ORGANIC LETTERS

2001
Vol. 3, No. 11
1777−1780

Stereospecific Anionically Promoted Transannular Hydride Shifts in Medium-Ring Hydroxy Ketones. Probe of Their Reversibility and the Potential for Regiocontrol

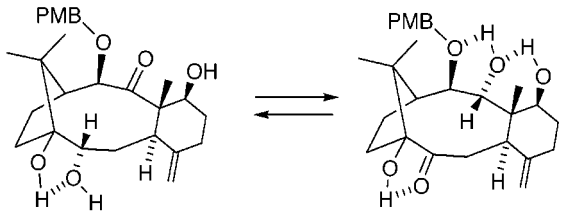
John E. Hofferberth, Ho Yin Lo, and Leo A. Paquette*

Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio 43210

paquette.1@osu.edu

Received April 16, 2001

ABSTRACT



Examples are provided of stereospecific transannular oxidation–reduction processes involving the conjugate bases of δ-hydroxy ketones in a nine-membered ring setting. The ability to control the direction of these equilibria by proper modulation of the solvent environment and level of hydroxyl group protection is demonstrated. MM3-derived steric energies of the isomer pairs suggest that the equilibrium distributions are the outcome of the extent to which intramolecular hydrogen bonding forces are disrupted by polar solvent molecules when present.

The transannular migration of hydride ions has long been recognized to be a fundamental and important reactivity feature of cyclic and bicyclic carbocations of medium-ring size.[1,2] One of the most advanced and elegant applications of this phenomenon is the preparation of stable carbenium ions containing symmetrical three-center, two-electron C−H−C bonds.[3,4] As extensive as these past studies have been, considerably less attention has been accorded to anionic counterparts. From among several possible lines of investigation,[5] that involving the conjugate bases of hydroxy ketones such as **1** and **2** holds significant attraction.[6] However, two limitations might be construed to restrict practical exploitation of these potentially useful processes. Hemiacetal formation is often readily accommodated in the neutral precursors, thereby depleting the equilibrium of the desired reactant. Two representative examples are given by **3**[7] and **4**.[8] Beyond this, these reactions feature concurrent Oppenauer oxidation[9] and

(1) Cope, A. C.; Martin, M. M.; McKervey, M. A. *Q. Rev.* **1966**, *20*, 119.

(2) For examples, see: (a) Appleton, R. A.; Dixon, J. R.; Evans, J. M.; Graham, S. H. *Tetrahedron* **1967**, *23*, 805. (b) Eakin, M. A.; Martin, J.; Parker, W. *Chem. Commun*. **1968**, 298. (c) Prelog, V.; Troxler, E.; Westen, H. H. *Helv. Chim. Acta* **1968**, *51*, 1678. (d) Ourrison, G.; Stehelin, L.; Lhomme, J. *J. Am. Chem. Soc*. **1971**, *93*, 1650. (e) Traynham, J. G.; Foster, A. W. *J. Am. Chem. Soc*. **1971**, *93*, 6216. (f) Doyle, M.; Parker, W. *J. Chem. Soc., Perkin Trans. 1* **1977**, 858. (g) Whalen, D. L.; Cooper, J. D. *J. Org. Chem*. **1978**, *43*, 432. (h) Schneider, H. J.; Heiske, D. *J. Am. Chem. Soc*. **1981**, *103*, 3501. (i) Momose, T.; Itooka, T.; Nishi, T.; Uchimoto, M.; Ohnishi, K.; Muraoka, O. *Tetrahedron* **1987**, *43*, 3713.

(3) Kirchen, R. P.; Ranganayakulu, K.; Rauk, A.; Singh, B. P.; Sorensen, T. S. *J. Am. Chem. Soc*. **1981**, *103*, 588.

(4) McMurry, J. E.; Lectka, T.; Hodge, C. N. *J. Am. Chem. Soc*. **1989**, *111*, 8867.

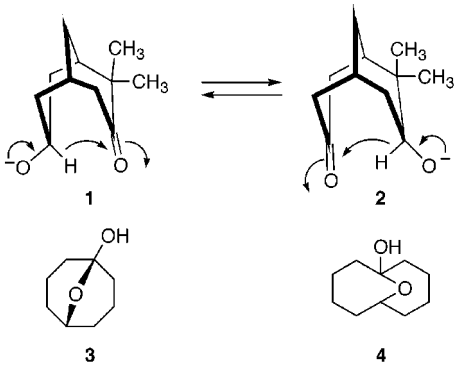
(5) The reaction of **3** with a primary amine constitutes an interesting variant: (a) Wiseman, J. R.; Lee, S. Y. *J. Org. Chem*. **1986**, *51*, 2485. (b) Aggarwal, V. K.; Humphries, P. S.; Fenwick, A. *Angew. Chem., Int. Ed*. **1999**, *38*, 1985.

