A Study of the Barriers to Rotation in Some Highly Substituted Diphenyl Ethers¹

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Energy barriers to rotation about Ar–O bonds have been obtained from an analysis of the variable temperature n.m.r. spectra of a number of highly substituted diphenyl ethers. These barriers are explained on the basis of structural and conformational effects and their implication for the resolution of optical isomers is discussed.

Les barrières d'énergie de rotation autour des liaisons Ar—O ont été obtenues à partir des spectres r.m.n. à température variable d'un certain nombre de diphényl éthers fortement substitués. Ces barrières sont expliquées en fonction des effets structuraux et conformationnels; leur conséquence en vue de la résolution d'isomères optiques est discutée.

[2]

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Introduction

It has been established that many triply ortho-substituted diphenyl ethers exist in solution preferentially in an H-inside conformation as shown in Fig. 1 (1, 2). Appropriately substituted ethers (e.g. 1) are dissymmetric (without reflection symmetry) in this conformation and could, in principle, be resolved into optical isomers. Several attempts to carry out resolution have, however, failed (3-7). Since rotation of either or both rings about the ether linkage would convert 1 to either an enantiomer or a diastereomer (see Discussion), it is of interest to determine the magnitude of the energy barriers for these rotational processes. This is especially important as these systems provide fundamental models to aid in the study of rotational barriers of ethers related to thyroxine and other medicinally important ethers which have been shown to exist in the same preferred conformation (8).



FIG. 1. H-Inside conformation of a triply ortho-substituted diphenyl ether.

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Nuclear magnetic resonance spectroscopy offers an excellent method for determining energy barriers if signal shapes or patterns are temperature dependent. Free energy barriers to rotation in diphenyl ethers may be calculated from coalescing signals by means of the Eyring equation, the logarithmic form of which is [1]

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$$\Delta G^{\dagger} = 4.57 T_{\rm c} (10.32 + \log (T_{\rm c}/k_{\rm c}))$$

where T_c is the coalescence temperature and k_c is the rate constant for rotation at the coalescence temperature (9). Equation 1 will be applicable to rotation about Ar—O bonds if the protons whose signals are coalescing are exchanged by this rotation. The value of k_c may be calculated for the collapse of two singlets to one singlet from eq. 2, where Δv is the chemical shift difference in Hz between the two singlets obtained from

$$k_{\rm c} = \pi \Delta v / \sqrt{2}$$

the n.m.r. spectrum taken well below T_c (9). Equation 2 assumes equal concentrations of the equilibrating species and no coupling between the protons whose signals are coalescing. If Δv is large compared with the natural line widths and coupling constants, coupling may be neglected but such coupling, when this is not the case, will result in an apparent k_c larger than the true one and too low a value for ΔG^{\ddagger} (10). There are other equations used to estimate k_c ; the validity of these and [2] for different situations has been investigated recently by Kost *et al.* (11).

Since the spectra of ethers we studied pre-



H-Inside conformation suggested by Bolon (12). FIG. 2.

viously (1, 2) indicated no temperature dependence, it seemed advisable to investigate ethers with larger ortho substituents. Bolan (12) has noted that the two t-butyl groups meta to the ether linkage in 2 appear to be non-equivalent from the n.m.r. spectrum, and this observation led him to suggest the H-inside conformation shown in Fig. 2. Kessler et al. (13) have calculated a free energy barrier to rotation of 17.8 kcal/mol for 3 based on the coalescence of the n.m.r. signals for the methyl groups within a given isopropyl group (henceforth referred to as the isopropyl methyl groups) at temperatures above 57°. This would appear to be the first direct measurement of the barrier in highly substituted diphenyl ethers although Lehmann (14) has argued that the coalescence phenomenon may be explained by hindered rotation about the Ar-isopropyl bond rather than about an Ar-O bond.

