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Shielding Effect of Carbonyl Group and its Application to the Conformational Analysis of 1,1,10,10-Tetramethyl[3.3]metacyclophane-2,11-dione

Yoshimasa Fukazawa,* Yanyan Yang, Tatsuhiko Hayashibara, and Shuji Usui

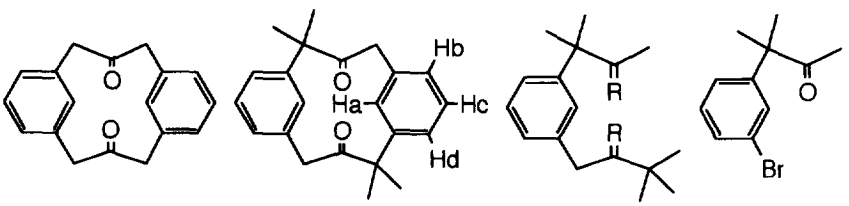
Department of Chemistry, Hiroshima University, Higashi-Hiroshima 739, Japan

Abstract: The conformational analysis of the title compound (**2**) using X-ray crystallographic analysis, molecular mechanics calculations, and chemical shift simulation method is presented. Temperature dependent signal behavior of **2** in its ^{1}H NMR spectrum showed that a single anti conformer plays a significant role in its conformational dynamic equilibrium with very small contribution of syn structures. The structure of the anti conformer was analyzed by our newly developed technique using chemical shift simulation. The structure of the anti conformer was thus determined unequivocally in solution, and is identical with the structure found in the crystalline state.

INTRODUCTION

Determination of significantly populating conformers in extremely flexible molecules such as macrocycles is a matter of long standing interest. Conformations of macrocycles have been analyzed mainly by NMR spectroscopy taking advantage of the torsional-dependent ^{3}J coupling constants[1] and distance-dependent NOE.[2] However, both methods may result in misleading conclusions if conformational dynamic equilibrium between the many different structures is operative. The observed coupling constants are the weighted average of those of the equilibrating conformers and it is not easy to separate them into individual conformers. The same difficulty is encountered in the latter method. Recently, an efficient method for conformer population analysis has been reported using NOE data.[3] We have developed a useful and very reliable method for the conformational analysis of the flexible molecules using a combination of molecular mechanics calculations and chemical shift simulation of certain protons.[4] For this method, information is necessary not only on the structures of dynamically equilibrating conformers but also on the calculated chemical shifts of the protons of these conformers. The calculation of the total chemical shift of a proton in a molecule can be achieved theoretically,[5] but it is still difficult to use this method practically. On the other hand, the calculation of the change in chemical shift of a proton produced by nearby substituents has been successfully accomplished.[6] The induced chemical shifts due to anisotropy effect of aromatic ring[7] as well as macrocyclic π system such as porphyrins[8] have been proved to be a useful geometrical probe of the structures. In our previous paper, the structures of three dynamically equilibrating conformers of a macrocyclic hydrocarbon containing two benzene rings have been determined by our new method without the use of the freezing technique.[9] Our continuous effort to widen the applicability of the chemical shift simulation method to heteroatom-containing compounds has succeeded in predicting the most

stable conformer of [3.3]metacyclophanedione (**2**)[10], a twelve membered ring compound having two benzenes and two carbonyls.[11] Our method for the analysis consists of three stages: the generation of plausible structure, estimation of the chemical shifts of the aromatic protons of these structures by induced shift caused by the aromatic ring and carbonyl group in the molecule, and selection of the most promising conformers by comparison of the observed and calculated shifts. Here, we present the details of the analysis.



1 **2** **3** R = H_2 **4**
5 R = O

RESULTS AND DISCUSSION

X-Ray Crystallography

The ORTEP drawing of **2** is shown in Figure 1. The structure found in the crystal is essentially C_i symmetric. The two aromatic rings are both planar and placed in a stepped anti fashion and hence parallel with each other. Similar stepped anti arrangement of the two aromatic rings has been observed in a derivative of **1**.[12] In the latter case highly symmetric C_{2v} structure was observed in the crystalline state. Hence, a small but conspicuous difference of the structures between the two is seen. Sliding sideways of the benzene ring with respect to the other, and tilting of the carbonyl oxygens from the C_2 axis of **1** are found in **2**. The sliding of the aromatic rings and the tilting of the carbonyls of **2** should thus arise from the asymmetric substitution of the bridging chains of **1**.

