

# Importance of Substituent Intramolecular Charge-Transfer Effect on the Molecular Conformation of Diphenyl Ethers

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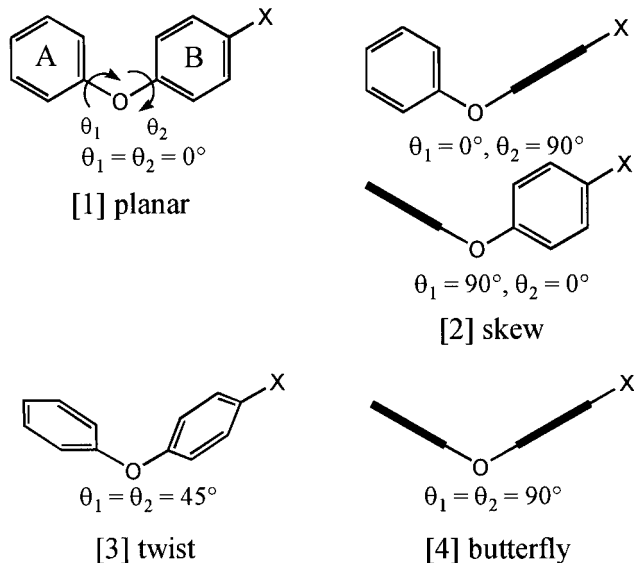
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The conformational control of diphenyl ethers by the electronic effect of substituents has been demonstrated by spectral measurements and their analyses based on CNDO/S-CI calculations and by minimum-energy optimization using the method of ab initio MO calculations with 6-31G(d) basis sets. Introduction of an electron-accepting substituent at the *para* position of either ring of diphenyl ether fixes the oxygen-bridged phenyl rings in the stable skew form, whereas unsubstituted diphenyl ether adopts the nonrigid form. The conformational stabilization is brought about by an intramolecular charge-transfer interaction of the electron-accepting substituent with a lone pair  $\pi$  orbital of the bridging oxygen atom through a  $\pi$ -electronic system of the benzene ring. On the other hand, the strong electron-donating substituent attached at the *para* position allows the diaryl ether moiety to be rigid in the preferable skew or twist conformation. This behavior is understood in terms of a competition between the electron-donating substituent and the ether oxygen for electron donation to the  $\pi$ -electronic system rather than a synergistic charge-transfer interaction between them. The electron-donating ability of the alkyl groups is insufficient to fix the nonrigid conformation of diphenyl ether. Thus, it has been demonstrated that the intramolecular charge-transfer interaction caused by strongly interacting substituents is important in governing the conformation of diphenyl ethers, and the substituent attached at the *para* position of either ring of diphenyl ether can control the conformation of whole molecule, depending on the electron donating/accepting character of the substituent.

## Introduction

The conformation of two aromatic rings bridged by an oxygen atom, such as diphenyl ether, has been a subject of continuing interest in regard to critical oxygen aromatic properties<sup>1–10</sup> and the structure–activity relationships of isodityrosines and thyroid hormones.<sup>11–14</sup> It is well known that the diaryl ether bond plays an important role in keeping the three-dimensional structure of natural products biologically active. The conformation is traditionally classified into four groups, that is, planar, skew, butterfly, and twist, as shown in Chart 1. Much attention has been diverted from the stationary conformation to

Chart 1. Stereoscopic View of Typical Conformations for 4-Substituted Diphenyl Ethers<sup>a</sup>



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<sup>a</sup>  $\theta_1$  and  $\theta_2$  denote the angles of twist about the C–O bonds and are defined as zero when the two rings are in the COC plane, just as shown in the planar form. Increases in the angles cause clockwise rotations of the phenyl rings around their O–C bonds. Rings A and B denote the benzene rings unsubstituted and substituted by the group X, respectively. See the text for details.

the internal rotation around C–O bonds on diphenyl ether,<sup>1,3–5</sup> because the barrier for the internal rotation around the C–O bonds is experimentally suggested to be too low to retain a rigid conformation.<sup>7,8</sup> IR and Raman spectrometry and semiempirical C-INDO calculations concluded that diphenyl ether preferentially adopts the equilibrium configuration involving the disrotatory in-

ternal rotation, losing the  $C_2$  symmetry on a shallow and periodic path on the potential energy surface.<sup>3</sup> Schaefer et al. have proposed the so-called one-ring flip mechanism for the internal motion of diphenyl ether with the aid of ab initio STO-3G calculations.<sup>4</sup> Ab initio calculations with 3-21G and STO-3G basis sets also support the internal rotation via the skew form as the transition state.<sup>5</sup> We have demonstrated that the conformation of diphenyl ether is nonrigid with a dihedral angle of the two phenyl rings of about  $90^\circ$  at room temperature.<sup>1</sup> Recent proposal of the nonrigid form is also provided by Verot et al. with the aid of semiempirical MO calculations.<sup>6</sup> These conclusions are synonymous, and the nonrigid form of diphenyl ether has been well documented at present.

