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Effects of *para*-Substituents on the Rates of Inversion of Biphenyl Derivatives. I. 5,7-Dihydrodibenzo[*c*,*e*]thiepins

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Several 3,9-disubstituted 5,7-dihydrodibenzo[*c*,*e*]thiepins were synthesized and temperature dependence of their NMR spectra was examined. All the substituted derivatives showed a lower energy barrier to inversion than the unsubstituted one. The effects of the substituents on the energy barrier may be interpreted in terms of resonance stabilization and/or out-of-plane bending of the axis bond at the transition state.

Many earlier works have revealed that the major part of the origin of energy barrier to inversion in biphenyl derivatives is the steric strain at the transition state due to non-bonded interactions between atoms or groups at the *ortho* positions.[1] Westheimer and his coworkers[2] successfully calculated the enthalpy of activation for racemization of 2,2′-dibromobiphenyl and 2,2′-diiodobiphenyl, assuming a planar transition state with deformation within the plane only and completely neglecting electronic factors.

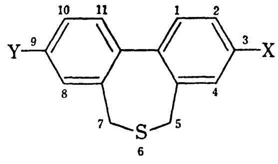
In contrast, the influence of electronic factors on the energy barrier has been left unclarified. The gain in resonance energy in the transition state may contribute in lowering the activation energy, but Westheimer's success in calculation can be taken as suggesting the existence of some compensating factors.

Although the assumption that the transition state is coaxial and coplanar has generally been accepted, some authors[3,4] suggested that bending of the axis bond out of plane of the benzene ring may decrease the non-bonded interactions and that the energy barrier to inversion is affected by the relative ease of the bending. Harris and Cheung King Ling[4] studied the racemization rates of optically active 4,4′-symmetrically substituted 2,2′-diiodobiphenyls and found that the energy barrier to inversion is considerably affected by the *para* substituents. They have claimed that in the transition state the two benzene rings are neither coaxial nor coplanar, but distorted out of the plane to each other, and the *para* substituents affect the ease of bending of the axis bond and thus the energy barrier. They also suggested that in this system *ortho* substituents are so bulky that even at the ground state it has a distorted non-coaxial conformation. It is then considered that with the extreme bulkiness of the *ortho* groups the biphenyl system experiences the distorted transition state.

From the above discussion, it will be interesting to known whether the out-of-plane bending of the axis bond is operating or not in biphenyl systems with less bulky *ortho* substituents. Such systems necessarily possess very low optical stability and polarimetric study may become impossible.

However, with dynamic NMR technique it is possible to obtain information on intramolecular motions with a specific rate of 1 to 10^3 sec^{-1}.[5] Energy barrier to inversion in several biphenyl systems has been studied by applying NMR technique.[6-10] Kurland and his coworkers[6] reported the temperature dependent NMR spectra of 5,7-dihydrodibenzo[*c*,*e*]thiepin (I). Methylene protons of I showed an AB quartet signal at low temperature, which coalesced at 43°C into a singlet. This change of spectra was correlated with the rate of inversion. The free energy of activation was calculated to be 16.1 kcal/mol with the entropy of activation less than 2 eu. This system seemed to be suitable for the present purpose because of synthetic ease and convenience in measurement and analysis of the NMR spectra.

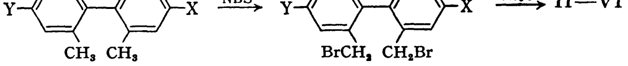
Thus five 3,9-disubstituted derivatives of I (II—VI) were synthesized and their NMR spectra were measured over a wide range of temperature to find out the effects of substituents on the energy barrier to inversion.



I: $X=Y=H$	IV: $X=Y=F$
II: $X=OCH_3, Y=NO_2$	V: $X=Y=Br$
III: $X=Y=OCH_3$	VI: $X=Y=CO_2CH_3$

Results

Compounds II—VI were synthesized by benzylic bromination of 4,4′-substituted *o*,*o*′-bitolyl followed by ring closure with sodium sulfide (Scheme).



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[1] R. Adams and H. C. Yuan, *Chem. Rev.*, **12**, 261 (1933).

[2] F. H. Westheimer, "Steric Effects in Organic Chemistry," ed. by M. S. Newman, Wiley, New York, N. Y. (1956), pp. 542—555.

[3] G. Baddeley, *Nature*, **157**, 694 (1946).

