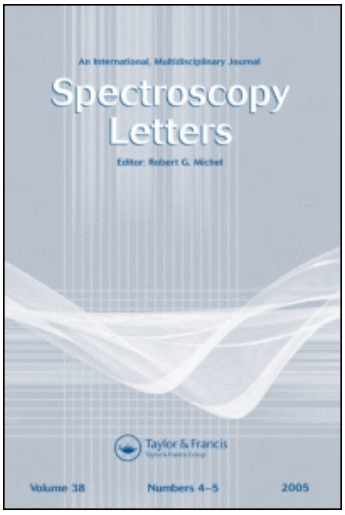

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NMR Investigation of Ring Conformation in Substituted Dihydronaphthalenes

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NMR INVESTIGATION OF RING CONFORMATION IN SUBSTITUTED DIHYDRONAPHTHALENES

Keywords: Substituted dihydronaphthalene, proton NMR, vicinal *J* coupling, Karplus equation, conformation analysis.

by

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ABSTRACT

Vicinal $^3J_{HH}$ couplings were investigated for a series of substituted dihydronaphthalenes allowing the conformation of the non-aromatic ring to be evaluated. It was found that the substitution of bromine for hydrogen increases the total puckering amplitude of the non-aromatic ring. Different formulations of the Karplus equation were investigated and the influence on the observed results are discussed.

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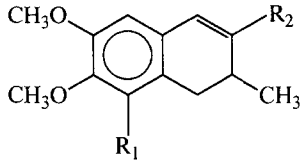
INTRODUCTION

Spectroscopic investigations of gossypol derivatives and related compounds continue to be of interest due to their wide range of biological activity. Previous ^{1}H and ^{13}C NMR studies of deoxyhemigossypol derivatives,[1] and the substituted dihydronaphthalene precursors[2] have shown variations in the internal dynamics and molecular conformation. For example, in the substituted dihydronaphthalenes large variations of the three bond vicinal J couplings ($^{3}J_{HH}$) in the non-aromatic ring have been observed following substitution of a hydrogen with bromine.[2] In this note variations of the $^{3}J_{HH}$ couplings and associated conformational changes for the substituted dihydronaphthalene compounds 1,2-dihydro-8-isopropyl-6,7-dimethoxy-2-methylnaphthalene **(1)**, 3-bromo-1,2-dihydro-8-isopropyl-6,7-dimethoxy-2-methyl-naphthalene **(2)**, 1,2-dihydro-6,7-dimethoxy-2,8-dimethylnaphthalene **(3)**, and 3-bromo-1,2-dihydro-6,7-dimethoxy-2,8-dimethylnaphthalene **(4)** are investigated.



(1) $R_1 = CH(CH_3)_2$, $R_2 = H$
(2) $R_1 = CH(CH_3)_2$, $R_2 = Br$
(3) $R_1 = CH_3$, $R_2 = H$
(4) $R_1 = CH_3$, $R_2 = Br$

EXPERIMENTAL

The synthesis of compounds **1-4** are described by Royer et al.[3] All ^{1}H NMR spectra were obtained at 250.1 MHz on a Bruker-AC using a 5 mm broadband probe. Spectra were recorded at 298 K using 5-10 mg of compounds **1-4** dissolved in 0.5 ml of $CDCl_3$ and referenced to the residual protio chloroform resonance ($\delta = 7.2$). NMR spectra were obtained using a 64 scan average, a recycle time of 2 s, 16K complex points and a spectral width of 3000 Hz. The data were transferred from the Bruker

Aspect 3000 computer to a PC using the software ZZNET.[4] Simulation of experimental spectra was performed using the spin simulation package in the software program NUTS (Acorn NMR) to obtain values for the geminal ($^2J_{HH}$), vicinal ($^3J_{HH}$) and other long range homonuclear couplings. Compounds **1** and **3** were simulated using a 7 spin system, while compounds **2** and **4** were calculated utilizing a 6 spin system. Complete ^1H and ^{13}C assignments for these compounds have been previously reported.[2] Molecular modeling simulations were performed using PCMODEL for windows (Serena Software, Indiana) operating on a 486 PC computer, using default MMX forcefields.[5]

THEORY

Since the introduction of the Karplus equation, vicinal *J* couplings have been used extensively to probe molecular conformation and structure in a variety of compounds.[6] It is commonly represented by

$$^3J_{HH}(\phi) = A\cos^2\phi + B\cos\phi + C \qquad (1)$$

where ϕ is the torsional angle between the coupled protons (See FIG. 1). It should be noted that numbering scheme utilized to describe the various angles is only concerned with those coupled protons in the non-aromatic ring of compounds **1-4**, and is different from the numbering used in naming the compounds. In the remaining sections of this paper proton number 1 will always be attached to the same carbon as the methyl substituent in the non-aromatic ring.