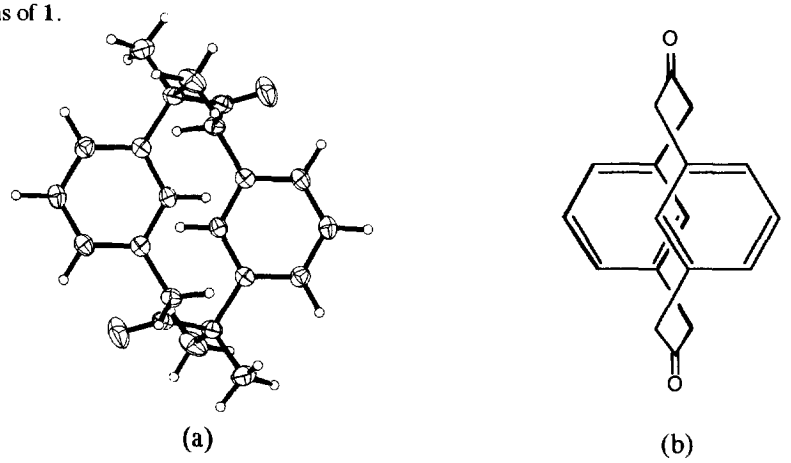


Figure 1. Structures of **1** and **2**; (a) ORTEP drawing of **2**, (b) C_{2v} structure of **1**.

Structure of Conformers

Although the anti-periplanar structure is obtained by the X-ray crystallographic analysis, it does not give the conclusive evidence of the most stable structure. It is quite often to find that the structure in solution is different from that in crystal and especially so in case of extremely flexible compounds.[13] In order to obtain information of the structures in solution, energies of all the possible conformers of **2** were estimated.

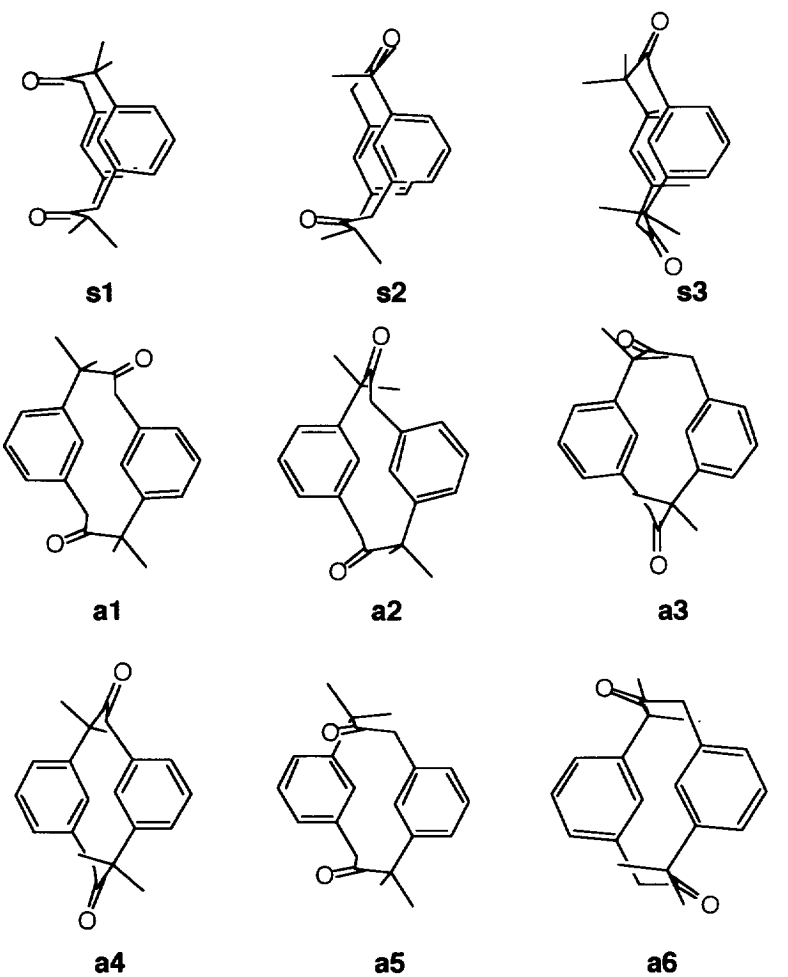


Figure 2. Structures of all the possible conformers of **2**.