In this paper we report a study of rotation in other highly substituted diphenyl ethers using variable temperature spectroscopy. In some cases ΔG^{\dagger} appears to be of suitable magnitude that optical resolution of the enantiomeric



conformers of similar ethers containing the necessary dissymmetry may be possible.

Results

Variable temperature n.m.r. spectra of 3, 4, 5, 6, and 8 are reproduced in Figs. 3-7. Table 1 contains coalescence data $(T_{\rm e} \text{ and } k_{\rm e})$ and ΔG^{\dagger} determined at T_c for 3, 4, 5, and 8. The parameters $k_{\rm c}$ and ΔG^{\dagger} were calculated from eqs. 1 and 2;⁴ the estimated error in values of the latter is

TABLE 1. Coalescence data and ΔG^{\dagger} values

Compound	Absorption measured	T_{c} (°C)	Δv (Hz) ^a	$k_{\rm c}({\rm s}^{-1})^b$	ΔG^{\dagger} (kcal/mol)
3	Isopropyl methyls	57			17.8ª
4	Isopropyl methyls Ring protons	$-70 \\ -60$	7.0 107.0	15.6 238.0	10.6 10.1
5	Isopropyl methyls	-70	6.0	13.3	10.7
8	Ring protons	67	66.7	150.0	16.5

^aThe Δv values for compounds 4 and 5 were obtained at 100 MHz. That for 8 was obtained at 60 MHz. ^bFrom eq. 2. ^cFrom eq. 1 at T_{e} . ^aReported by Kessler *et al.* (9, 13).

⁴Although the exchanging ring protons couple in these compounds, $\Delta v \gg J$ so that eq. 2 was used without correction for the coupling (9-11). It has been pointed out that the use of [2] for the isopropyl methyl absorptions is suspect. However, even if k, were wrong by an order of magnitude, which is unlikely, ΔG^{\dagger} would be wrong by less than 1 kcal/mol.

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 \pm 0.4 kcal/mol, based almost exclusively on uncertainties in $T_{\rm c}$.

Compound 7 was found to undergo coalescence around ambient temperature at 60 MHz, having what appeared to be an AA'BB'C pattern for the protons of the non-alkylated ring above this temperature and an ABCDE pattern below it. No indication of n.m.r. changes were noted for 9 or 10 over a temperature range of -70 to 150° at 60 MHz.

Discussion

The basis for the observation of non-equivalence of the isopropyl methyl groups of an ether such as 3 (Fig. 3) is that in one H-inside conformer⁵ the methyl groups within each isopropyl are anisochronous (15) although the two isopropyls are themselves enantiotopic⁶ and are therefore normally equivalent in the n.m.r. spectrum. This non-equivalence of the methyl groups holds for all conditions of rotation about the Ar—isopropyl bond and is an example of a

⁶Groups are enantiotopic if they can be interchanged by a rotation-reflection operation (S_n) to give a structure indistinguishable from the original (15).

⁵In this case there are two identical H-inside conformers, differing only by rotation of the di-isopropyl-substituted ring through 180° . If the alkyl-substituted ring had no plane of symmetry these two conformers would be enantiomers (see later discussion and Fig. 10). There is no spectral indication of any NO₂-inside conformers.



FIG. 4. Variable temperature n.m.r. spectra of 4.

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FIG. 5. Variable temperature n.m.r. spectra of 5.

fairly well documented phenomenon (16–18) which produces non-equivalence of the X groups in any A-CX₂-B system where either A or B is asymmetric. Since the rate of rotation about the Ar—O bond increases with temperature, the n.m.r. spectrometer sees only a time average of the conformers above T_c (Fig. 8). The methyls in an isopropyl group exchange identity when the conformers are interconverted and are therefore seen as equivalent. At tempera-

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tures below T_c , interconversion of the conformers is slow enough for the spectrometer to be able to distinguish two different methyls. Thus, a study of the variable temperature behavior of isopropyl methyl signals is a study of rotation of the isopropyl-substituted ring about the Ar—O bond.