Investigations into the effects of substituents, bond angles and bond lengths have lead to continued refinement of the relationship between the vicinal coupling and the torsional angle. The effect of substituent electronegativities was addressed by Haasnoot and co-workers[7] and leads to the empirical generalization

$$^3J(\phi,\chi) = P_1\cos^2\phi + P_2\cos\phi + \sum_{i=1}^{4}\Delta\chi_i[P_4 + P_5\cos^2(\xi_i\cdot\phi + P_6|\Delta\chi_i|)] \qquad (2)$$

where P_i are parameters given in Table 2 of Haasnoot and co-workers,[7] ϕ is the torsional angle as shown in FIG. 1, $\Delta\chi_i$ is the electronegativity difference between the

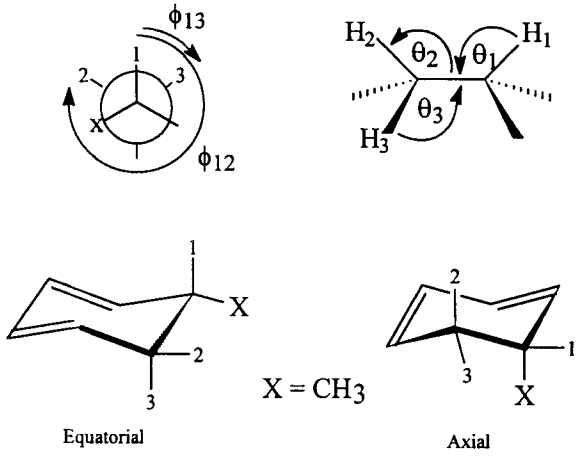


FIG. 1 Proton Numbering, Internal Angles and Conformations of Monosubstituted Ethane Fragments.

substituent on the ethane fragment and hydrogen, and ξ_i (± 1) determines the relative phase of the substituent *i* contribution.

This relationship has proven quite successful in the analysis of vicinal couplings, and is the formalism incorporated into the molecular modeling program PCMODEL.[5] The influence of electronegative substituents not directly bonded to the ethane fragment (the β position) can be approximated by modifying the effect of the electronegative behavior of the primary substituents (α position) as described by Haasnoot et. al [7] using

$$\Delta\chi^{group} = \Delta\chi^{\alpha} - P_7 \sum \Delta\chi_i^{\beta} \qquad (3)$$

where the eletronegativity of the substituents are described by $\Delta\chi^{group}$ and replace the electronegativity effects of the α substituent, $\Delta\chi_i$ in Eq. 2.

In contrast to the effect of substituent electronegativity, the influence of the internal C-C-H bond angle or the C-C bond length is expected to have smaller contributions on the observed couplings. The effect of the C-C-H bond angle on the vicinal coupling has been investigated.[8,9] These studies show that for torsional angles

(ϕ) greater or less than 90°, the value of the internal C-C-H bond angle plays an important role in the magnitude of the observed vicinal coupling. Expressions for the coupling are given by[8]

$$^3J(\theta_i,\theta_j,\phi_{ij}) = 33.8a(\theta_i,\theta_j)\cos^2\phi_{ij} + [-1258.4b_1(\theta_i,\theta_j) - 650.5b_2(\theta_i,\theta_j) - 905.3b_3(\theta_i,\theta_j)]\cos\phi_{ij} - 0.3 \text{ Hz} \quad (4)$$

where θ_i and θ_j denote the internal C-C-$H_{i,j}$ bond angles and ϕ_{ij} the torsion angle as defined in FIG. 1. The coefficients have been discussed and are defined by [8]

$$a(\theta_i,\theta_j) = (1 + \cos\theta_i)(1 + \cos\theta_j) \quad (5)$$

$$b_1(\theta_i,\theta_j) = \cot(\theta_i/2)\cot(\theta_j/2)\cos\theta_i\cos\theta_j$$

$$b_2(\theta_i,\theta_j) = \cot(\theta_i/2)\cot(\theta_j/2)(\cos\theta_i\cos\theta_j)^{1/2}$$

$$b_3(\theta_i,\theta_j) = \cot(\theta_i/2)\cot(\theta_j/2)[\cos\theta_j(-\cos\theta_i)^{1/2} + \cos\theta_i(-\cos\theta_j)^{1/2}]$$