Since **2** has extremely flexible 12-membered carbocycle, all the plausible geometries are generated by the use of a systematic conformer search program.[14] We have already prepared such a program, MMRS[15] and by applying the program three syn and six anti conformers were obtained (Figure 2). Since calculated NMR shifts are known to be dependent on the molecular geometries, all of these structures were optimized by three different methods,

Table 1. Steric Energies (MM3) and Heat of Formations (AM1, PM3) for Conformers of **2** (kcal/mol)[a].

Conformer	MM3	AM1	PM3
s 1	21.781	-32.355	-43.230
s 2	22.384	-32.332	-44.417
s 3	22.990	-31.479	-45.468
a 1	23.500	-33.945	-44.857
a 2	24.087	-33.945	-43.810
a 3	25.918	-30.620	-42.758
a 4	26.346	-33.945	-41.640
a 5	27.248	-31.004	-42.583
a 6	29.529	-30.118	-42.521

[a] cal=4.18 J

a molecular mechanics method (MM3[16]) and two semiempirical molecular orbital methods (AM1[17] and PM3[18]). Although MM3 and PM3 calculations gave all the nine optimized structures, some of the anti structures (**a 1**, **a 2** and **a 4**) are converged to the single structure (**a 1**) by AM1. MM3 calculations suggested that all the syn structures are more stable than any one of the anti structure. While the most stable conformer predicted by AM1 is **a 1** that for PM3 is **s 3**. Steric energies (MM3) and heat of formations (AM1 and PM3) for these conformers are summarized in Table 1. Relative stability of these conformers by the three optimization methods are compared in Figure 3. Since a harmonic vibrational frequency analysis with MM3 disclosed that conformer **a 4** has two imaginary frequencies, we excluded the conformer from further analysis. Structures obtained by the different optimization methods are not identical to each other. For example, the dihedral angles between the two aromatic rings are different in the three **s 1** structures (18.0°, MM3; 41.5°, AM1; 36.7°, PM3), and the distances between the centroids of the two benzene rings in conformer **a 1** increase in the order of MM3 < AM1< PM3.

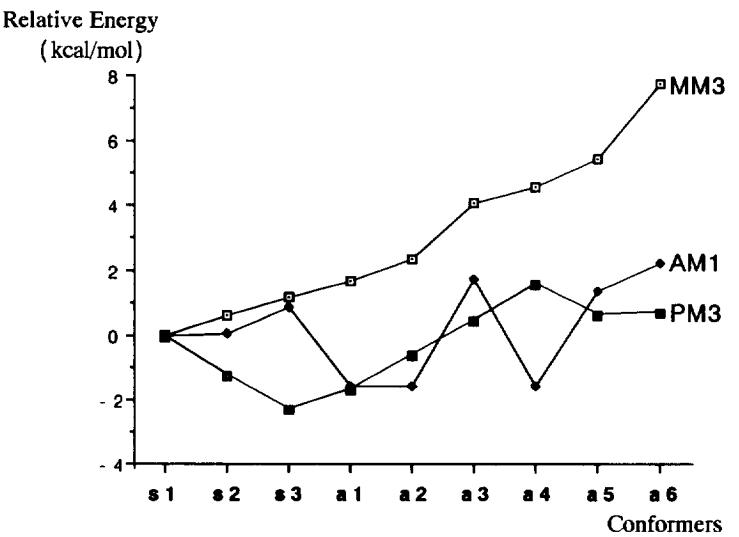


Figure 3. Comparison of conformers for **2**.

We must appreciate the reliability of these optimized structures and select the most trustworthy one. For this purpose, the three structures of conformer **a1** were compared to that found in crystal. A superimposed analysis of the calculated structures with the observed one was carried out. When one of the benzene rings of a calculated structure was superimposed onto that of the observed, the other benzene rings of the two structures did not completely overlap. Separation of the two benzene rings was estimated by the root mean square deviations between the six benzene carbons of the two structures (rmsd; MM3 = 0.031 Å, AM1 = 0.169 Å, PM3 = 0.622 Å). Obviously, the structure predicted by the MM3 calculation is almost completely superimposable to that obtained by the X-ray crystallographic analysis. On the other hand, the structures of the two semiempirical MO methods showed large deviations suggesting smaller reliability as far as the structures are concerned. As a result of the analysis we can conclude that MM3 calculations give correct geometries for these type of cyclophanes. It also suggested that the reliability of the structure of the other conformers predicted by the MM3 calculation should be sufficiently high.