The nonrigid conformation of diphenyl ether is brought about by the balance between the electronic stabilization (conjugation) and the steric crowding.<sup>1,2,4-6</sup> The *ortho* steric hindrance therefore easily governs the configuration of the diaryl ether bond.<sup>1,9,10,15</sup> Montaudou et al. have prospectively wrestled with the NMR and dipole moment studies on the relation between the number of *ortho* substituents and control of internal rotation in diphenyl ether,<sup>15</sup> with the results showing that the *ortho* substituents allow it to be rigid in the skew and butterfly forms. In a series of our conformational investigations on oxygen-bridged aromatic rings, the disubstituted product by the bulky Me group at the *ortho* positions of a benzene ring, that is, 1,3-dimethyl-2-phenoxybenzene, predominantly occupies a symmetric skew form due to steric crowding.<sup>1</sup> The *ortho* effect on the conformation is extended to discuss the structure–activity relationships of thyroxin analogues.<sup>10</sup> The electronic effect of substituents on the conformation, however, has not yet been investigated in spite of the fact that the substituent effect on  $\pi$ -electronic conjugation is an important factor in controlling the conformation of diaryl ethers. It may be expected that the substituents attached at the *para* position of either ring of diphenyl ether sensitively affect the conformation of the whole molecule, depending on the electron donating/accepting character of the substituent. The purpose of this paper is to determine whether the substituent electronic effect governs the conformation of diphenyl ether and to gain deeper insight into the problem with regard to the conformational preference of the oxygen-bridged aromatic rings. It is of interest and importance in structural chemistry and the investigation of structure–activity relationships to determine the substituent electronic effect on the conformation of diaryl ethers.

## Experimental Section

**Chemicals and Solvents.** The samples used here were diphenyl ethers substituted by the CN, COOEt, Ac, and NO<sub>2</sub> groups as electron acceptors and by the Me, Et, OMe, NH<sub>2</sub>, and NMe<sub>2</sub> groups as electron donors at the *para* position of a benzene ring. The *para* substituent seems to easily affect the  $\pi$ -electronic system without steric crowding. These compounds were synthesized according to the method of Ullman<sup>16-18</sup>

except for X = NO<sub>2</sub> and X = NH<sub>2</sub>, which were commercially available from Aldrich Chem Co. and Tokyo Chemical Ind. Co., respectively. The commercial products were recrystallized from a mixture of MeOH and water before use. For the CN, COOEt, and Ac substitution products, a mixture of bromobenzene with the corresponding substituent at the *para* position, cuprous powder, and potassium phenoxide dried well under high vacuum was refluxed at 190–200 °C for 6 h. In the case of X = Me, Et, and OMe, bromobenzene, cuprous powder, and the well-dried potassium phenoxide with the corresponding substituent at the *para* position were used for the refluxed mixture. Ether extracts from the reaction mixtures were washed with 10% KOH solution and dried over anhydrous K<sub>2</sub>CO<sub>3</sub>. The crude products of the CN, COOEt, and Ac derivatives were purified by column chromatography and recrystallized from petroleum ether (mp 45.0 °C for X = CN, mp 59.0 °C for X = COOEt, and mp 47.0 °C for X = Ac). Diphenyl ethers of X = Me, Et, and OMe were rectified under reduced pressure after passage through a silica gel column. Methylation using dimethyl sulfate easily afforded the NMe<sub>2</sub> substitution product from the NH<sub>2</sub> derivative. The structure and purity of all the samples were checked by thin-layer chromatography, elemental analyses, and mass spectrometry. A good agreement within 0.5% was obtained between calculated and experimental values in the elemental analyses.

The solvents used for spectral measurements were heptane, methylcyclohexane, and 2-methylbutane of spectrograde purity. These were sufficiently dried over CaH<sub>2</sub> and then carefully rectified. Methylcyclohexane and 2-methylbutane were further purified through a column packed in the order of anhydrous sodium sulfate, aluminum oxide, and silicon dioxide.

**Absorption Spectral Measurements.** These were performed in the usual manner at room temperature in heptane with a Hitachi spectrophotometer (model 323) unless otherwise stated. The spectra at 77 K were measured in a mixed solvent of methylcyclohexane and 2-methylbutane (1:13) using a Dewar-type cell<sup>19</sup> under N<sub>2</sub> atmosphere to check whether the preferable conformation of 4-substituted diphenyl ethers is nonrigid. The recorded absorbance was multiplied by 0.798 to correct for any concentration change arising from contraction of the sample solution upon cooling.<sup>1</sup>

**MO Calculations.** Ab initio MO calculations with 6-31G-(d) basis sets were carried out to analyze the minimum energy conformation of diphenyl ether and the derivatives substituted at the *para* position by the CN, COOEt, Ac, NO<sub>2</sub>, Me, OMe, and NH<sub>2</sub> groups. The calculations were simply performed as X = COOH, X = CHO, and X = OH instead of X = COOEt, X = Ac, and X = OMe, respectively. The unsubstituted and substituted benzene rings bridged by the oxygen atom are referred to as rings A and B, respectively, as is illustrated in Chart 1. A regular hexagon of 1.385 Å was assumed for the aromatic rings,<sup>9</sup> in which the C–H distance was fixed at 1.084 Å. Initial bond lengths and bond angles of the substituents employed here were cited from our foregoing paper.<sup>20</sup> The minimum protocol to give credence to evaluation of the conformation of diphenyl ethers may be a full energy minimization of bond lengths, valence angles, and torsion angles of the ether bond and the substituents.<sup>21</sup> The conformational energies optimized for these were therefore computed in the counter rotations ( $\theta_1$  and  $\theta_2$  in Chart 1) to each other at every 15° angle.

