where

$$Q \equiv 1 - 2\beta(\beta + 1)k^2\sum_i f_i + (\beta^2 - 1)k^2R$$

$$W = \beta k\sum_i 2\pi(\nu - \nu_i)f_i + (\beta^2 - 1)k^2S$$

$$R = 4(\beta + 1)^2k^2\sum_{i=\mathrm{a,b}} f_i \sum_{i=\mathrm{c',c''}} f_i - \sum_{i=\mathrm{a,b}} 2\pi(\nu-\nu_i)f_i\sum_{i=\mathrm{c',c''}} 2\pi(\nu - \nu_i)f_i$$

$$S = -2(\beta + 1)k\Big[\sum_{i=\mathrm{a,b}} f_i\sum_{i=\mathrm{c',c''}} 2\pi(\nu - \nu_i)f_i + \sum_{i=\mathrm{c',c''}} f_i\sum_{i=\mathrm{a,b}} 2\pi(\nu - \nu_i)f_i\Big]$$

$$f_i = [4(\beta + 1)^2k^2 + (2\pi)^2(\nu - \nu_i)^2]^{-1}$$

$$k = k_1 + k_2$$

$$\beta = (k_2 + k_3)/(k_1 + k_2)$$

and ν_i is the resonant frequency (hertz) for site i = a, b, c′, c″.

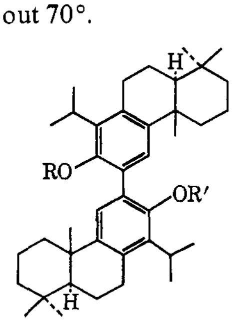
A Nuclear Magnetic Resonance Study of Hindered Rotation in Biphenyls. Podototarin Diacetate and Podototarin Dimethyl Ether[1]

L. D. Colebrook and J. A. Jahnke[2]

Contribution from the Department of Chemistry, University of Rochester, Rochester, New York 14627. *Received December 28, 1967*

Abstract: Activation energies and other kinetic data have been obtained for rotation of the hindered biphenyl system in podototarin diacetate (I, R = R′ = Ac) and podototarin dimethyl ether (I, R = R′ = CH_3). Asymmetry inherent in these molecules results in the rotational conformers being diastereomeric. Rotational rate constants at various temperatures have been determined from line-shape analysis of the superimposed, nonidentical, nmr spectra of the conformers, using an iterative nonlinear least-squares computer program. The activation energies for biphenyl rotation determined from these rate constants are lower than can be measured by the racemization method.

Podototarin[3,4] (I, R = R′ = H) is a naturally occurring biphenyl obtained from the New Zealand species *Podocarpus totara* G. Benn. The identity of the stereochemistry of the two halves of the molecule has been established by synthesis.[4] Since the biphenyl system carries substituents in the *ortho* and *ortho′* positions, it is to be expected that the molecule will prefer conformations in which the dihedral angle between the two aromatic rings is large. That this is the case is shown by the ultraviolet and nmr spectra of podototarin.[3,4] It has been estimated earlier[3,4] from chemical shift data that the preferred dihedral angle of podototarin is about 70°.



I

Because each half of the molecule is intrinsically asymmetric, the two major conformers resulting from rotation about the central bond of the biphenyl system are not identical. Instead, they are diastereomers. In order to visualize the difference between these conformers it is convenient to use the approximation that the aromatic rings are at right angles to each other. A simplified representation of the two isomers in this conformation is shown in Newman projection in Figure 1. The substituents in which we are interested are represented by "X" and the asymmetric portions of the molecules by the triangles. Form A is converted to form B by rotating the front half of the molecule through 180°. The difference in the environments of the "X" groups in forms A and B is clear from these diagrams. Within each conformer the environments of the two "X" groups are indistinguishable. There are two possible transition states in which the biphenyl system is planar, but only the less energetic of these is likely to make a significant contribution to the interconversion process. This transition state can be approximately represented by I.

If these diasteriomeric conformers have long enough lifetimes on the nmr time scale, we may expect that the nmr spectrum will show the superimposed (nonidentical) spectra of the two species. Further, the spectrum should be temperature dependent, collapsing to a single time-averaged spectrum as the temperature is raised and the lifetimes of the conformers are reduced.

