Pergamon

Tetrahedron Letters, Vol. 38, No. 46, pp. 7981-7984, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)10145-9

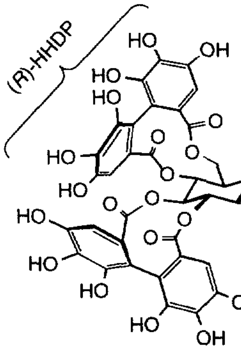
Probing Ellagitannin Stereochemistry: The Rotational Barrier of a Model (4,6)-Hexamethoxydiphenoyl Glucopyranoside.

Ken S. Feldman* and Kathryn A. Kirchgessner

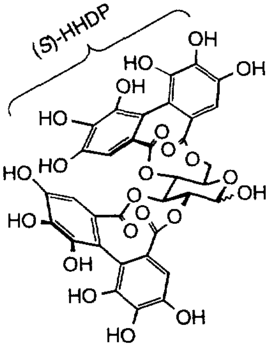
Department of Chemistry, The Pennsylvania State University, University Park, PA 16802

Abstract: Activation parameters for isomerization of the (*R*)- to the (*S*)-atropisomer in a (4,6)-HHDP ellagitannin model were calculated from rate vs. temperature data acquired through variable temperature ^{1}H NMR experiments. © 1997 Elsevier Science Ltd.

The ellagitannin family of secondary plant metabolites consists largely of galloylated glucose species which have suffered some type of oxidative phenolic coupling.[1] The galloyl esters are linked through both C-C and C-O connections in almost every conceivable combination and permutation of intra- and intermolecular couplings to furnish the 500+ structurally characterized members of this class of natural products. Despite this structural diversity, a large contingent of ellagitannins feature, in particular, a C-C coupled digalloyl unit (hexahydroxydiphenoyl, HHDP, cf. **1** and **2**) spanning positions 4 and 6 of the glucose core. This biaryl unit can exist as either the (*R*)- or the (*S*)-atropisomer, but the vast majority of the ellagitannins display the (*S*)-stereochemistry. Both molecular mechanics modeling and experimental results suggest that the (*S*)-configuration is the kinetically favored outcome of galloyl coupling as a consequence, perhaps, of the conformational preferences imparted by the glucopyranose ring on the appended C-4 and C-6 galloyl units.[2] Exceptions to this stereochemical generality exist. For example, platycaryanin D (**1**) bears (*R*)-HHDP groups at both the (4,6)- and (2,3)-positions, in contrast to its diastereomeric congener pedunculagin (**2**), which displays the more common (*S*)-stereochemistry at both sites.[3]



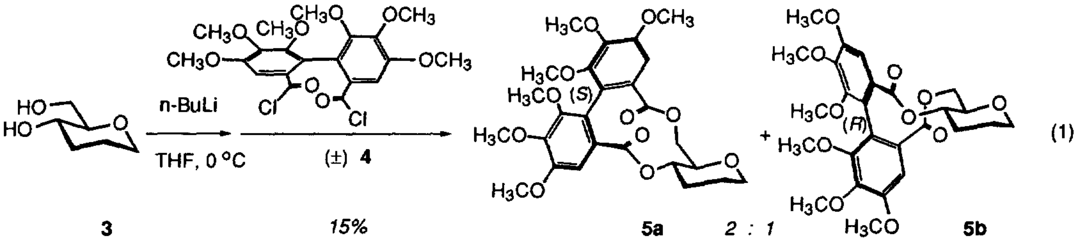
1



2

What, then, is the basis for formation of the rare (*R*)-atropisomer in vivo? A priori, three hypotheses can be formulated: 1) The natural conformational preferences of the oxidative cyclization precursor might be modified by enzymic action to favor the (*R*)-product upon C-C bond formation, 2) a preformed (*R*)-HHDP unit might be attached directly to a glucose 4,6-diol,[4] or 3) (enzymically mediated?) isomerization of a first-formed (*S*)-HHDP-containing ellagitannin might provide the (*R*)-atropisomer. This latter proposal is probed herein by 1) synthesis of both (4,6)-(*R*) and (*S*)-HHDP-containing model glucopyranosides, and 2) measurement of their rate of isomerization by variable temperature ^{1}H NMR spectroscopy to obtain activation parameters.