The spectrum of **6** (Fig. 6) shows one set of absorptions for the two sec-butyl groups at temperatures above 50° and two sets at lower



FIG. 6. Variable temperature n.m.r. spectra of 6.

temperatures. Compound 6 possesses two asymmetric carbons in the sec-butyl substituents so the possibility of RR, SS, and RS combinations exists. Since in the meso RS form the sec-butyls are enantiotopic under all conditions of rotation about AR—O, it would be expected to show a temperature independent sec-butyl absorption provided that only the two identical H-inside conformers are equilibrating. If either the RR or SS form is *frozen into* one of the identical H-inside conformations, the two sec-butyl groups are diastereotopic (15) and are therefore magnetically non-equivalent. Rotation of the alkylated ring through 180° (see Fig. 8 for 3)



FIG. 7. Variable temperature n.m.r. spectra of 8.

exchanges the identity of the two groups and they are seen as being equivalent in the high temperature spectrum.

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The variable temperature n.m.r. spectra of 5 (Fig. 5) are quite revealing; in the high temperature extreme the meta-methyl appears as a slightly broadened singlet, the nitrated ring protons as an AMX pattern and the isopropyl

methyl groups as a single doublet. All of this is consistent with fast exchange between two different H-inside conformations which, for convenience, we will refer to as the methylinside and the methyl-outside conformations⁷

⁷Each H-inside conformer is really two identical conformers differing by rotation of the alkylated ring (*cf.* footnote 5).



FIG. 8. Equilibration of conformers in 3.

Ēн_з



FIG. 9. (i) -ethyl-inside and (ii) Methyl-outside conformations of 5.

(Fig. 9). At -100° there are two sets of absorptions for all the protons including the isopropyls. This observation and the observed chemical shifts are consistent only with the freezing out of both conformations as well as the rotation of the di-isopropyl-substituted ring. The sets of signals for the two conformers are of unequal intensity since the methyl-outside conformer, in which there is less steric interaction between the methyl and the other ring is present in higher concentration.⁸ The low intensity signals for the meta-methyl (D') and for $H_{C'}$ (methyl-inside) appear at higher field than the corresponding high intensity signals (methyl-outside). This is due to the long-range shielding experienced in an H-inside conformation arising from the induced ring current of the other ring.⁹ Similarly, the high intensity signals for H_A and H_B appear at higher field than the corresponding low intensity signals for $H_{A'}$ and $H_{B'}$.

The n.m.r. spectra of 4, 7, and 8 are also consistent with frequent interconversion between equivalent H-inside conformers at temperatures above T_c . Below T_c one observes ABCD or ABCDE patterns for the non-alkylated ring protons. Above T_c only the average resultant AA'BB' or AA'BB'C patterns are observed.

That 9 showed no indication of hindered rotation is not surprising since there are only the two identical H-inside conformers resulting from rotation of the alkylated ring. Because the *t*-butyl groups, unlike isopropyls, are symmetric and are unable to be used as probes in the same way, one cannot observe the *freezing out* of the alkylated ring–O rotation even though it must occur.

In view of the results obtained by Kessler et al. (13) for 3, the more hindered 10 might be expected to show similar results with an even higher coalescence temperature and ΔG^{\dagger} . That it does not may be explained in one of two ways: (i) free rotation occurs over the entire temperature range studied (-70 to 150°) or, (ii) the compound is locked into some symmetrical conformation (or exchange occurs between two or more symmetrical conformations). In support of the former explanation is the fact that for 10

⁸Although the two methyl signals overlap the isopropyl methine H signal at -100° , from their relative intensities the equilibrium constant was calculated to be about 3.5 leading to a value of 0.4 kcal/mol for ΔG . This appears to be the first experimental estimate of a conformational energy difference in diphenyl ethers.

 $^{^{9}}$ For a discussion of this effect in diphenyl ethers see ref. 2.