At normal temperatures (about 40°) the 60-MHz spectrum of podototarin itself shows no unusual fea-

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[1] This work was supported by Grant No. GM-12468 from the National Institutes of Health, U. S. Public Health Service.

[2] National Science Foundation Summer Research Participant, 1964.

[3] R. C. Cambie, W. R. J. Simpson, and L. D. Colebrook, *Chem. Ind.* (London), 1757 (1962).

[4] R. C. Cambie, W. R. J. Simpson, and L. D. Colebrook, *Tetrahedron*, **19**, 209 (1963).

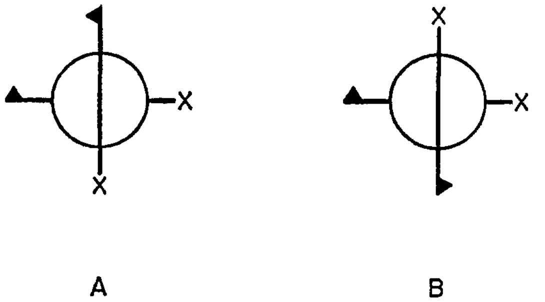

Figure 1. Simplified representation (Newman projection) of the podototarin derivatives, showing the difference in the environments of the X substituents in the two conformers. The triangles represent the asymmetric portions of the molecules.

tures, but that of the diacetate (I, R = R′ = Ac) shows that two species, with slightly different spectra, are present in unequal concentrations. The acetyl methyl protons, in particular, give rise to two overlapping, temperature-dependent peaks, with an intensity ratio of about 1.6:1, centered at δ 1.80 (ppm from internal TMS). These peaks collapse to a single peak when the sample is heated to about 75°. Podototarin dimethyl ether (I, R = R′ = CH_3) shows a time-averaged spectrum at normal temperatures, but when the sample is cooled below about −5° two superimposed spectra appear. Two peaks of unequal intensity (about 1.1:1) arising from the methoxyl methyl protons and centered at δ 3.28 form a prominent feature of the low-temperature spectrum. Podototarin monoacetate (I, R = H; R′ = Ac) shows a similar spectrum, the acetyl methyl groups of the two conformers giving rise to two peaks at normal temperatures. A description of this spectrum has been given elsewhere.[5]

Evidently the acetoxy and methoxy groups are sufficiently bulky to restrict rotation about the central bond of the biphenyl system, presumably with some assistance from the buttressing effect of the isopropyl groups. Since the two conformers are neither identical nor mirror images their energies are different, resulting in unequal populations of the two conformational states. This shows up as a significant difference in the intensities of the superimposed spectra below the coalescence temperature.

Restricted rotation in *ortho*-substituted biphenyls has been extensively studied by following the racemization of optically active compounds.[6,7] In order that these enantiomers have sufficiently long lifetimes at normal temperatures to be studied by this method it is necessary that the energy barrier to rotation be not less than about 20 kcal/mol.[7]

Less stable conformers have been isolated and studied by working at lower temperatures. Optically active 2,2′-dimethylbiphenyl, for which an Arrhenius activation energy of 15.1 kcal/mol is reported, has been prepared and the kinetics of racemization measured at temperatures between −30 and −36°.[8]

Nmr techniques have been used to investigate conformational changes in various types of molecules.[9] The energy barriers to conformational change which can be evaluated by nmr are usually much lower than 20 kcal/mol, so the newer method offers the possibility of obtaining information which was not readily available earlier. Nmr methods are not directly applicable to biphenyls in which the conformational changes involve interconversion of enantiomers unless the molecules contain groupings whose spectra are affected by the dissymmetry which is present. Meyer and Meyer[10] were able to evaluate the energy barrier (13 kcal/mol) to rotation in *dl*-2,2′-bis(acetoxymethyl)-biphenyl by an nmr method through the use of the methylene groups as "probes" to sense the dissymmetry. If further dissymmetry is present, so that the rotational isomers are no longer enantiomers, the nmr method may be applied. In the case of the two podototarin derivatives described in this paper the necessary additional dissymmetry is provided by the asymmetric centers in the two halves of the molecules. In principle, the isopropyl substituents in these two compounds could be used as the "probes" to sense the dissymmetry, since the methyl groups should be nonequivalent at low temperatures, independently of the influence of the asymmetric centers. However, the isopropyl methyl lines are largely masked by lines from other methyl groups and so are unsuitable for this purpose.