To describe the solution conformation of the non-aromatic ring the Truncated Fourier (TF) formalism of Haasnoot was utilized.[10,11] Determination of the endocyclic torsional angles ϕ^l ($l = 0,1,...5$) in the six membered ring allows the puckering coordinates (Φ_2, P_2, Φ_3) to be evaluated. The experimental vicinal torsional angle is related to the corresponding endocyclic torsion by

$$\phi_{ij}^l = a + \phi^l \quad (6)$$

where the constant a is 0° and ±118° for cis and trans protons respectively. The various endocyclic angles of the non-aromatic ring (ϕ^l) can be related to the puckering coordinates by[10,11]

$$\phi^l = \Phi_2\cos(P_2 + 4\pi l/6) + \Phi_3\cos(\pi l) \quad (7)$$

These coordinates can also be rewritten using a spherical polar representation (P_2, Θ, Q) where

$$Q = \sqrt{\Phi_2^2 + \Phi_3^2} \quad (8)$$

and

$$\Theta = \arctan(\Phi_2 / \Phi_3) \quad (9)$$

In this representation the total puckering amplitude is given by Q, and Θ ranges from 0 to π.

RESULTS AND DISCUSSION

Investigation of the vicinal coupling provides information regarding the conformational variation of the non-aromatic ring due to the substitution of bromine for a hydrogen. The experimental geminal and vicinal couplings of the isopropyl substituted dihydronaphthalenes **1** and **2** are given in Table 1, and for the methyl substituted dihydronaphthalenes **3** and **4**, Table 2. It is easily seen that the substitution of a methyl for an isopropyl group on the aromatic ring produces little or no variation in the observed vicinal couplings or conformation of the non-aromatic ring. From dynamic investigations[1,12] interactions of the isopropyl group with adjacent methoxy and non-aromatic ring atoms produced exchange modified line shapes with variation in temperature. The present study suggests that the interaction between the isopropyl group and the methylene protons is insufficient to influence the final conformational state of the non-aromatic ring, or that the methyl and the isopropyl group have an almost identical influence. In contrast, the substitution of bromine for hydrogen in the non-aromatic ring produces large changes in the observed vicinal coupling constants. This can be seen by comparing the experimental values found for compounds **1** and **2** in Table 1 or compounds **3** and **4** in Table 2. For example the $^3J_{HH}(1,3)$ coupling changes from approximately 11.2 Hz to 6.9 Hz with substitution of bromine in both the isopropyl and methyl dihydronaphthalenes.

As a first step to analyze the variation in the vicinal coupling of these compounds, the minimized structures for **1-4** were obtained with the molecular mechanics modeling program PCMODEL and default MMX forcefields. Two local minima were observed for each compound corresponding approximately to an *axial* or an *equatorial* conformation of the methyl substituent ($X = CH_3$) in the non-aromatic ring. The predicted vicinal couplings, torsional angles ϕ_{12} and ϕ_{13} and corresponding MMX energies for these PCMODEL minimized structures are given in Tables 1 and 2.