To interpret the experimental absorption spectra, CNDO/S-CI calculations were carried out. The parameters necessary for the calculations were taken from the literature of Jaffé's group and others.<sup>22</sup> Two-center repulsion integrals were evaluated using the Nishimoto–Mataga equation.<sup>23</sup> Only the one-electron transition was taken into account for CI calculations.

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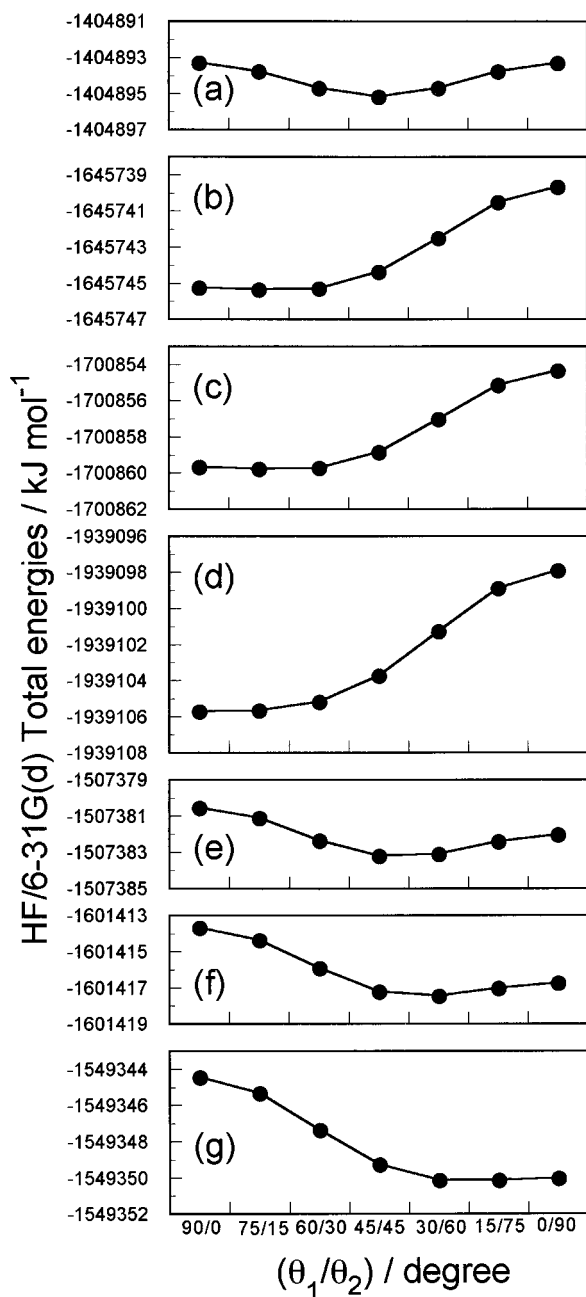
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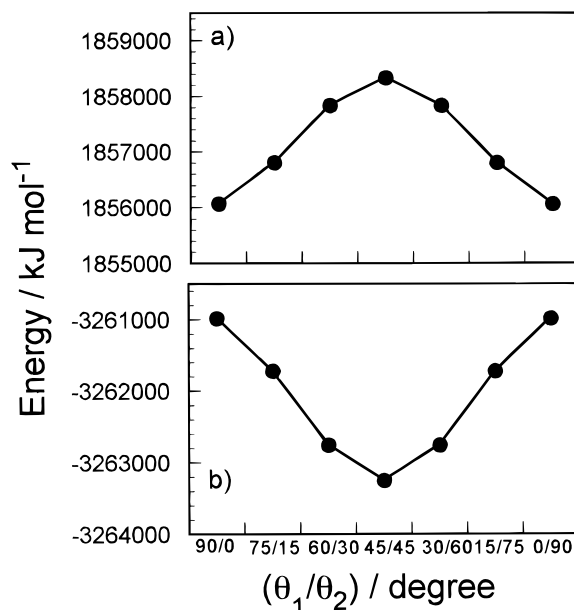


**Figure 1.** HF/6-31G(d) total energies of diphenyl ether (a) and 4-substituted diphenyl ethers with the CN (b), CHO (c), NO<sub>2</sub> (d), Me (e), OH (f), and NH<sub>2</sub> (g) groups pertinent to change in the  $\theta_1$  and  $\theta_2$  angles from 0° to 90° and from 90° to 0°, respectively.

Optimized molecular geometries obtained by the HF/6-31G-(d) calculations were used for the calculations.

## Results and Discussion

**Minimum Energy Conformations of Diphenyl Ether and the 4-Substituted Derivatives.** Although the minimum energy conformation of diphenyl ether was



**Figure 2.** Nuclear repulsion and electronic energies of diphenyl ether calculated by the HF/6-31G(d) method pertinent to change in the  $\theta_1$  and  $\theta_2$  angles from 0° to 90° and from 90° to 0°, respectively.