Estimation of Energy Barriers

The rate constants, k_A and k_B, for the interconversion of the two conformers, A and B, are related to the mean lifetimes, τ_A and τ_B, as $k_A = 1/\tau_A$ and $k_B = 1/\tau_B$. τ_A and τ_B were determined over a range of temperatures from the shapes of the lines arising from the acetyl methyl and methoxyl methyl protons of podototarin diacetate and podototarin dimethyl ether, respectively. Other lines in the spectra, such as those arising from the aromatic protons, were too closely spaced to be suitable for this purpose. These line shapes, as a function of the conformer lifetimes, can be predicted by using the general line-shape equation of Gutowsky and Holm[11] for exchange between two unequally populated sites. The intensity of absorption, $g(\nu)$, at a point ν (in units of hertz) in the spectrum may be calculated in terms of six parameters: ν_A and ν_B, the chemical shifts (in hertz) in the absence of exchange of protons on the A and B sites; τ_A and τ_B, the mean lifetimes of protons on the A and B sites; T_2, a measure of the natural line width; and K, a scaling factor. This line-shape equation is applicable only when spin–spin coupling to the nuclei undergoing exchange is absent or negligibly small, as is the case in the present examples.

The complexity of the calculations is reduced if the two sites are equally populated (hence $\tau_A = \tau_B$) and if the natural line width is small compared to the exchange-broadened line width (when it can be assumed that $1/T_2 = 0$). Methods have been developed for the analysis of experimentally determined spectra to which these restrictions apply, and a number of examples appear in the literature.[9] Applications to systems in-

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(5) C. R. Bennett and R. C. Cambie, *Phytochemistry*, **6**, 883 (1967).

(6) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp 156–165.

(7) F. H. Westheimer in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, pp 543–554.

(8) W. Theilacker and H. Bohm, *Angew. Chem. Intern. Ed. Engl.*, **6**, 251 (1967).

(9) C. S. Johnson, Jr., *Advan. Magnetic Resonance*, **1**, 33 (1965).

(10) W. L. Meyer and R. B. Meyer, *J. Am. Chem. Soc.*, **85**, 2170 (1963).

(11) H. S. Gutowsky and C. H. Holm, *J. Chem. Phys.*, **25**, 1228 (1956).

volving exchange between unequally populated sites have been reported, and an approach to this more complicated problem has been described in detail.[12] In the present case no simplifying assumptions could be applied, so it proved necessary to use the complete Gutowsky and Holm equation and to find a suitable method of analysis.

It is usually possible to determine ν_A and ν_B, the chemical shifts in the absence of exchange, by cooling the sample to a temperature below which the line positions have become independent of temperature and taking these positions as ν_A and ν_B. This method involves the assumption that ν_A and ν_B are themselves independent of temperature. Attempted measurement of ν_A and ν_B by this means in the present case yielded figures which appeared unreliable, as there was evidence for an additional temperature-dependent process involving the methyl protons. In the absence of a direct method for the evaluation of ν_A and ν_B they were treated as parameters in the computer procedure described below and found in the same manner as τ_A and τ_B.

The five parameters, τ_A, τ_B, ν_A, ν_B, and K, were evaluated at each temperature by least-squares analysis of the complete experimental line shape. In a recent critical evaluation of various approximation approaches to the estimation of conformer lifetimes the desirability of this type of curve-fitting procedure has been pointed out.[13] A FORTRAN version of the complete Gutowsky and Holm equation was combined with a nonlinear least-squares regression computer program,[14] calculations being carried out with an IBM 7074 computer used in conjunction with a Calcomp digital plotter. The computer fitted the theoretical to the experimental spectrum in each case by varying the magnitudes of the five parameters until no further improvement could be obtained. The remaining parameter, T_2, was estimated from measured line widths. Experimental conditions were chosen so that exchange broadening was absent or minimal. Uncertainty in the determination of T_2 is a source of some of the error in the calculated values of τ_A and τ_B, particularly at lower temperatures when exchange broadening makes a relatively small contribution to the total line width.