TABLE 1: Selected Bond and Torsional Angles Plus Experimental and Modeled Coupling Constants for the Isopropyl Substituted Dihydronaphthalenes **1** and **2**.[a]

	Compound (1)			Compound (2)		
	Exp.	Ax.	Eq.	Exp.	Ax.	Eq.
ϕ_{12}		50.9	58.2		50.5	55.7
ϕ_{13}		295.2	174.5		296.3	171.6
θ_1		108.1	109.5		106.7	109.8
θ_2		109.5	106.5		108.9	106.9
θ_3		106.7	109.5		108.4	109.0
MMX Energy (kcal mol^{-1})		28.0	28.6		30.4	32.3
$^2J_{HH}$(2,3) Hz	-15.6			-15.7		
$^3J_{HH}$(1,2) Hz	6.8	4.4	3.2	4.7	4.4	3.6
$^3J_{HH}$(1,3) Hz	11.2	2.3	12.2	6.9	2.5	12.1

TABLE 2: Selected Bond and Torsional Angles Plus Experimental and Modeled Coupling Constants for the Methyl Substituted Dihydronaphthalenes **3** and **4**.[a]

	Compound (3)			Compound (4)		
	Exp.	Ax.	Eq.	Exp.	Ax.	Eq.
ϕ_{12}		49.2	55.3		48.4	51.7
ϕ_{13}		292.6	172.3		292.0	168.5
θ_1		108.0	109.2		106.5	109.5
θ_2		109.8	107.8		109.6	107.9
θ_3		108.2	109.9		108.3	109.5
MMX Energy (kcal mol^{-1})		22.4	22.3		24.3	25.9
$^2J_{HH}$(2,3) Hz	-15.6			-15.7		
$^3J_{HH}$(1,2) Hz	6.6	4.6	3.7	4.8	4.8	4.5
$^3J_{HH}$(1,3) Hz	11.3	2.0	12.1	6.9	2.0	11.9

[a] Exp. = experimental, Ax. = Axial, Eq. = Equatorial, modeled using Eq. 2 and the parameters P_i from Ref. 7.

(By definition proton 1 is always the proton attached to the same carbon as the methyl group substituent in the non-aromatic ring. See FIG. 1). The axial and equatorial conformations have similar predicted energies, with the axial conformation having the lowest energy except in **3** where the equatorial conformation is predicted to be the most stable. In Table 3 the predicted coupling constants and the sum of deviations, ΔJ_{HH}, for different Karplus representations are presented. For compounds **1** and **3** the large $^3J_{HH}(1,3)$ couplings observed are similar to that predicted for an axial-axial coupling in the equatorial ring conformation. The lowest sum of deviations, ΔJ_{HH}, is seen for the equatorial conformation in **1** and **3**. As noted above, the equatorial conformation is opposite of the predicted minimum in compound **1**. In compounds **2** and **4** the axial conformation gives the lowest sum of deviations, ΔJ_{HH}, and corresponds to the predicted conformational minimum. Overall the agreement between the experimental and observed vicinal couplings is weak for compounds **1-4**.

To address the influence of the model on the predicted vicinal couplings, the minimized structures for **1-4** were used to estimate the coupling constants for the three different generalized Karplus equations described by Eqs.1-6 in the theory section as shown in Table 3. The vicinal coupling values predicted modeling the effects of substituent electronegativities (Eq. 2) are the same as given by PCMODEL and were discussed above. Incorporation of β substituent effects (Eqs. 2-3) did not improve the observed deviation, ΔJ_{HH}, for compounds **1-4**. In **1** and **3** the minimum deviation was for the equatorial conformation, while in **2** and **4** the axial conformation predicted the smallest deviation. For compounds **1-4**, predictions of the vicinal coupling based on the influence of the C-C-H bond angle (Eqs. 4-5) gave the largest deviation from experimental values. This may reflect inconsistencies in the structures obtained from PCMODEL instead of weaknesses in the derived coupling dependence. For all three generalized Karplus equations, the observed J coupling in these compounds could be the average of the two predicted conformations as a result of molecular fluctuations in the non-aromatic ring. Inspection of Table 3 shows that this is not the case, since it is impossible to average the predicted *axial* and *equatorial* couplings to produce both of the observed J coupling constants.