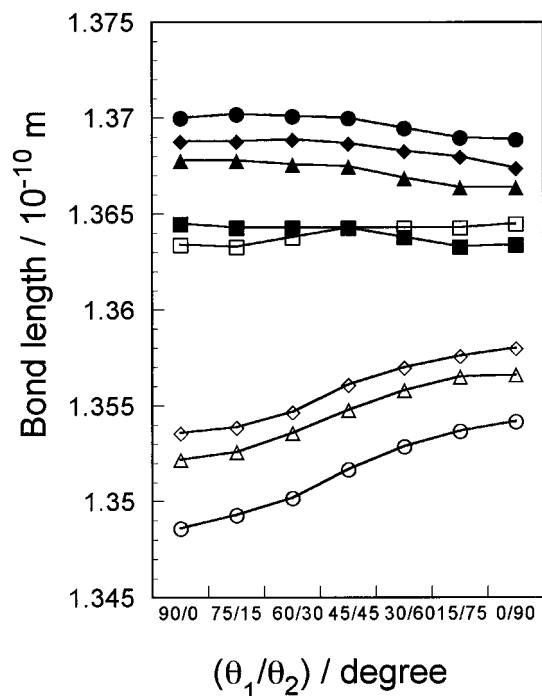
discussed mainly within a framework of HF calculations using the ab initio method with minimal basis sets and semiempirical methods at a single point on the potential energy surface up to the present,<sup>1,3-6</sup> important concepts have been proposed in terms of the conformation, such as the so-called one-ring flip mechanism<sup>4</sup> and the skew form for the internal motion. These results were derived from discussion with regard to a ravine on the conformational energy map of diphenyl ether, as well as from spectroscopic experiments.<sup>1,3-8</sup> We have easily found that the change in the  $\theta_1$  and  $\theta_2$  angles under the condition that  $\theta_1 + \theta_2 \approx 90^\circ$  gives rise to a ravine on the present 6-31G(d) energy map showing the relative total energies calculated at 15° intervals of  $\theta_1$  and  $\theta_2$ . In these conformers, rings A and B form a dihedral angle of almost 90°. The energy of the twist form ( $\theta_1 = \theta_2 = 45^\circ$ ), which is the lowest among the conformers, is only 1.9 kJ mol<sup>-1</sup> lower than that of the highest energy skew conformer, as is illustrated in Figure 1a. The calculations also indicate that the changes in the nuclear repulsion and electronic energies with a conformational alteration from the twist to skew forms are quite large but are just the reverse in the direction of energy change, as seen from Figure 2. The total energies are therefore almost constant for the conformational alteration within the rotation expressed by  $\theta_1 + \theta_2 \approx 90^\circ$ . The fact that the electronic energy is remarkably stabilized in the twist form may be due to the conjugation between rings A and B through a lone-pair  $\pi$ -orbital on the bridging oxygen atom. On the contrary, the nuclear repulsion energy is remarkably larger in the twist form than in the skew form. This would undoubtedly arise from the steric hindrance between the *ortho* hydrogen atoms.<sup>24</sup> Present calculations suggest that diphenyl ethers easily internally rotate around the C–O bonds, keeping the dihedral angle of the two phenyl rings at about 90°, and provide

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**Figure 3.** Change in the HF/6-31G(d) optimized C–O bond lengths to ring A (■ for X = H, ▲ for X = CHO, ◆ for X = CN, and ● for X = NO<sub>2</sub>) and to ring B (□ for X = H, △ for X = CHO, ◇ for X = CN, and ○ for X = NO<sub>2</sub>) with the conformational alteration within the ravine on the energy maps for diphenyl ether and the substitution products by the electron-accepting group.

good agreement with recent experiments and calculations.<sup>1,3–8</sup>

It is clearly found that the nonrigid conformation of diphenyl ether mentioned above is brought about by the balance between conjugation and steric crowding, as seen from Figure 2. This suggests that substituent electronic effect on the  $\pi$ -electronic system of diphenyl ether is advantageous to the conformational control of the oxygen-bridged aromatic rings. In fact, the ravine ( $\theta_1 + \theta_2 \approx 90^\circ$ ) of the conformational HF/6-31G(d) energy map descends to the skew form of  $\theta_1 = 90^\circ$  and  $\theta_2 = 0^\circ$  with the introduction of an electron-acceptor at the *para* position of ring B. It may be said that this behavior favorably correlates with an increase in the electron-accepting ability of substituents, as can be clearly seen from Figure 1a–d. Although the skew model of diphenyl ethers is unfavorable in terms of  $\pi$ -electronic interaction between rings A and B (Figure 2), some characteristic interaction may be expected between the electron-accepting substituent and the diaryl ether moiety. It is reasonable that the  $\theta_2$  angle of  $0^\circ$  occurs due to the intramolecular charge-transfer interaction of the electron-withdrawing substituents with the  $\pi$ -lone pair of the ether oxygen through the  $\pi$ -electronic system of ring B. Figure 3 shows the optimized C–O bonds of the diphenyl ether and the derivatives with the electron-accepting substituent. In the preferable  $\theta_1 = 90^\circ$  and  $\theta_2 = 0^\circ$  skew conformation, the optimized C–O bond length to ring B is noticeable short compared to the other conformers. It is strongly suggested that the substituent effect allows the conformations to be rigid in the preferable skew form ( $\theta_1 = 90^\circ$  and  $\theta_2 = 0^\circ$ ), with the balance between steric repulsion and conjugation being lost by the intramolecular charge-transfer interaction.