Experimental Section

Solutions of podototarin diacetate and of podototarin dimethyl ether in deuteriochloroform with tetramethylsilane as an internal reference were sealed in 5-mm sample tubes. Spectra were determined using a Varian A-60 spectrometer equipped with a variable-temperature probe. Temperatures were measured by the use of standard Varian ethylene glycol and methanol reference samples which had previously been calibrated against a thermocouple in an HR-60 nmr spectrometer. Immediately before each spectrum was recorded the temperature was measured using the temperature reference sample, care being taken to ensure that the equipment had reached thermal equilibrium before proceeding.

The ν-$g(\nu)$ data pairs (position and intensity, respectively), required by the computer program were measured at 0.2- to 0.5-Hz intervals on the recorded spectrum and punched on computer cards. From 36 to 49 data pairs were taken from a podototarin diacetate spectrum, and 49 data pairs from a podototarin dimethyl ether spectrum. Since the absorption of interest in the spectra of both compounds was superimposed on weak, broad absorption arising from ring protons it was necessary to make base-line corrections in each case. As the accuracy of these corrections was difficult to determine this procedure was a source of error, particularly in the case of podototarin diacetate.

By first calculating a number of spectra with varying values of the parameters and visually comparing theoretical and experimental spectra, it was possible to make reasonable guesses at the values of the parameters to be used for the initial calculation. The computer then carried out a least-squares analysis at up to 49 points on the curves and proceeded to vary the magnitudes of the parameters until the best fit between theoretical and experimental spectra was obtained. Satisfactory convergence was achieved in all cases.

Results and Discussion

A valuable feature of this method of calculation is that no assumptions (apart from the initial guesses for the trial spectra) need be made on the magnitudes of ν_A and ν_B. The quantity $\Delta\nu = \nu_A - \nu_B$ appears in the Gutowsky and Holm equation. Since $\Delta\nu$ is the chemical shift between protons on the A and B sites in the absence of exchange it must remain constant, *i.e.*, for a particular compound every set of calculations must produce the same value of $\Delta\nu$, provided, of course, that $\Delta\nu$ really is independent of temperature over the range employed. Possible errors resulting from the use of values of $\Delta\nu$ taken outside the temperature range of the experiments are eliminated when this approach is used.

The mean values of the chemical shift obtained in this way were $\Delta\nu = 4.6$ Hz for podototarin diacetate and $\Delta\nu = 5.5$ Hz for podototarin dimethyl ether. These shifts were independent of temperature over the ranges covered.

Data derived from spectra measured over the range 319.0 to 346.5°K for podototarin diacetate and 248.0 to 261.8°K for podototarin dimethyl ether were used in determining the activation energies. The upper temperature limit in each case was near the coalescence point. At higher temperatures the error in curve fitting became excessively large. Uncertainty in the estimation of T_2 imposes a lower temperature limit. It is necessary to restrict analysis to spectra which show appreciable exchange broadening in order that errors in T_2 will not contribute significantly to the calculated values of τ. Least-squares Arrhenius analysis yielded the values for the activation energy, E_a, shown in Table I.[15] There are two activation energies for each compound, corresponding to promotion from the two energy minima to the common transition-state energy. The A conformer in each case is the one with the lower field methyl resonance.

Table I. Arrhenius Activation Energies (kcal/mol)

	E_a(A)	E_a(B)
Podototarin diacetate	11.0 ± 0.9	10.6 ± 0.9
Podototarin dimethyl ether	6.5 ± 0.3	6.7 ± 0.3

The activation free energy, $\Delta G^{\ddagger}$, enthalpy, $\Delta H^{\ddagger}$, and entropy, $\Delta S^{\ddagger}$, were calculated using the Eyring formulation.[16] A transmission coefficient of unity was assumed. Values of these three quantities at the upper and lower temperature limits of measurements are listed in Table II.[15]

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[12] F. A. Bovey, E. W. Anderson, F. P. Hood, and R. L. Kornegay, *J. Chem. Phys.*, 40, 3099 (1964).

[13] A. Allerhand, H. S. Gutowsky, J. Jonas, and R. A. Meinzer, *J. Am. Chem. Soc.*, **88**, 3185 (1966).

[14] We are indebted to Dr. W. D. Smith, Jr., for this program.

[15] Error limits in Tables I and II are based on computed standard errors in τ_A, τ_B, and E_a. The larger errors estimated for podototarin diacetate reflect uncertainty in the base-line corrections.