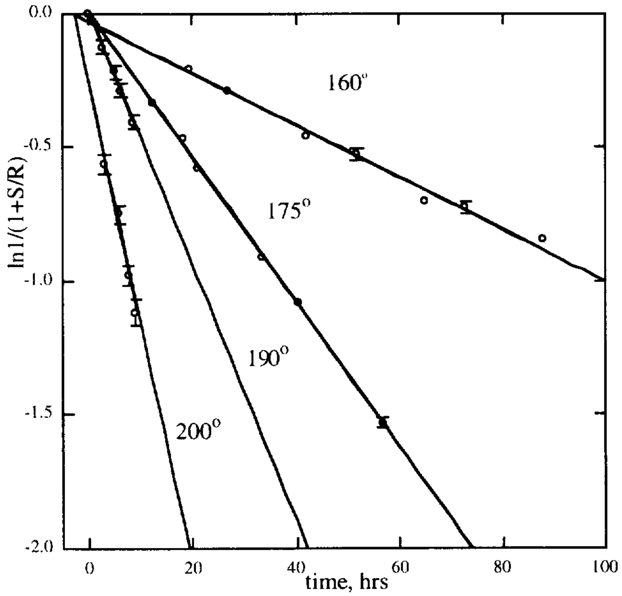
The preparation of (*S*)- and (*R*)-diastereomers **5a** and **5b**, respectively, takes advantage of Ito's recent report on the synthesis of permethylated pedunculagin via HHDP-Cl/glucose diol double esterification.[4] Thus, chiral glucose-derived diol **3**[2a] was combined with racemic bis acid chloride **4**[4] to furnish a modest yield of chromatographically separable diastereomeric HHDP-containing diesters **5a** and **5b** (Eq. 1). The stereochemical assignments of **5a/b** rested on comparison with literature data in the case of the known diester **5a**[2a] and CD measurements for both isomers.



Heating both diastereomers **5a** and **5b**, independently, in d_6-DMSO (150 °C) revealed that 1) clean interconversion occurred without any evidence for decomposition, and 2) atropisomer **5a** was strongly favored. Careful ^{1}H NMR analysis of the time course of **5a** evolution upon heating **5b** in d_5-nitrobenzene at different temperatures furnished the data shown in Fig. 1. Key signals for each isomer were cleanly resolved in this solvent and could be integrated to follow the isomerization. Again no decomposition accompanied isomerization, even at the higher temperatures, nor was there any deviation from first-order kinetics. Activation parameters were calculated via the Eyring equation.

A molecular mechanics study of this isomerization accurately reflected these data (Scheme 1).[5] The (*S*)-atropisomer **5a** was calculated to be ca. 2.2 kcal/mol less strained than the (*R*)-isomer **5b** in accord with the "complete" conversion of **5b** into **5a** upon prolonged heating. The calculated activation enthalpy (~ ΔSE) for rotation of the biaryl bond of **5b** into planarity in a hypothetical transition state **6** was within 12% of the experimental value.

Schmidt and Demmler measured the racemization rate for hexamethoxydiphenoate in aqueous base at 81 and 100 °C.[6] An Eyring treatment of these limited data revealed the following activation parameters for rotation about the aryl-aryl bond in this unconstrained permethylated HHDP diacid: $\Delta H^\ddagger$ = 24.2 kcal/mol, $\Delta S^\ddagger$ = -15.7 e.u., $\Delta G^\ddagger$ = 30.1 kcal/mol (100 °C). Thus, constraining the HHDP unit in an ellagitannin-like macrocycle raises the barrier for isomerization, and the primary effect appears to reside in the entropy term.



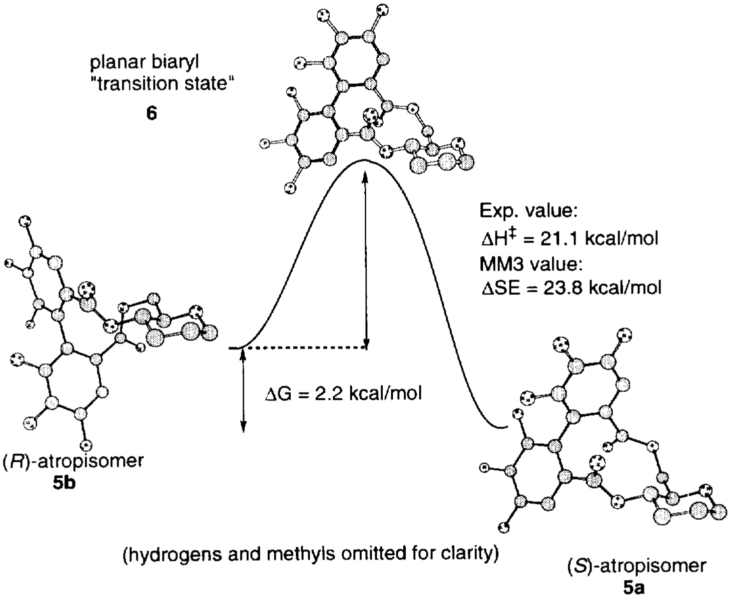
Eyring activation parameters for the conversion of **5b** into **5a** at 160 °C