[4] M. M. Harris and C. Cheung King Ling *J. Chem. Soc.*, **1964**, 1825.

[5] G. Binsch, "Topics in Stereochemistry," Vol. 3, ed. by E. L. Eliel and N. L. Allinger, Interscience Publishers, New York, London, Sydney (1968), p. 97.

[6] R. J. Kurland, M. B. Rubin, and W. B. Wise, *J. Chem. Phys.*, **40**, 2426 (1964).

[7] W. L. Meyer and R. B. Meyer, *J. Amer. Chem. Soc.*, **85**, 2170 (1963).

[8] M. Ōki, H. Iwamura, and N. Hayakawa, This Bulletin, **37**, 1865 (1964).

[9] I. O. Sutherland and M. V. J. Ramsay, *Tetrahedron*, **21**, 3401 (1965).

[10] M. Ōki and H. Iwamura, *ibid.*, **24**, 2377 (1967).

Table 1. NMR Spectral parameters of 5,7-dihydrodibenzo[*c*,*e*]thiepins

Compound	Solvent	Frequency (MHz)	T_c (°C)	δ_{AB} (Hz)	J_{AB} (Hz)	Ref
I	CS_2	60	43±1	13.1	12.4	6)
	$CDCl_3$	60	45	12.7	12.6	9)
II	$CHCl_2CHCl_2$	100	20±5	10.0b)	13.5b)	a)
				13.0c)	12.7c)	a)
III	$CHCl_2CHCl_2$	60	24±2	15.6	12.6	a)
IV	$CHCl_2CHCl_2$	60	38±2	10.3	12.9	a)

a) The present work.
b) Represents the quartet at higher field.
c) Represents the quartet at lower field.

Table 2. Kinetic parameters of the inversion of 5,7-dihydrodibenzo[*c*,*e*]thiepins

Compound	Solvent	$\Delta G_c^{\neq}$ (kcal/mol)	$\Delta H^{\neq}$ (kcal/mol)	$\Delta S^{\neq}$ (eu)	Ref
I	CS_2	16.1±0.3		<2	6)
	$CDCl_3$	16.0			9)
II	$CHCl_2CHCl_2$	14.6±0.3	13.6±1.0	−3±4	a)
III	$CHCl_2CHCl_2$	15.2±0.3	13.1±1.0	−7±4	a)
IV	$CHCl_2CHCl_2$	16.1±0.3	16.0±0.5	0±2	a)

a) The present work.

In NMR spectra, the protons of each methylene group of compounds II, III and IV showed an AB quartet signal at low temperature due to the non-equivalence of protons, indicating slow inversion. The quartet signal coalesced into a single broad line at about room temperature, then gradually sharpened with increasing temperature. The obtained spectral parameters are summarized in Table 1. For compound II, two AB quartets due to 5- and 7-methylenes overlapped each other, and this made the determination of the coalescence temperature (T_c) somewhat inaccurate.11)

The inversion rate k_c at T_c was calculated using the equation10)

$$k_c = \frac{\pi}{\sqrt{2}}(\delta_{AB}^2+6J_{AB}^2)^{1/2} \qquad (1)$$

From the line width W of the coalesced singlet, the approximate inversion rate k at various temperatures could be obtained by means of

$$k = \frac{\pi\delta_{AB}^2}{2(W-W_0)} \qquad (2)$$

where W_0 is the extrapolated line width for $k=\infty$. Arrhenius plots gave parameters E_a and $\log A$. Eyring parameters, $\Delta G^{\neq}$, $\Delta H^{\neq}$ and $\Delta S^{\neq}$ could be derived from the following equations.

$$\Delta G^{\neq} = -RT\ln\frac{hk}{k_B T} \qquad (3)$$

$$\Delta H^{\neq} = E_a - RT \qquad (4)$$

$$\Delta S^{\neq} = \frac{\Delta H^{\neq} - \Delta G^{\neq}}{T} \qquad (5)$$

The results are summarized in Table 2.

The methylene protons of V and VI were observed as a singlet down to the lowest attainable temperature (−50°C). Slight broadening was observed with lowering temperature. This seems to be due to the increased viscosity of the sample solution, because reference signals also showed broadening. Although this might be interpreted in terms of rapid inversion down to the lowest temperature, it is unreasonable to think that substitution at *para* positions caused such a large lowering of coalescence temperature. An alternative and more probable interpretation is that the lack of splitting is due to accidental magnetic equivalence of the methylene protons although the inversion is slow on the NMR time scale. Several examples have been reported in which diastereotopic protons show magnetic equivalence. Sometimes aromatic solvents give rise to magnetic non-equivalence of the protons which are equivalent in non-aromatic solvents such as chloroform and carbon tetrachloride. However, attempts to measure the NMR spectra of V and VI in pyridine and *o*-dichlorobenzene failed because of the low solubility of the samples in these solvents.