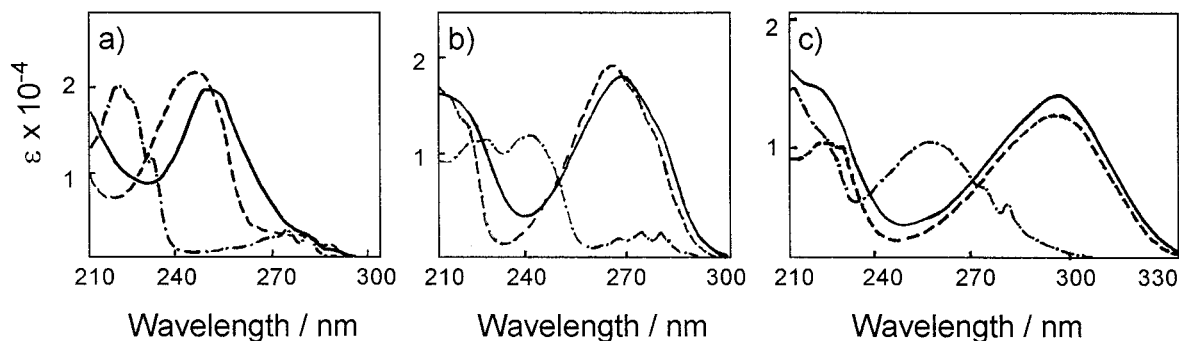
The change in the conformational energy for the electron-donor substituted derivatives looks very different from that for the electron-accepting substituents (Figure 1e–g). It seems that the substituent competes with the bridging oxygen  $\pi$ -lone pair for electron donation to the  $\pi$ -electronic system of ring B rather than contributing to the stabilization of ring B by the intramolecular charge-transfer interaction, because both the substituent and the ether oxygen have electron-donating nature.<sup>25,26</sup> This is supported experimentally by the fact that additivity of the substituent effect on the  $\pi$ -electronic system of benzene is not so good on the *para*-disubstitution products of donors.<sup>25,26</sup> The calculation results reasonably show that the twist conformation in conjugation of ring A with ring B is most favorable if the substituent is not so strong. However, in the case of substitution by strongly donating groups, the competitive electron donation to ring B allows the conformation to be in the neighborhood of  $\theta_1 = 0^\circ$  and  $\theta_2 = 90^\circ$ , the independent conjugation of the oxygen  $\pi$ -lone pair with ring A taking precedence of the conjugation over the whole molecule through the bridging oxygen. This behavior is in contrast to a synergistic effect in terms of the strong intramolecular charge-transfer interaction by electron-accepting substituents. The derivatives with the strong donor may therefore preferentially adopt the skew conformation of  $\theta_1 = 0^\circ$  and  $\theta_2 = 90^\circ$ , avoiding the competition for electron donation and the steric hindrance.

**Electronic Spectra of 4-Substituted Diphenyl Ethers with an Electron Acceptor and Their Conformations.** Figure 4 shows the absorption spectra of 4-substituted diphenyl ethers with the electron-accepting group. The spectra of diphenyl ethers adopting the skew form should be similar to the composite spectra of the corresponding 4-substituted anisole and toluene (model 1) or of the corresponding substituted benzene and anisole (model 2), because there is no interaction between the  $\pi$ -electronic systems of rings A and B. These composite spectra for the models of 1 and 2 are also illustrated in Figure 4. The longest wavelength band in the composite spectra of model 1 is assigned to the intensive  ${}^1L_a$  band arising from the benzenoid  ${}^1A_{1g} \rightarrow {}^1B_{1u}$  transition of 4-substituted anisole over the weak  ${}^1L_b$  band arising from the benzenoid  ${}^1A_{1g} \rightarrow {}^1B_{2u}$  transition of toluene.<sup>25,26</sup> The characteristic  ${}^1L_a$  band of 4-substituted anisoles with a strongly electron-accepting group is contributed from the intramolecular charge-transfer configuration from the  $\pi$ -electronic system of the ring involving the oxygen atom to the substituent.<sup>26,27</sup> It is found that the spectra of the diphenyl ethers with an electron-withdrawing substituent observed here are similar to the composite spectra of model 1 and agree with the composite spectra as the electron-accepting ability of the substituent increases. The derivative of X = COOEt showed the same spectral profile as that of X = CN. When the NO<sub>2</sub> group is introduced, the spectra provide excellent agreement with the composite spectra of model 1. These results imply that 4-substituted diphenyl ethers with an electron-accepting group preferentially adopt the conformation in which the  $\pi$ -lone pair

