KINETIC AND THERMODYNAMIC ENOLIZATION OF 3-PYRANONES#

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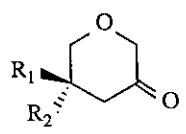
Abstract — Kinetic enolization of 3-pyranones is favored toward the α-position away from the heterocyclic oxygen. This preference is even more marked under conditions of thermodynamic enol acetate and enolate formation.

Anions α– to the oxygen atoms of pyran rings are useful for the synthesis of naturally occurring heterocycles as divergent as carbohydrates, trichothecene sesquiterpenes, and polyether antibiotics. Formation of the unsubstituted tetrahydropyranyl α-anion itself has been described recently.[1] Pyranyl-3-ketones are a second potential source of anions α- to the ring heteroatom. However, the regiochemistry of enolization of these compounds, for example, tetrahydropyran-3-one, **1**, is ambiguous. Little or no information is available on either the kinetic or the thermodynamic acidity of pyran-3-ones although one case drawn from our work has been published[2]. We have, therefore, examined the enolic properties of several mono and bicyclic pyranyl ketones and report the results herein.

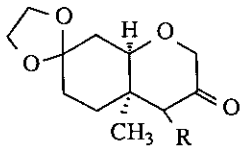
The compounds chosen for study were ketones **1**-**5**. Compound **1** was prepared by hydroboration-oxidation of dihydropyran while **2** and **3** were obtained by the route shown in Scheme 1. In a similar fashion bicyclic ketones **4** and **5** were derived from lithium dimethyl cuprate additions to the corresponding bicyclic enones [3].



1 $R_1 = R_2 = H$

2 $R_1 = H, R_2 = CH_3$

3 $R_1 = R_2 = CH_3$

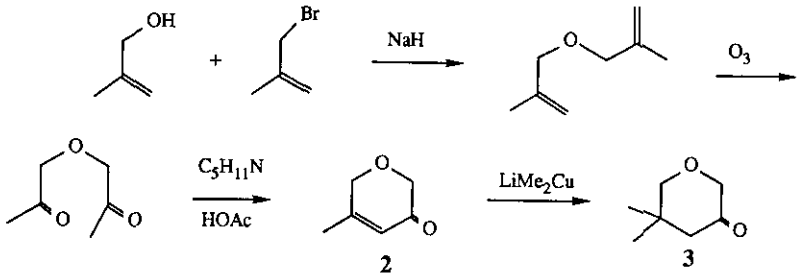


4 R = H

5 $R = CH_3$

Submitted in honor of the 65th birthday of Professor Gilbert Stork

Scheme 1



Kinetic enolization of these ketones was studied by treatment of each compound with an excess of freshly prepared lithium diisopropylamide in DME at -78° C, followed, after 15-30 min at this temperature, by quenching with acetic anhydride[4]. For determination of the equilibrium positions of the isomeric *enol acetates* **6** - **11**, ketones **1**, **2**, and **3** were treated with perchloric acid in acetic anhydride-carbon tetrachloride[5]. In the case of ketone **4** the enolate was allowed to equilibrate at -40° C and then trapped again with acetic anhydride. We were unable to achieve equilibration of the enolate of **5**, however. At temperatures higher than -78° C or in the presence of less than an equivalent of base, side reactions ensued. In every case the mixtures of isomers were analyzed by integration of their ^1H nmr spectra utilizing the vinyl proton resonance of the enol acetate function. The results of these measurements are shown in TABLE I.

TABLE I Kinetic vs Thermodynamic Formation of Enol Acetates

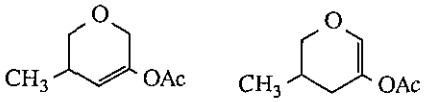
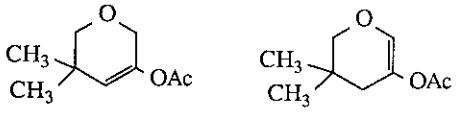
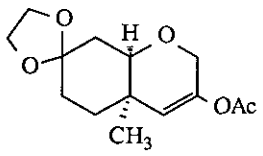
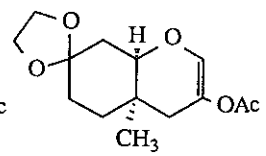
KETONE	KINETIC PRODUCTS	EQUILIBRIUM PRODUCTS
1	 **6** 3.3 : 1 **9**	**6**
2	 **7** 4 : 1 **10**	**7** : **10** ; 16 : 1
3	 **8** 5.7 : 1 **11**	**8** : **11** ; >99 : 1

TABLE I (cont..)