Using the Karplus relations in Eqs.1-5 torsional angles could similarly be calculated from the observed coupling constants. These results are shown in Table 4

TABLE 3: Experimental and Modeled Vicinal Coupling Constants Using Different Generalized Karplus Relations.[a]

	(1)		(2)		(3)		(4)	
	Ax.	Eq.	Ax.	Eq.	Ax.	Eq.	Ax.	Eq.
$^3J_{HH}^{exp}(1,2)$ Hz	6.8 ± 0.2		4.7 ± 0.2		6.6 ± 0.2		4.8 ± 0.2	
$^3J_{HH}^{exp}(1,3)$ Hz	11.2 ± 0.2		6.9 ± 0.2		11.3 ± 0.2		6.9 ± 0.2	
$^3J_{HH}(1,2)$ Hz [b]	4.4	3.2	4.4	3.6	4.6	3.7	4.8	4.2
$^3J_{HH}(1,3)$ Hz [b]	2.3	12.2	2.5	12.1	2.0	12.1	2.0	11.9
ΔJ_{HH} [c]	11.3	4.6	4.7	6.4	11.2	3.8	4.9	5.5
$^3J_{HH}(1,2)$ Hz [d]	4.5	3.2	4.5	3.6	4.8	3.7	4.9	4.3
$^3J_{HH}(1,3)$ Hz [d]	2.3	12.4	2.4	12.4	1.9	12.3	1.8	12.2
ΔJ_{HH} [c]	11.3	6.0	4.6	6.7	11.2	3.9	5.2	5.8
$^3J_{HH}(1,2)$ Hz [e]	2.9	1.4	2.8	1.4	3.3	2.0	3.3	2.8
$^3J_{HH}(1,3)$ Hz [e]	0.2	18.6	0.4	18.6	0.0	18.4	-0.2	18.1
ΔJ_{HH} [c]	14.8	12.9	8.4	15.0	14.5	11.7	8.5	13.3

[a] Ax. = Axial, Eq. = Equatorial.
[b] Evaluated using Eq. 2 and the parameters P_i from Ref. 7.
[c] $\Delta J_{HH} = \sum_{i=2}^{3} |^3J_{HH}(1,i) - {}^3J_{HH}(1,i)^{Exp.}|$
[d] Evaluated using Eqs. 2 and 3.
[e] Evaluated using Eqs. 4 and 5.

TABLE 4: Modeled Torsional Angles Using Different Generalized Karplus Equations.

	(1)	(2)	(3)	(4)
ϕ_{12} [a]	36.3	122.8	37.5	123.4
ϕ_{13} [a]	161.7	224.2	162.6	224.2
$\Delta\phi$ [b]	125.1	101.4	125.1	100.8
ϕ_{12} [c]	38.6	124.4	39.6	124.9
ϕ_{13} [c]	159.2	224.3	160.0	224.3
$\Delta\phi$ [b]	120.6	99.9	120.4	99.4
ϕ_{12} [d]	33.1	117.2	34.1	117.5
ϕ_{13} [d]	138.5	235.3	138.9	235.3
$\Delta\phi$ [b]	105.4	118.1	104.8	117.8

[a] Evaluated using Eq. 2 and the parameters P_i from Ref. 7.
[b] $\Delta\phi = \phi_{13} - \phi_{12}$.
[c] Evaluated using Eqs. 2 and 3.
[d] Evaluated using Eqs. 4 and 5.

for the different generalized models. There are typically multiple solutions for the torsional angles ϕ_{1j}, except for the large $^3J_{HH}(1,3)$ of approximately 11.2 Hz, where only one solution exists. To select between the various solutions, the pair of ϕ_{12} and ϕ_{13} that gave a $\Delta\phi$ closest to the predicted tetrahedron projection angle of 118° were reported in Table 4. The two models based on electronegativity effects gave very similar conformations, with compounds **2** and **4** showing the largest deviation in $\Delta\phi$. This is in contrast to predictions based on the influence of the C-C-H bond angle (assuming $\theta_{12} = \theta_{13} = 109.5°$) where compounds **1** and **3** show the largest deviation in $\Delta\phi$. As discussed previously, the observed couplings may also represent the time average couplings of different conformations and their relative weights. Due to the paucity of experimental values this possibility was not pursued, and only a single conformation was assumed to determine the observed coupling constants. Regardless of the model chosen it is clear that there is a variation in conformation with the substitution of bromine for hydrogen in the non-aromatic ring.