(6) The parent degenerate reaction has been reported: Parker, W.; Stevenson, J. R. *J. Chem. Soc. D* **1969**, 1289.

(7) Hemiketal **3** shows no carbonyl band in the infrared [Quinn, C. B.; Wiseman, J. R. *J. Am. Chem. Soc*. **1973**, *95*, 1342]. Nevertheless, both tautomers can be brought into reaction depending upon the specific transformation in question: (a) Braish, T. F.; Fuchs, P. L. *Synth. Commun*.

10.1021/ol0100733 CCC: $20.00
Published on Web 05/05/2001

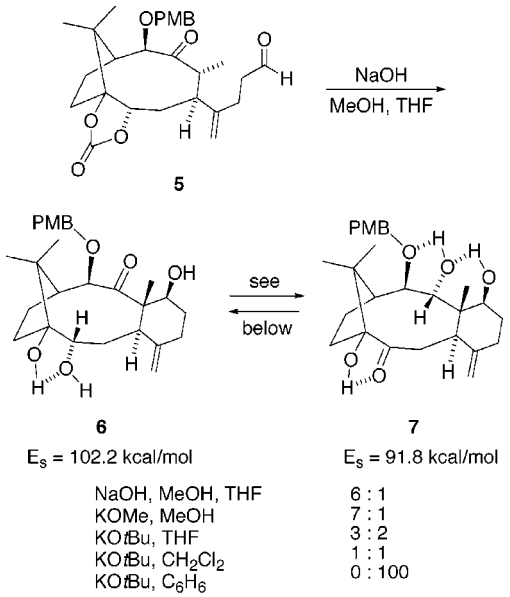
Meerwein−Ponndorf−Verley reduction steps,[10] but practical means for driving a given process to the left or right *at will* as is possible for the classical reactions[11] have been intimated to be unavailable.[12]



Herein we report the results of the first coordinated experimental and theoretical study of nondegenerate, anionically driven, transannular hydride migratability in a medium-ring setting. The present investigation sheds light on the fundamental manner in which hydrogen bonding can contribute in a useful manner to the thermodynamic control of these equilibria. In addition, the impressive extent to which these effects can be outweighed by solvation influences is illustrated. In the examples that follow, the MM3-derived steric energies that are provided were obtained on the actual molecules carrying the bulky *p*-methoxyphenoxy and *tert*-butyldimethylsilyloxy substituents. Simplification by alternative substitution with methoxy and trimethylsilyloxy, respectively, in an attempt to place added emphasis on the contributions of the other structural sectors did not affect the outcome of the computational results. All equilibrium ratios were determined by integration of high-field ^{1}H NMR spectra. The number of runs made for each experiment varied from 2 to >10, and the error limits in Schemes 1−3 are considered to be no greater than ±5%.

In an initial experiment, treatment of keto aldehyde **5** with 0.5 N NaOH in MeOH/THF (2:3:1 v:v) for 12 h at 20 °C was noted to result in very efficient conversion to a 6:1 mixture of **6** and **7** (Scheme 1). Aldol cyclization to construct

Scheme 1



the six-membered ring is recognized to be more rapid than hydrolysis of the cyclic carbonate functionality since the unprotected diol undergoes hemiacetal formation exclusively under the same conditions. Our structural assignments to **6** and **7** were corroborated by single-crystal X-ray diffraction methods (Figures 1 and 2, respectively). Attention is called

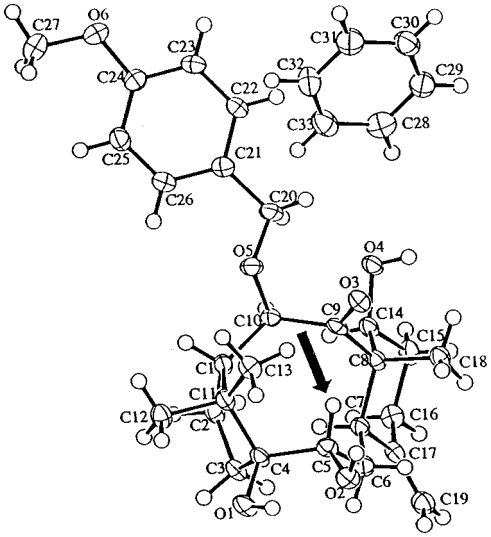


Figure 1. Molecular structure of **6**·C_6H_6 in the solid state.