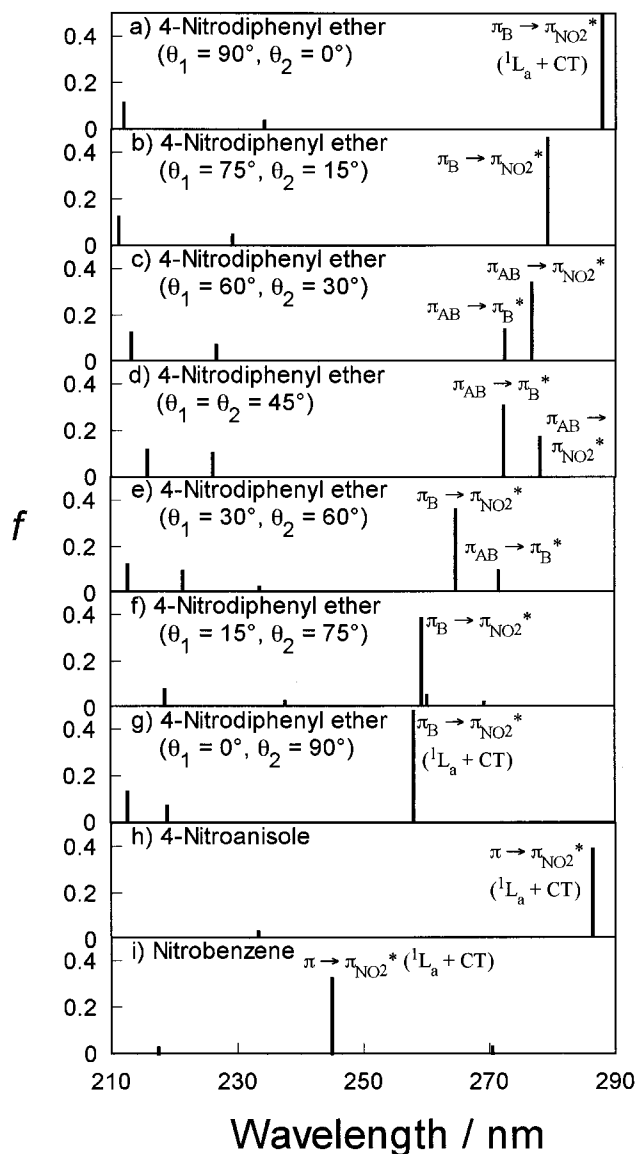
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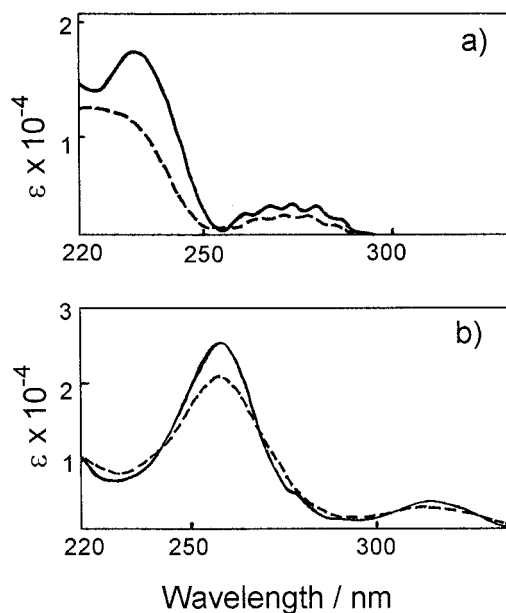
**Figure 4.** Absorption spectra of 4-substituted diphenyl ethers with an electron-accepting group (solid line) and of the composite models of 1 (---) and 2 (-·-) in heptane (a for X = CN, b for X = Ac, and c for X = NO<sub>2</sub>).



**Figure 5.** CNDO/S-CI calculation results for 4-nitrodiphenyl ether (a–g), 4-nitroanisole (h), and nitrobenzene (i). The  $f$  values denote the calculated oscillator strength. The symbols of  $\pi_A$ ,  $\pi_B$ ,  $\pi_{AB}$ , and  $\pi_{NO_2}$  denote the  $\pi$ -orbitals localized or delocalized in rings A, B, both A and B, and the NO<sub>2</sub> group, respectively.

of the ether oxygen conjugates with the  $\pi$ -electronic system of ring B.

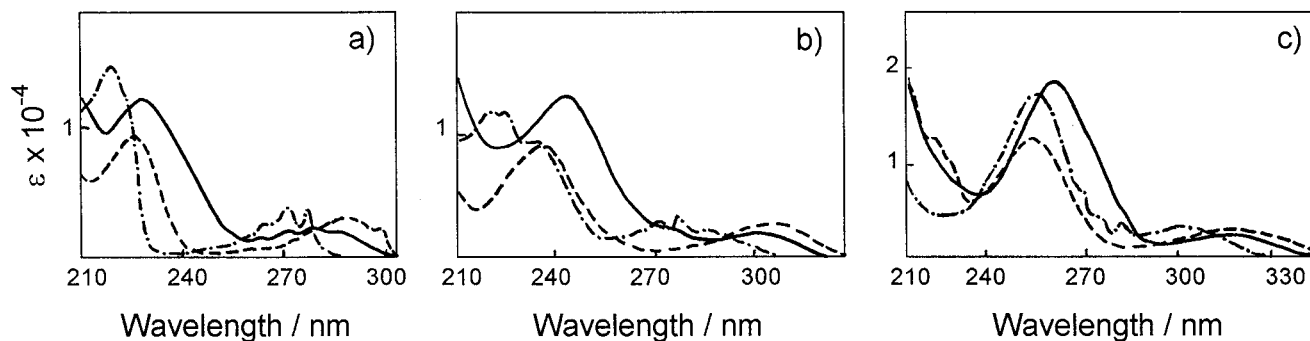
CNDO/S-CI calculations were performed to gain more insight into the relation between the spectra and the



**Figure 6.** Absorption spectra of X = Me (a) and X = NMe<sub>2</sub> (b) in a mixture of methylcyclohexane and 2-methylbutane (1:13) at 77 K (solid line) and room temperature (---).