[16] W. J. Moore, "Physical Chemistry," Prentice-Hall Inc., Englewood Cliffs, N. J., 1962, p 297.

Table II. Enthalpies, Free Energies, and Entropies of Activation

Temp, °K	$\Delta H^{\ddagger}$(A), kcal/mol	$\Delta H^{\ddagger}$(B), kcal/mol	$\Delta G^{\ddagger}$(A), kcal/mol	$\Delta G^{\ddagger}$(B), kcal/mol	$\Delta S^{\ddagger}$(A), eu	$\Delta S^{\ddagger}$(B), eu
			Podototarin Diacetate			
319.0	10.3 ± 0.9	9.9 ± 0.9	18.4 ± 0.3	18.7 ± 0.3	−25.3 ± 4.0	−27.4 ± 4.0
346.5	10.3 ± 0.9	9.9 ± 0.9	19.1 ± 0.3	19.4 ± 0.3	−25.5 ± 4.0	−27.6 ± 4.0
			Podototarin Dimethyl Ether			
248.0	6.0 ± 0.3	6.2 ± 0.3	13.7 ± 0.2	13.8 ± 0.2	−31.1 ± 2.0	−30.5 ± 2.0
261.8	6.0 ± 0.3	6.1 ± 0.3	14.2 ± 0.2	14.2 ± 0.2	−31.2 ± 2.0	−30.6 ± 2.0

The activation energies determined by this method are much lower than can be measured by racemization techniques, the average lifetimes of the conformers ranging from about 0.1 to about 0.9 sec. These data, therefore, complement those obtained from earlier studies of hindered biphenyls. If it is assumed that the major function of the saturated rings in the podototarin derivatives is to provide the asymmetry necessary to make possible this method of measurement then the activation energy data should be applicable to simple biphenyls.

The activation energies reflect the steric requirements of the acetoxy and methoxy groups and are in accord with the relative sizes of these groups. They also appear to correlate satisfactorily with the reported values for 2,2′-dimethylbiphenyl[8] and 2,2′-bis(acetoxymethyl)biphenyl.[10] The activation energies of the podototarin derivatives are probably higher than might be expected for the corresponding 2,2′-disubstituted biphenyls because of the buttressing effect of the isopropyl groups in the 3 and 3′ positions. Such buttressing effects in optically active biphenyls have been well documented.[17]

In view of the rather low activation energies of these compounds, the stability of the conformers is of interest. The relatively long lifetimes are a consequence of the very unfavorable activation entropies. Large negative entropies have been reported for biphenyls with much simpler substitution patterns, *e.g.*, 2,2′-dimethylbiphenyl ($\Delta S^{\ddagger} = -11.6$ eu)[8] and 2,2′-dicarboxy-6-nitrobiphenyl ($\Delta S^{\ddagger} = -12.2$ eu).[18] A study of models indicates that the podototarin derivatives possess an additional source of entropy loss. Freedom of rotation of the acetoxy and methoxy groups must be severely restricted in the transition state, the acetyl or methyl group, respectively, being forced away from the other aromatic ring of the biphenyl system. This in turn must restrict rotation of the adjacent isopropyl groups. It is probable that a substantial fraction of the entropy loss in the transition state arises from restriction of rotation of these four groups. For both compounds the frequency factors are very low, being of the order of 10^6 to 10^8.

An as yet unexplained feature of the temperature dependence of the spectrum of podototarin diacetate is the increase in line width at low temperatures. As the temperature is lowered from the coalescence point the two methyl lines separate and become narrow, as expected. On further cooling of the sample the lines broaden again. This cannot be attributed to an increase in viscosity (since other lines remain sharp) so it appears that the acetyl methyl groups must be involved in an additional temperature-dependent process at low temperatures. Because of the lower temperatures involved the corresponding phenomenon has not been investigated in the case of podototarin dimethyl ether.

Acknowledgment. We are indebted to Dr. R. C. Cambie, University of Auckland, Auckland, New Zealand, for samples of podototarin diacetate and podototarin dimethyl ether and for valuable discussions.

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(17) Reference 6, p 163.

(18) J. W. Brooks, M. M. Harris, and K. E. Hawlett, *J. Chem. Soc.*, 1934 (1957).