to the adventitious placement of the migratory hydrogen in the central cavity of this pair of isomers (see arrows). The subsequent equilibration experiments, approached from either

1986, *16*, 111. (b) Kobayashi, K.; Sasaki, A.; Kanno, Y.; Suginome, H. *Tetrahedron* **1991**, *47*, 7245. (c) Zhao, S.; Mehta, G.; Helquist, P. *Tetrahedron Lett*. **1991**, *32*, 5753. (d) Molander, G. A.; McKie, J. A. *J. Org. Chem*. **1993**, *58*, 7216.

(8) 6-Hydroxycyclodecanone exists in the hemiacetal form to the extent of 39−77% depending upon solvent [Mijs, W. J.; De Vries, K. S.; Westra, J. G.; Gaur, H. A. A.; Smidt, J.; Vriend, J. *Recl. Trav. Chim. Pays-Bas* **1968**, *87*, 580]. For representative reactions of this substance, consult: (a) Thies, R. W.; Yue, S. T. *J. Org. Chem*. **1982**, *47*, 2681. (b) McMurry, J. E.; Hodge, C. N. *J. Am. Chem. Soc*. **1984**, *106*, 6450. (c) Hamon, D. P. G.; Krippner, G. Y. *J. Org. Chem*. **1992**, *57*, 7109.

(9) Djerassi, C. *Org. React*. **1951**, *6*, 207.

(10) Wilds, A. L. *Org. React*. **1944**, *2*, 178.

(11) In the intramolecular variants, neither of the two functional groups is present in excess and no volatile byproduct is generated as reaction progresses.

(12) For example, see: (a) Berner, H.; Vyplel, H.; Schulz, G. *Monatsh. Chem*. **1983**, *114*, 501. (b) Paquette, L. A.; Huber, S. K.; Thompson, R. C. *J. Org. Chem*. **1993**, *58*, 6874. (c) Paquette, L. A.; Bailey, S. *J. Org. Chem*. **1995**, *60*, 7849. (d) Paquette, L. A.; Zeng, Q.; Tsui, H.-C.; Johnston, J. N. *J. Org. Chem*. **1998**, *63*, 8491. (e) Magnus, P.; Booth, J.; Diorazio, L.; Donohoe, T.; Lynch, V.; Magnus, N.; Mendoza, J.; Pye, P.; Tarrant, J. *Tetrahedron* **1996**, *52*, 14103. (f) Appendino, G.; Fenoglio, I.; Vander Velde, D. G. *J. Nat. Prod*. **1997**, *60*, 464. (g) Magnus, P.; Ujjainwalla, F.; Westwood, N.; Lynch, V. *Tetrahedron* **1998**, *54*, 3069.

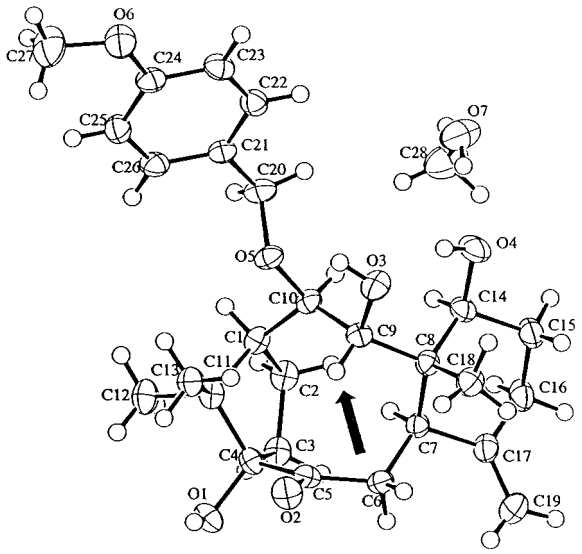
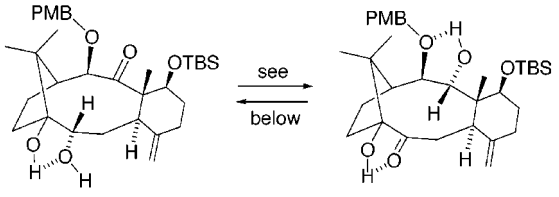


Figure 2. Molecular structure of **7**·CH_3OH in the solid state.

direction, demonstrate that interruption of the internal hydrogen bonding pattern by dissolution in a protic solvent favors **6**. To form **7** completely, one needs to simulate gas-phase conditions as much as possible in order to maximize the effects of intramolecular hydrogen bonding as recognized by the molecular mechanics software package. Evidently, benzene solvent serves well in this capacity. Since we have not been able to produce **6** totally free of **7**, the energetics do not appear to be completely reversed by external influences.