conformation of 4-substituted diphenyl ethers, and the results for X = NO<sub>2</sub> are illustrated in Figure 5. The longest wavelength high-intensity band for the skew form ( $\theta_1 = 90^\circ$ ,  $\theta_2 = 0^\circ$ ) of 4-nitrodiphenyl ether and 4-nitroanisole is contributed mainly from the  ${}^1L_a$ -type intramolecular charge-transfer configuration ( $\pi_B \rightarrow \pi_{NO_2}^*$ ) from the HOMO delocalized in ring B involving the bridging oxygen ( $\pi_B$ ) to the LUMO localized in the NO<sub>2</sub> group ( $\pi_{NO_2}^*$ ). The conformational change from skew ( $\theta_1 = 90^\circ$ ,  $\theta_2 = 0^\circ$ ) to twist ( $\theta_1 = \theta_2 = 45^\circ$ ) allows the characteristic band to be blue-shifted and weakened and split into two due to interaction with the electronic configuration delocalized in both rings A and B. The further alteration in conformation from twist to skew ( $\theta_1 = 0^\circ$ ,  $\theta_2 = 90^\circ$ ) causes the remarkable blue-shift of the band, as shown in Figure 5. Note here that the skew form of  $\theta_1 = 0^\circ$  and  $\theta_2 = 90^\circ$  shows the  ${}^1L_a$  band at a wavelength longer than that for nitrobenzene because of through-space and through-bond interactions.<sup>1,28</sup> Thus, the calculations for the skew form of  $\theta_1 = 90^\circ$  and  $\theta_2 = 0^\circ$  reasonably reproduce the experimental spectra of the NO<sub>2</sub> derivative. The calculations for the  $\theta_1 = 90^\circ$  and  $\theta_2$

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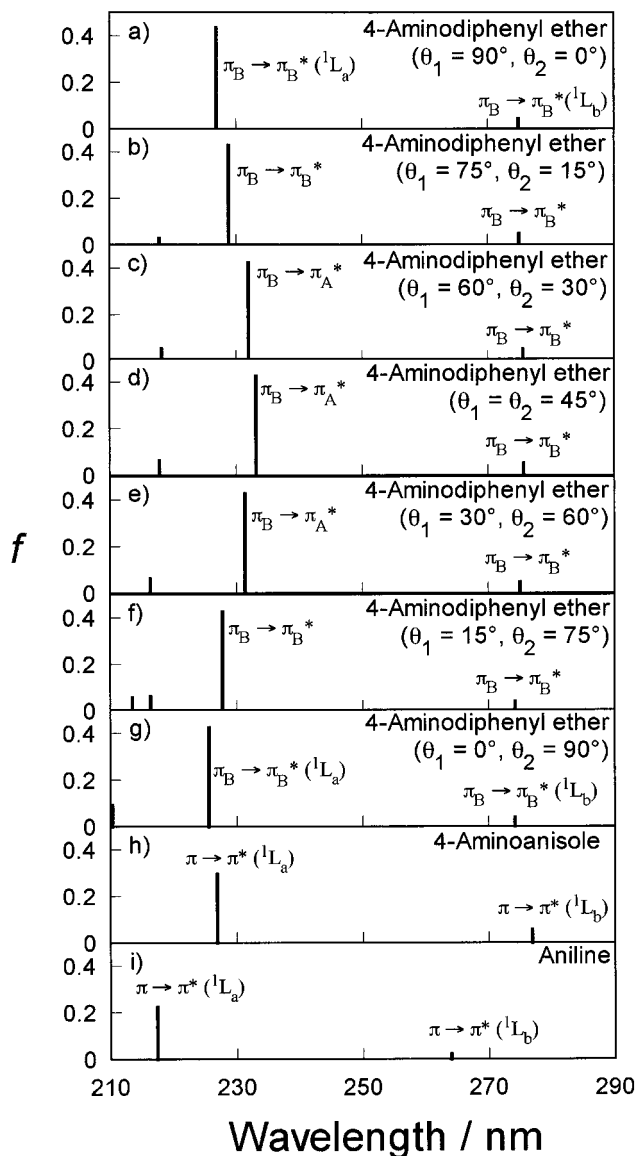


**Figure 7.** Absorption spectra of 4-substituted diphenyl ethers with an electron-donating group (solid line) and of the composite models of 1 (---) and 2 (-·-) in heptane (a for X = OMe, b for X = NH<sub>2</sub>, and c for X = NMe<sub>2</sub>).

= 0° skew form of the Ac derivative also provide good agreement with experiments. On the other hand, the calculation results for X = COOEt and X = CN reproduce the experimental spectra when  $\theta_1 = 75^\circ$  and  $\theta_2 = 15^\circ$  rather than  $\theta_1 = 90^\circ$  and  $\theta_2 = 0^\circ$ . These results, as well as the HF/6-31(d) calculations, reasonably indicate that the electron-accepting effect of substituents on the  $\pi$ -electronic system of diphenyl ether allows the nonrigid conformation to be fixed into the preferable skew form of  $\theta_1 = 90^\circ$  and  $\theta_2 = 0^\circ$  due to the stabilization arising from the intramolecular charge-transfer interaction.

