species is expected to proceed via antiperiplanar transition structure T_5 since, (1) hydrogen bonding to the positive oxygen is expected to be highly unfavorable.7 (2) the carbonyl group is highly activated anyway and (3) the repulsion between the developing positive charge on the oxygens is minimized. The dependence on solvent composition can now be understood in the extent of available protons. In highly aqueous medium, the free aldehydc is the major reactive species and thus reaction via T_3 leads to high syn selectivity. In anhydrous or strongly acidic aqueous medium the protonated form is present in significant concentration and reaction via T_5 (leading to *anti*-**2**) erodes the net syn selectivity.

The lack of correlation between the base-induced, anti-selective reactions of 1 and the synclinal reaction modus in the aldomerization of glycoaldehyde phosphate is not surprising in view of the significant differences in reactant structures. Nonetheless, this divergence underscores the remarkable behavior of the glycoaldehyde reaction which must overcome the energetic cost of charge repulsion in the synclinal transition structure.

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