Regioselective silylation of **7** gives rise to **9** wherein one of the hydrogen bonding opportunities available to the progenitor triol is now deleted.[13] This feature is seen to narrow substantially the strain energy gap separating **8** and **9**. Scheme 2 summarizes the equilibration ratios determined

Scheme 2



8 E_s = 105.0 kcal/mol

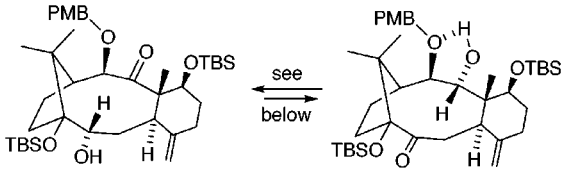
9 E_s = 101.0 kcal/mol

NaOH, MeOH, THF	100 : 0
KOMe, MeOH	12 : 1
KO*t*Bu, THF	9 : 1
KO*t*Bu, CH_2Cl_2	4 : 1
KO*t*Bu, C_6H_6	1 : 1

for the **8**/**9** isomeric pair at 20 °C. Our inability to detect the presence of **9** in the MeOH/THF experiments and the general tendency to minimize the proportion of **9** suggests a reduced connectivity between the stabilization derived from intramolecular hydrogen bonds and solvent effects. The more polar the medium, the more **8** is favored. This trend parallels that seen earlier in the **6**/**7** series, except that a greater displacement toward **8** is now operative.

The disilylated analogue **10** presents an equally striking distribution profile (Scheme 3). Despite an appreciable gas-

Scheme 3



10 E_s = 113.8 kcal/mol

11 E_s = 104.4 kcal/mol

NaOH, MeOH, THF	100 : 0
KOMe, MeOH	100 : 0
KO*t*Bu, THF	100 : 0
KO*t*Bu, CH_2Cl_2	100 : 0
KO*t*Bu, C_6H_6	100 : 0

phase bias favoring **11**, the formation of even low concentrations of this isomer has not been observed. These results, in combination with the behavior exhibited by isotaxanes **6**−**9**, suggests that hydrogen bonding along the northern rim of these molecules is more sensitive to solvent interruption relative to those control mechanisms at play along the leading edge. These differing sensitivities conform in degree and direction to the pharmacophore model most widely accepted for the ability of paclitaxel and related bioactive molecules to stabilize microtubules along their more accessible leading edge[14] (note also Figures 1 and 2).

Our results are entirely consistent with the basic notion of solvent competition with intramolecular hydrogen bonding. The effect is envisioned as a preempting of stabilizing internal interactions by solvents containing polar functional groups, particularly ones with a known capacity for strong coordination. Such a process may operate by several mechanisms, not only by making sites unavailable for internal substrate interactions. Alternatively, steric interactions probably develop as well by adding bulk to those sites most available for solvent interaction. It is possible that the preference of **10** over **11** in the range of media examined is directly attributable to increased congestion along the already crowded northern ridge of **11**.

The test reported herein has been designed to enable regiocontrol in proper structural contexts under suitable experimental conditions. Indeed, an important preparative method has been uncovered whose merits in the context of total synthesis will be illustrated in future reports.

(13) At ordinary temperatures, **9** is constituted of a mixture of two atropisomers in which the carbonyl group is projected in either an upward or downward direction.

(14) Ojima, I.; Chakravarty, S.; Inoue, T.; Lin, S.; He, L.; Horwitz, S. B.; Kuduk, S. D.; Danishefsky, S. J. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 4256.

Acknowledgment. This work is financially supported by a grant from the National Cancer Institute (CA-83830). J.E.H. is a trainee in the NIH Chemistry/Biology Interface Program. We are grateful for Dr. Judith Gallucci for the X-ray crystallographic analyses.

Supporting Information Available: Illustrative equilibration experimental conditions and X-ray crystallographic details for **6**·C_6H_6 and **7**·CH_3OH. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0100733