If the torsional angles ϕ_{12} and ϕ_{13} predicted using Eqs. 4-5 are used to obtain an average endocyclic angle ϕ' as defined in Eq. 6, the puckering coordinates (Φ_2, P_2, Φ_3) can be obtained by evaluation of Eq. 7. The endocyclic torsion angle determined from the observed coupling constants will be defined as ϕ^0. Two other endocyclic torsional angles in the six membered ring can be deduced directly from the chemical structure since they encompass double or aromatic bonds ($\phi' = 0$). These will be defined as ϕ^2 and ϕ^4. For compound **1** the ring conformation is characterized by $P_2 = 0$, $\Theta = 63.4°$, and $Q = 20°$. This corresponds to a $^1S_6$ screw-boat or a 1,3 diplanar conformation.[10,11] Analysis of compound **3** provides a similar $^1S_6$ conformation with $P_2 = 0$, $\Theta = 63.4°$, and $Q = 20.5°$. Analysis of the torsional angles in compounds **2** and **4** also gives a $^1S_6$ screw-boat conformation with $P_2 = 0$, $\Theta = 63.4°$, and $Q = 87.4°$.

CONCLUSIONS

In this study the effects of substituting a bromine for a hydrogen in the dihydronaphthalenes **1-4** were addressed. The form of the generalized Karplus equation employed was shown to have only a small effect. While there is a large change in the observed vicinal couplings with bromine substitution, a $^1S_6$ conformation is observed for all compounds. This is not surprising since the screw-boat or 1,3 diplanar

conformation is imposed on the non-aromatic ring as a result of the aromatic and double bonds in **1-4**. The substitution of bromine for a hydrogen does produce a change in the total puckering amplitude from 20° to 87° .

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REFERENCES

1. Alam, T. M., Rosay, M., Deck, L. and Royer, R. Complete Assignment of the ^{1}H and ^{13}C NMR Spectra of Deoxyhemigossypol Derivatives, Magn. Reson. in Chem. 1994; 32: 561.

2. Alam, T. M., Liu, M.-E., Garcia, D. K., Hernandez, V., Malone, R. R., Bennett, D. E., Deck, L. M. and Royer, R. E. Investigation of Substituted Dihydronaphthalenes Using ^{1}H and ^{13}C NMR Spectroscopy, Magn. Reson. in Chem. 1995; (In Press):

3. Royer, R. E., Deck, L. M., Vander Jagt, T. J., Martinez, F. J., Mills, R. G., Young, S. A. and Vander Jagt, D. L. Synthesis and Anti-HIV Activity of 1,1'-Bisdeoxygossypol and Related Compounds, J. Medicinal Chem. 1995; (In press).

4. Zolnai, Z., Westler, W. M., Ulrich, E. L. and Markley, J. L. Drafting Table and Light-Box Software for Multidimensional NMR Spectral Analysis (PIXI). The Personal Computer Workstation, J. Magn. Reson. 1990; 88: 511.

5. Gajewski, J. J., Gilbert, K. E. and McKelvey, J. MMX an Enhanced Version of MM2, Advances in Molecular Modeling 1990; 2: 65.

6. Karplus, M. Contact Electron-Spin Coupling of Nuclear Magnetic Moments, J. Chem. Phys. 1959; 30: 11.

7. Haasnoot, C. A. G., De Leeuw, F. A. A. M. and Altona, C. The Relationship Between Proton-Proton NMR Coupling Constants and Substituent Electronegativities-I, Terahedron 1980; 36: 2783.

8. Barfield, M. and Smith, W. B. Internal H-C-C Angle Dependence of Vicinal ^{1}H-^{1}H Coupling Constants, J. Am. Chem. Soc. 1992; 114: 1574.

9. Smith, W. B. and Barfield, M. Predictions of $^{3}J(HH)$ Near 180° - Reparameterization of the sp^3-sp^3 Equation, Magn. Reson. in Chem. 1993; 31: 696.

10. Haasnoot, C. A. G. The Conformation of Six-Membered Rings Described by Puckering Coordinates Derived From Endocyclic Torsion Angles, J. Am. Chem. Soc. 1992; 114: 882.

11. Haasnoot, C. A. G. Conformational Analysis of Six-Membered Rings in Solution: Ring Puckering Coordinates Derived from Vicinal NMR Proton-Proton Coupling Constants, J. Am. Chem. Soc. 1993; 115: 1460.

12. Alam, T. M., Rosay, M., Deck, L. M. and Royer, R. E. A Dynamic ^{1}H NMR Investigation of the Isopropyl Rotational Barrier in Substituted Hemigossypol Derivatives, (In Preparation).

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