**Electronic Spectra of 4-Substituted Diphenyl Ethers with an Electron Donor and Their Conformations.** Figure 6 shows the electronic spectra of the derivatives of X = Me and X = NMe<sub>2</sub> at room temperature and 77 K. A decrease in temperature in spectral measurements generally makes the absorption band sharp without affecting the absorption maximum and the integrated intensity.<sup>29</sup> It is clearly found that the broad <sup>1</sup>L<sub>a</sub> band of the alkyl substitution derivatives is remarkably intensified and red-shifted at 77 K, as is shown in Figure 6. These phenomena are reasonably interpreted as indicating that the derivatives with the alkyl group, as well as diphenyl ether, are in a nonrigid conformation at room temperature and adopt a fixed one at 77 K because the substituent effect of the alkyl groups is insufficient to fix the flexible conformation. However, the <sup>1</sup>L<sub>a</sub> and <sup>1</sup>L<sub>b</sub> bands of the other derivatives show a tendency to become sharp without shift of the absorption maximum, as is seen from the spectra of the NMe<sub>2</sub> derivative illustrated in Figure 6. This implies that the strongly electron-donating substituents are enough to control the conformation of the oxygen-bridged aromatic rings.

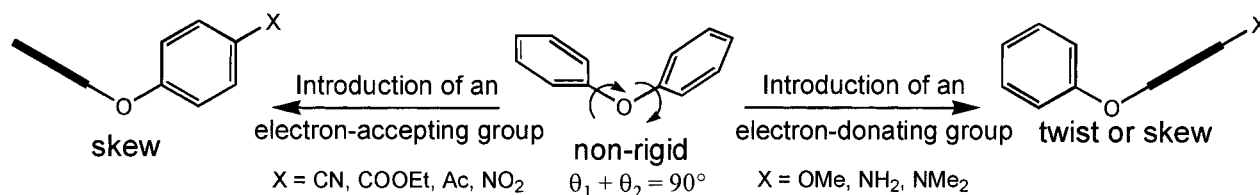
Next, the discussion was extended to the conformation fixed by the strongly electron-donating substituents. Introduction of the electron-donating substituent somewhat complicates the interpretation of the spectra compared to that of the electron-withdrawing substituent. Figure 7 shows the absorption spectra of diphenyl ethers with the OMe, NH<sub>2</sub>, and NMe<sub>2</sub> groups and their composite models as mentioned above. The longest wavelength band of the diphenyl ethers is close to the composite spectra of model 1 as the electron-donating ability of the substituents increases. However, the high-intensity band appears at a wavelength longer than those of both of the composite models. Clear-cut evidence has been yielded by CNDO/S-CI calculations for the spectral



**Figure 8.** CNDO/S-CI calculation results for 4-aminodiphenyl ether (a–g), 4-aminoanisole (h), and aniline (i). The  $f$  values denote the calculated oscillator strength. The symbols of  $\pi_A$  and  $\pi_B$  denote the  $\pi$ -orbitals delocalized in rings A and B, respectively.

characteristics. Figure 8 shows the calculated spectra for X = NH<sub>2</sub>. The longest wavelength band is assigned to the <sup>1</sup>L<sub>b</sub>-type band (benzenoid <sup>1</sup>A<sub>1g</sub> → <sup>1</sup>B<sub>2u</sub> transition)<sup>25,26,30,31</sup> taking its rise in ring B and is calculated at the same

(29) Yamakawa, M.; Kubota, T.; Ezumi, K.; Mizuno, Y. *Spectrochim. Acta* **1974**, *30*, 2103.

**Chart 2. Proposed Conformational Alteration of the Diaryl Ether Moiety with Introduction of a Substituent**

transition energy independent of whether the conformation is skew or twist. However, the strong band contributed mainly from the typical  ${}^1L_a$ -type configurations of ring B appears at the longest wavelength for the twist conformer, sensitively affected by conjugation between rings A and B. On the basis of the observed and calculated relative transition energies for the composite models and the diphenyl ether, the derivative of  $X = \text{NH}_2$  seems to adopt the preferable twist conformation. These behaviors also appeared in the case of substitution by the OMe group. The calculated spectra of the  $\theta_1 = 30^\circ$  and  $\theta_2 = 60^\circ$  twist conformer agreed well with the observed spectra for the derivative of  $X = \text{NMe}_2$ . A consideration of the 6-31G(d) calculation results has reasonably led to the conclusion that the strongly electron-donating substituents allow the diaryl ether moiety to adopt the rigid twist or skew ( $\theta_1 = 0^\circ$ ,  $\theta_2 = 90^\circ$ ) form, although the present CNDO/S-CI interpretation is not sufficient to identify the precise conformation from the experiments.

### Conclusions

It has been found that the conformation around the diaryl ether bond is governed by substituent electronic

effect on the  $\pi$ -electronic system, as well as by steric effect. An electron-accepting substituent attached at the *para* position of a benzene ring allows the conformation to adopt the stable skew form of  $\theta_1 = 90^\circ$  and  $\theta_2 = 0^\circ$ , and derivatives with an electron-donating substituent prefer the twist or skew form in which the C–O bond to ring B is twisted, as is illustrated in Chart 2. The preferable skew form of diphenyl ethers with an electron-accepting substituent is contributed by the synergistic intramolecular charge-transfer interaction between the bridging oxygen  $\pi$ -lone pair and the substituent through ring B. The twist or skew ( $\theta_1 = 0^\circ$ ,  $\theta_2 = 90^\circ$ ) conformation produced by introduction of an electron-donating group arises from a competition between the substituent and the ether oxygen for intramolecular charge-transfer interaction. The alkyl substituents have insufficient electronic effect to govern the conformation of diaryl ethers. The present conclusion is important to the extended discussion of the structure–activity relationships of isodityrosines and thyroid hormones.

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