$\Delta H^{\ddagger} = 21.1$ kcal/mol

$\Delta S^{\ddagger} = -36.6$ e.u.

$\Delta G^{\ddagger} = 36.6$ kcal/mol

Fig. 1. Rate data for the isomerization of **5b** into **5a.**



Scheme 1

The structural differences between model system **5a/b** and an authentic ellagitannin (e.g., **1** and **2**) suggest caution in extrapolating from these experimental activation energy values to processes that might occur during ellagitannin formation in vivo.[7,8] Nevertheless, it is difficult to reconcile the imposing barrier to permethoxy HHDP isomerization with an ellagitannin biosynthesis proposal featuring (*S*)- and (*R*)-HHDP interconversion under ambient conditions. Whether enzymic intervention could lower the barrier to (*R*)/(*S*)-HHDP interconversion remains a matter of speculation, as the role that enzymes play in influencing atropselectivity during HHDP formation, or even galloyl coupling in general, has yet to be unveiled.

Acknowledgment: We thank the NIH (GM35727) for financial support of this work.

REFERENCES

1. a) Quideau, S.; Feldman, K. S. *Chem. Rev.* **1996**, *96*, 475, and references cited therein. b. Okuda, T.; Yoshida, T.; Hatano, T. *Prog. Chem. Org. Nat. Prod.* **1995**, *66*, 1, and references cited therein.
2. a) Feldman, K. S.; Ensel. S, M. *J. Am. Chem. Soc.* **1994**, *116*, 3357. b) Feldman, K. S.; Ensel, S. M.; Minard, R. D. *J. Am. Chem. Soc.* **1994**, *116*, 1742. c) Feldman, K. S.; Sambandam, A. *J. Org. Chem.* **1995**, *60*, 8171. d) Feldman, K. S.; Smith, R. S. *J. Org. Chem.* **1996**, *61*, 2606.
3. Tanaka, T.; Kirihara, S.; Nonaka, G.; Nishioka, I. *Chem. Pharm. Bull.* **1993**, *41*, 1708.
4. a) Itoh, T.; Chika, J.; Shirakami, S.; Ito, H.; Yoshida, T.; Kubo, Y.; Uenishi, J. *J. Org. Chem.* **1996**, *61*, 3700. b) An alternative preparation of dimethyl hexamethoxydiphenoate, a key intermediate en route to **4**, proceeds via methylation of dimethyl HHDP (55%), whose synthesis is described in: Quideau, S.; Feldman, K. S. *J. Org. Chem.*, submitted.
5. Molecular mechanics calculations on **5a/b** and **6** were performed on a Silicon Graphics Power Indigo 2XZ computer equipped with version 5.5 of Macromodel (MM3* force field). A 1000-step conformational search utilizing a Monte Carlo algorithm was employed. Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.
6. Schmidt, O. T.; Demmler, K. *Liebigs Ann. Chem.* **1954**, *586*, 85.
7. Schmidt, O. T.; Demmler, K. *Liebigs Ann. Chem.* **1954**, *586*, 179. These authors report that a solution of chiral hexa*hydroxy*diphenic acid in CH_3OH looses its optical activity with a half-life of 281 min at 20 ^oC. The facile conversion of this compound into (achiral) ellagic acid clouds interpretation of this experiment.
8. The role that H-bonding might play in modulating this barrier in a native ellagitannin remains a matter of speculation. Wilcox and Adrian have shown, in a structurally unrelated system, that the presence or absence of H-bonding opportunities, in either $CDCl_3$ or CD_3OD, had little effect on the measured barrier for atropisomerization in a biaryl unit. Adrian, J. C., Jr.; Wilcox, C. S. *J. Am. Chem. Soc.* **1992**, *114*, 1398.

(Received in USA 24 *July* 1997; *accepted* 2 *September* 1997)