KETONE	KINETIC PRODUCTS	EQUILIBRIUM PRODUCTS
4	 **12** 1.38 : 1  **13**	**12 : 13** ; 49 : 1

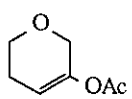
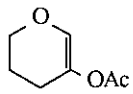
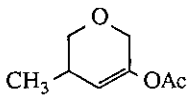
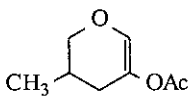
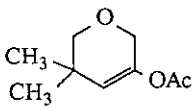
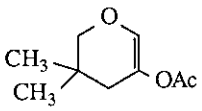
From these data is its clear that kinetic enolization of the simple monocyclic ketones **1, 2,** and **3** is strongly favored toward the α-position *away* from the pyranyl oxygen. Even more striking are the equilibrium data for the enol acetates in which isomers **6, 7,** and **8** dominate to an even greater extent. Thus in the case of **1** we observe isomer **6** only and even in the least selective of the three cases a maximum of 6% of the "endiol" isomer is formed.

Similar results are observed for the more complex bicyclic ketones **4** and **5** except that kinetic enolization of **4** is not strongly favored in either direction. Under equilibration conditions, however, the non oxygen substituted isomer ,**12,** is formed almost exclusively. In the case of **5** an additional factor, differential substitution of the α-position, clearly favors enolization *toward* the pyranyl oxygen in a ratio of 6 : 1.

An oxygen atom next to a carbanionic center is predicted on a polarization basis to provide 10-15 kcal of stabilization relative to a CH_2 group[6]. In addition, conformational analysis of the isomeric enol acetates derived from **1, 2,** and **3** indicates that the endiol structures are uniformly favored. The results of MM2[7] molecular mechanics calculations are shown in TABLE II. While the differences in calculated steric energies for each pair of isomers are not large it is significant that they are all at variance with the experimental results. Thus, the unfavorable stereoelectronic effect of oxygen unshared pairs having an *antiperiplanar* arrangement[2] appears to be sufficient to overcome conformational steric effects. It is interesting to note moreover that this effect appears to govern the behavior of the enol acetates as much as it might be expected to control the equilibria of the corresponding enolates.

MM2 calculations on the bicyclic compounds **12** and **13** indicate that the enediol structure is again favored conformationally. Kinetic enolization of **4**, however, shows little preference. This result may be a function of steric effects on the approach of the base to an axial proton in one or the other conformations of the starting ketone. On the other hand the favored isomer in thermodynamic enolization of **4** is overwhelmingly the non conjugated isomer **12.**

TABLE II MM2[a] Energies of Monocyclic 3-Pyranones

Enol Acetate	Steric Energy[b]	Enol Acetate	Steric Energy
 **6**	13.43	 **9**	13.10
 **7**	14.34	 **10**	13.3
 **8**	15.14	 **11**	14.30

[a] Calculated using the MODEL program of W.C. Still, Columbia University
[b] Steric energies in Kcal/mol

These results should be useful in the synthesis of pyran containing natural products. Clearly for maximum selectivity thermodynamically controlled enolization should be employed for electrophilic substitution of symmetrically substituted 3-pyranone rings with high selectivity.

ACKNOWLEDGEMENT

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REFERENCES AND NOTES

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4. H. O. House, M. Gall and H. D. Olmstead, *J. Org. Chem.*, 1971, **36**, 2361.

5. H. O. House, L. J. Czuba, M. Gall and H. D. Olmstead, *J. Org. Chem.*, 1969, **34,** 2324, and references therein.

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