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FIG. 10. The four stereoisomers of a dissymmetric, di-ortho-substituted diphenyl ether adopting H-inside conformations.

there can be no relatively low energy, H-inside conformation which the molecule can adopt. As a result, the conformer energies are high and the ΔG^{\dagger} to rotation about the Ar—O bonds is low when compared with that of other molecules considered in this study.

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It is worth mentioning again that calculation of an energy barrier using the data from ring proton coalescence is inherently more reliable than using data from the isopropyl methyl groups. In the former case Δv is very large. Because of this it is possible to neglect coupling of the protons undergoing coalescence without introducing serious error into the calculated ΔG^{\dagger} (see footnote 4). The major factor influencing the calculation of ΔG^{\ddagger} in either case is T_{c} .

The problem remains of assigning ΔG^{\dagger} values to particular rotational processes. For a dissymmetric diphenyl ether with two vacant ortho positions on the same ring there may be four possible stereoisomeric H-inside conformers (Fig. 10, see also footnote 7 for the case when one ring has a plane of symmetry). This particular example was chosen because of its maximum lack of symmetry and the possibility of two enantiomeric pairs of H-inside conformers (the pair A and B and the pair C and D). Rotation about the alkylated ring-O bond alone interconverts enantiomers while rotation about the other Ar-O bond alone produces a diastereomer (A and C are interconverted as are B and D). A third rotational process that has been suggested (3) is the cogwheel rotation in which both rings rotate synchronously interconverting the pair A and D, and the pair B and C. Although a cogwheel mechanism will not by itself produce racemization of an optically active ether, the cogwheel rotation in concert with either or both of the other two processes can cause racemization. In order to isolate pure optical isomers, all of these rotational processes would have to be inhibited.

The variable temperature n.m.r. spectra of 4 could be accounted for by either the one-step, cogwheel rotation or by a two-step process in which rotation occurs first about one Ar—O bond and then the other. Inspection of molecular models suggests that rotation of the alkylated ring should be more hindered (should have a larger ΔG^{\dagger}) than rotation of the nitrated ring. The fact that, within experimental error, the values of ΔG^{\dagger} determined from T_c and k_c for isopropyl and ring proton exchange are the same (Table 1) would seem to indicate that a one-step process occurs in ethers of this type (that would include 7 and 8 as well as 4).

For triply ortho-substituted ethers (3, 6, 9) the cogwheel process would force the molecule into a high energy NO₂-inside conformation which is not observed by the n.m.r. spectrometer. It would seem unlikely that rotation of the alkyl-substituted ring occurs alone as that rotation would be highly hindered in the ethers studied. It would be possible for the two rings

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BUTTERFLY

FIG. 11. Butterfly mechanism for rotation about an Ar-O bond in triply ortho-substituted diphenyl ethers.

to slip by one another through a *butterfly* intermediate (Fig. 11). This process could be envisaged as a three-step one involving both rings although not simultaneously as for the cogwheel mechanism. The butterfly mechanism could also account for the observations noted with the doubly ortho-substituted ethers as a single ΔG^{\dagger} would be expected for both ring rotations; the final step could be rotation of the non-alkyl-substituted ring by 90° in either sense.

It appears likely, in the light of the experimental evidence, that a diphenyl ether such as 11 could be resolved into enantiomers. Com-



paring 3 and 4, one sees that the introduction of an ortho-nitro group in 3 raises the T_c for rotation of the alkylated ring by about 130° .¹⁰ A similar structural change in 8 would raise ΔG^{\dagger} to around 23 kcal/mol, a barrier sufficient to allow separation of individual, enantiomeric H-inside conformers (9). Compound 11, then should have a barrier to rotation sufficiently

¹⁰It is interesting to note that a meta-methyl does not increase T_c or ΔG^{\ddagger} for this rotation (cf. values for 4 and 5).

high and both rings are dissymmetric so that the two enantiomers could, in theory, be resolved at room temperature. It may be that the use of an ortho substituent such as CHO, CN or CO_2R which is less easily distorted from coplanarity with the ring than NO_2 might effect an even larger increment in the rotational barrier. The failure to observe hindered rotation in 10 indicates that one vacant ortho position should be maintained if diphenyl ethers for optical resolution studies are being synthesized.