Discussion

The lack of full line shape analysis of the NMR spectra of these compounds and the essential tendency of the data of enthalpy and entropy of activation to include rather large systematic errors as pointed out by Gutowsky12) prevent a direct comparison of the $\Delta H^{\neq}$ values obtained and the delicate quantitative discussions about the transition state of inversion. Qualitatively, however, we might conclude from these data (Table 2) that the barrier to inversion decreases in the order I≈IV>III≥II.

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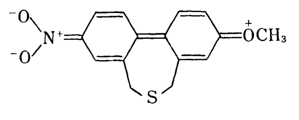
11) Theoretically two T_c's corresponding to the two kinds of methylene should exist, but could not be detected separately.

12) A. Allerhand, H. S. Gutowsky, J. Jones, and R. A. Meinzer, *J. Amer. Chem. Soc.*, **88**, 3185 (1966).

Fluorine atom is known to exert no large electronic effect on the *para* position, and it may be reasonable for compounds I and IV to have nearly the same value of activation parameters.

Several factors can be considered by which the substituents at *para* positions influence the energy barrier to inversion in this system. It may be reasonably assumed that the effects of the substituents on the ground state energy of this system are negligible, and only those on the transition state energy should be considered.

In 3,9-unsymmetrically substituted derivatives such as II with an electron-withdrawing group at one *para* position and an electron-releasing group at the other, resonance stabilization as represented by the canonical structure VII should contribute in lowering the energy level of the transition state. A farily large decrease in $\Delta H^{\ddagger}$ value of II agrees with this prediction.

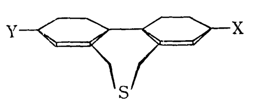


VII

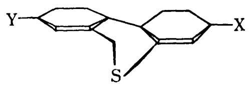
It has been suggested[13] that the large contribution of VII in the resonance hybrid would increase the double bond character of the axis bond, causing a shortening of the bond which would result in the increase of the nonbonded interaction. That is, the energy barrier would be heightened in contrast to the effect of the resonance stabilization. The present data show that the effect of bond shortening is rather unimportant. Here, the two benzene rings may be considered to be coaxial and coplanar at the transition state and the release of steric strain by the out-of-plane bending of the axis bond is much less important.

In 3,9-symmetrically substituted derivatives (III—VI), large resonance stabilization as observed in II can not be expected. Ultraviolet spectroscopic studies of 4,4′-disubstituted biphenyls[14] showed that all the substituents, irrespective of their nature, increase conjugation between the two rings to some extent. If such conjugation really contributes to stabilize the transition state for inversion, all the derivatives III—VI should have lower barriers than unsubstituted I.

In the coaxial and copolanar transition state (VIII), nonbonded interactions involving internal strains of the seven-membered ring would be the greatest, causing the barrier to inversion. These interactions would be considerably released if the axis bond could be bent out of the plane of the benzene rings as schematically shown in IX. The higher the π-electron density at the 1,1′-positions of the biphenyl skeleton, the easier will be the bending motion of the axis bond.[15]



VIII



IX

Derivative III, with methoxyl groups at 3- and 9-positions, shows a lower barrier to inversion than I, which can be explained by either of two factors. On one hand, the methoxyl group will lower the energy barrier because of the contribution of resonance structure through the two benzene rings. On the other hand, the same group will make it easy to take the transition state IX because of electron-releasing tendency.

The lack of data on the effect of electron-withdrawing substituents prevents us from determiniing which of these factors is more important. Considerable drop in $\Delta H^{\ddagger}$ value in III relative to I does not seem to be explained only in terms of resonance stabilization, and the out-of-plane bending is likely to contribute in lowering the barrier of III.

Further study is necessary for a definite conclusion on the ratio of contribution of these factors, but we may tentatively conclude as follows. In the case of compounds in which a strong resonance interaction is expected, the planar transition state is important, whereas in the case in which no strong resonance interaction is expected, both the planar and bent transition state must be considered.