Experimental

The n.m.r. spectra were recorded on Varian A-60A and HA-100 spectrometers. For studies at low temperatures the samples were dissolved in acetone- d_6 ; otherwise chloroform-d was used as solvent. The chemical shifts of the aromatic protons on the brominated ring of **8**, in the low temperature spectrum, were reproduced to within ± 0.1 Hz by means of an iterative computer calculation in order to estimate k_c .

Compounds 4 and 5 were prepared by the method of Wright and Jorgensen (19). Compounds 3 and 9 have been reported previously (20) while 6 and 10 were synthesized by the method of that reference. The properties of 6 and 10 are recorded in Table 2.

The n.m.r. and i.r. spectra of all compounds were consistent with the assigned structures.

2-Phenoxy-1,3,5-tri-t-butylbenzene (7)

2-(2',4'-Dinitrophenoxy)-1,3,5,-tri-t-butylbenzene (9, 1.0 g) was dissolved in 95% ethanol (200 ml) and about 2 g of W-2 Raney Nickel added. Hydrogenation was performed in a Parr shaker apparatus for 12 h at a pressure of 40 lb/in^2 and the catalyst was removed by filtration. The resulting colorless solution was evaporated to give off-white crystals (0.8 g, 95%) of what, from n.m.r. and i.r. spectra, appeared to be 2-(2',4'-diaminophenoxy)-1,3,5-tri-t-butylbenzene.

Without further purification, the crude diamine was dis-

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Compound	m.p. or b.p. (°C/mm Hg)	Yield (%)	Analysis (%)					
			Calculated			Found		
			c	н	N	С	Н	N
6 10	213-216/0.4 113-115	28 24	64.50 62.78	6.50 5.85	7.52 8.14	64.22 62.67	6.36 5.74	7.41 7.97

TABLE 2. Properties of some new diphenvl ethers

solved in a mixture of concentrated sulfuric acid and glacial acetic acid (40 ml, 1:1). A solution of sodium nitrite (0.5 g) in concentrated sulfuric acid (20 ml) was prepared and both solutions were cooled to 5°. The nitrous acid solution was added to the amine over a period of 45 min and the deep red product was allowed to stand at 5° for a further 30 min. It was then added slowly to a mixture of hypophosphorus acid (75 ml, 50%) and crushed ice (300 g) and left for 24 h. At the end of this time, the contents were extracted with chloroform (100 ml) and the chloroform was evaporated to yield a red oil (0.66 g, 90%). A portion of this product was used without purification in the n.m.r. experiments then was recovered and combined with the remainder for use in the next synthetic step.

2-(4'-Bromophenoxy)-1,3,5-tri-t-butylbenzene (8)

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Crude 2-phenoxy-1,3,5-tri-t-butylbenzene (0.6 g) was dissolved in glacial acetic acid (10 ml) and a solution of bromine (0.28 g) in acetic acid (10 ml) was added dropwise as described by Hamilton and Blanchard (21) for the bromination of other highly substituted diphenyl ethers. Even after standing for 15 h, the mixture did not appear to have reacted so that ferric chloride (0.01 g) was added and stirring was continued for another 24 h. During this time there was a slow evolution of HCl and/or HBr. The solution was poured into water (200 ml) and the precipitate collected by filtration. This solid could not be purified by recrystallization from common solvents but was obtained as white crystals after being eluted through an alumina column (neutral, Brockman activity 1, 80-200 mesh) with petroleum ether (b.p. 30-60). The pure product was obtained in 61% (0.42 g), m.p. 146-148°

Anal. Calcd. for C₂₄H₃₃BrO: C, 69.05; H, 7.97; Br, 19.14. Found: C, 69.23; H, 7.90; Br, 19.30.

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