Experimental

Spectra. The NMR spectra of II were obtained on a JNM 4H-100 spectrometer operating at 100 MHz, and those of III and IV on a JNM C-60H spectrometer at 60 MHz. Temperatures were read with methanol or ethylene glycol sample and are accurate to ±2°C. Approximately 10% (w/w) solutions in 1,1,2,2-tetrachloroethane were employed.

Materials.[19] *4-Methoxy-4′-nitro-2,2′-bitolyl*: 2-Bromo-5-nitrotoluene[18] (43 g, 0.2 mol) and 2-iodo-5-methoxytoluene[17] (50 g, 0.2 mol) were heated with copper bronze (100 g) at 220—230°C over a period of 5 hr. The reaction mixture was extracted with acetone and distilled *in vacuo*. Repeated recrystallization of the fraction boiling at 158—163°C/1 mmHg from methanol gave yellowish white crystals; yield 3.2 g (6%), mp 91—92°C.

Found: C, 70.35; H, 5.88; N, 5.44%. Calcd for $C_{15}H_{15}O_3N$: C, 70.02; H, 5.88; N, 5.44%.

4,4′-Difluoro-2,2′-bitolyl: *m*-Tolidine hydrochloride (114 g, 0.4 mol), prepared according to Wenner's method[20] was suspended in 20% hydrochloric acid (400 m*l*) and tetrazotized with aqueous solution of sodium nitrite (61 g, 0.88 mol). The reaction mixture was filtered and treated with a saturated aqueous solution of sodium fluoroborate. The tetrazonium fluoroborate was filtered, washed with saturated solution of sodium fluoroborate and cold water, dried in a vacuum desiccator, pyrolyzed and distilled with steam. Yellow oil boiling at 100—102°C/1.2 mmHg was obtained, which crystallized on cooling; yield 25 g (29%), mp 25—26°C (from methanol).

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[13] M. Calvin, *J. Org. Chem.*, **4**, 256 (1939).

[14] B. Williamson and W. H. Rodebush, *J. Amer. Chem. Soc.*, **63**, 3018 (1941).

[15] The correlation of the electron density and the ease of the out-of-plane bending has been observed. In IR spectra, the absorption due to out-of-plane bending of C–H bonds of mono-substituted benzenes appears in 750 cm^{-1} region and electron-withdrawing groups shift the absorption to higher wave number. These phenomena were interpreted in terms of "orbital following".[16]

[16] R. D. Kross, V. A. Fassel, and M. Margoshes, *J. Amer. Chem. Soc.*, **78**, 1332 (1956).

[17] All the melting points are uncorrected.

[18] C. S. Gibson and J. D. A. Johnson, *J. Chem. Soc.*, **1929**, 1229.

[19] T. Sato and M. Ōki, This Bulletin, **30**, 857 (1957).

[20] W. Wenner, *J. Org. Chem.*, **17**, 523 (1952).

Found: C, 76.87; H, 5.56%. Calcd for $C_{14}H_{12}F_2$: C, 77.04; H, 5.54%.

4,4′-Dibromo-2,2′-bitolyl: Tetrazotization of *m*-tolidine hydrochloride (71 g, 0.25 mol) with 48% hydrobromic acid (350 m*l*) and sodium nitrite (39 g) followed by decomposition with copper bronze (5 g) gave an oil boiling at 170—175°C/3 mmHg. Recrystallization of the distillate from acetone-methanol (1 : 1) afforded white crystals; yield 11 g (13%), mp 57—58°C.

Found: C, 49.50; H, 3.47%. Calcd for $C_{14}H_{12}Br_2$: C, 49.45; H, 3.56%.

Dimethyl 2,2′-Bitolyl-4,4′-dicarboxylate: 4,4′-Dicyano-2,2′-bitolyl, propared according to the method of Theilacker[21] was hydrolyzed with alkali. The crude carboxylic acid was suspended in ether and treated with the ether solution of diazomethane. The solvent and excess diazomethane were evaporated and the residue was recrystallized from methanol affording white crystals, mp 98—99°C.

Found: C, 72.61; H, 6.07%. Calcd for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08%.

2,2′-Bisbromomethyl-4-methoxy-4′-nitrobiphenyl: 4-Methoxy-4′-nitro-2,2′-bitolyl (5.1 g, 0.02 mol), *N*-bromosuccinimide (7.1 g, 0.04 mol) and benzoyl peroxide (0.2 g) were heated under reflux in carbon tetrachloride (150 m*l*) for 2.5 hr. Succinimide was filtered off and the filtrate was evaporated. Chromatography of the residual oil on alumina gave the desired compound by elution with petroleum ether - benzene (1 : 1); mp 115—116°C (from acetone - methanol (1 : 1)).

Found: C, 43.02; H, 3.22; N, 3.36%. Calcd for $C_{15}H_{13}O_3NBr_2$: C, 43.40; H, 3.16; N, 3.38%.

Elution of the column with benzene gave yellow crystals melting at 148—150°C, which were identified as 3-methoxy-9-nitro-5,7-dihydrodibenz[*c*,*e*]oxepin. The oxepin was inferred to be formed by the reaction of the dibromide with a trace of water existing in the column under the catalysis of alumina.

Found: C, 66.16; H, 4.97; N, 5.49%. Calcd for $C_{15}H_{13}O_4N$: C, 66.41; H, 4.83; N, 5.16%.

3-Methoxy-9-nitro-5,7-dihydrodibenzo[c,e]*thiepin (II)*: 2,2′-Bisbromomethyl-4-methoxy-4′-nitrobiphenyl (2.1 g, 0.005 mol) and sodium sulfide nonahydrate (1.4 g, 0.0055 mol) in methanol (300 m*l*) were heated under reflux for 10 hr. A major portion of the solvent was evaporated. The residue was poured into water and extracted with benzene. The combined extracts were dried with anhydrous sodium sulfate, evaporated and chromatographed on an alumina column. The eluate with petroleum ether - benzene (1 : 1) gave pale yellow crystals; mp 140—141°C (from methanol).

Found: C, 62.28; H, 4.72; N, 4.98%. Calcd for $C_{15}H_{13}O_3NS$: C, 62.70; H, 4.56; N, 4.88%.

3,9-Dimethoxy-5,7-dihydrodibenzo[c,e]*thiepin (III)*: 4,4′-Dimethoxy-2,2′-bitolyl[22] (9.7 g, 0.04 mol), *N*-bromosuccinimide (16.0 g, 0.09 mol) and benzyol peroxide (0.2 g) in carbon tetrachloride (200 m*l*) were heated under reflux for 2 hr. Filtration of succinimide and evaporation of the solvent gave an oily residue, which without purification was heated with sodium sulfide nonahydrate (10 g) in methanol for 8 hr. The product was recrystallized from acetone to afford white crystals, mp 141—142°C.

Found: C, 70.20; H, 6.38%. Calcd for $C_{16}H_{16}O_2S$: C, 70.55; H, 5.92%.

3,9-Difluoro-5,7-dihydrodibenzo[c,e]*thiepin (IV)*: 4,4′-Difluoro-2,2′-bitolyl was similarly treated with *N*-bromosuccinimide to give the dibromide which boiled at 155—156°C/1 mmHg and was heated with sodium sulfide. The product was distilled at 134—135°C/1.5 mmHg and recrystallized from methanol, affording colorless crystals melting at 88—89°C.

Found: C, 67.82; H, 4.13%. Calcd for $C_{14}H_{10}F_2S$: C, 67.72; H, 4.06%.

3,9-Dibromo-5,7-dihydrodibenzo[c,e]*thiepin (V)*: A similar treatment of 4,4′-dibromo-2,2′-bitolyl with *N*-bromosuccinimide and then with sodium sulfide afforded white crystals, mp 184.5—185°C (lit,[23] 191—192°C), after recrystallization from acetone.

Dimethyl 5,7-Dihydrodibenzo[c,e]*thiepin-3,9-dicarboxylate (VI)*. Dimethyl 2,2′-bitolyl-4,4′-dicarboxylate, treated similarly with *N*-bromosuccinimide followed by sodium sulfide, yielded the desired compound, mp 107—108°C, on recrystallization from ethanol - acetone (1 : 1).

Found: C, 65.77; H, 5.19%. Calcd for $C_{18}H_{16}O_4S$: C, 65.84; H, 4.91%.

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21) W. Theilacker and W. Ozegowski, *Ber.* **73B**, 33 (1940).

22) Y. Osawa, *Nippon Kagaku Zasshi*, **84**, 140 (1963).

23) W. E. Truce and D. D. Emrick, *J. Amer. Chem. Soc.*, **78**, 6130 (1956).