Calculation of the Substituent-Induced Chemical Shift for Carbonyl Group

Substituent-induced shift (SIS) is defined by a change in chemical shift of a proton in a C-H bond produced by a substituent in a molecule. Two mechanisms have been proposed responsible for the chemical shift increment. One is based on the anisotropy of the magnetic susceptibility[19] and the other is on the electric-field effects[20] due to the dipole moment of the substituent. Several models for estimation of SIS for carbonyl group have been proposed. They usually employed a combination of the two effects. Zürcher[21] as well as ApSimons[22] employed several different keto-steroids to observe the SIS values of angular methyl groups, and proposed their NMR shielding parameters. Recently, the revised parameters of the old ApSimon's values have been reported using new SIS values of not only the angular methyl group but all the proton chemical shifts of three different oxo-5α-androstanes whose structures were obtained by MM2 calculations.[23] ApSimon's method, however, is rather complicated because the magnetic anisotropy of C-H bond should be taken into account. On the other hand, Zürcher's approach is more simple because it can neglect the magnetic anisotropy of the C-H bond[21,24] and it is known to give satisfactory result. Hence, we employed the latter model. To obtain the NMR shielding parameters for estimating the effect due to the anisotropy and the electric field, several geometric factors between the substituents and the proton in question are needed. Since the Zürcher's original shielding parameters were obtained without using MM3 calculation we calculated the geometrical factors by MM3 in order to get consistency of the analysis.

A least-squares multiple regression analysis using these geometrical factors and the Zürcher's observed SIS values of the angular methyl of several ketosteroids leads new NMR shielding parameters for carbonyl group [$\Delta\chi_1^{C=O}$ = 29.2 (25.7), $\Delta\chi_2^{C=O}$ = 15.9 (12.2) ($\times 10^{-30}$ cm/molecule), and κ = -12.5 (-12.2) ($\times 10^{-12}$ e.s.u., old Zürcher's values in parentheses)]. Excellent correlation of these data is obtained in a linear regression analysis [$\Delta\delta_{calc} = a \cdot \Delta\delta_{obs} + b$; a = 0.935, b = 0.008, R = 0.947, for 14 data set (range of the observed data -0.033 ~ 0.367 ppm)].

Table 2. The Observed and Calculated Induced Shifts of Oxo-5α-androstane.

proton position	shift value (ppm)			
	obs (3-oxo)[a]	calc (3-oxo)	obs (11-oxo)[a]	calc (11-oxo)
1α	0.45	0.402	-0.13	-0.288
1β	0.35	0.452	0.74	0.769
2α	0.77	1.381	0.00	0.006
2β	0.96	1.224	0.00	-0.059
3α			-0.04	-0.035
3β			-0.02	0.015
4α	0.84	1.395	0.01	0.014
4β	1.02	1.220	0.01	0.048
5	0.45	0.387	-0.07	0.049
6α	0.11	0.196	0.01	0.098
6β	0.11	0.165	0.01	0.096
7α	0.03	0.068	0.19	0.171
7β	0.04	0.091	0.10	0.171
8	0.05	0.077	0.36	0.397
9	0.07	0.101	1.00	1.319
11α	0.02	0.057		
11β	0.13	0.072		
12α	0.02	0.032	1.15	1.206
12β	0.02	0.045	0.54	1.332
14	0.02	0.029	0.64	0.459
15α	0.00	0.024	0.12	0.151
15β	0.01	0.017	0.08	0.127
16α	0.03	0.020	0.16	0.109
16β	0.03	0.018	0.16	0.104
17α	0.00	0.015	0.22	0.160
17β	-0.02	0.022	0.03	0.183
18	0.03	0.022	-0.03	-0.045
19	0.23	0.226	0.22	0.125

[a] Values are taken from ref. 22.

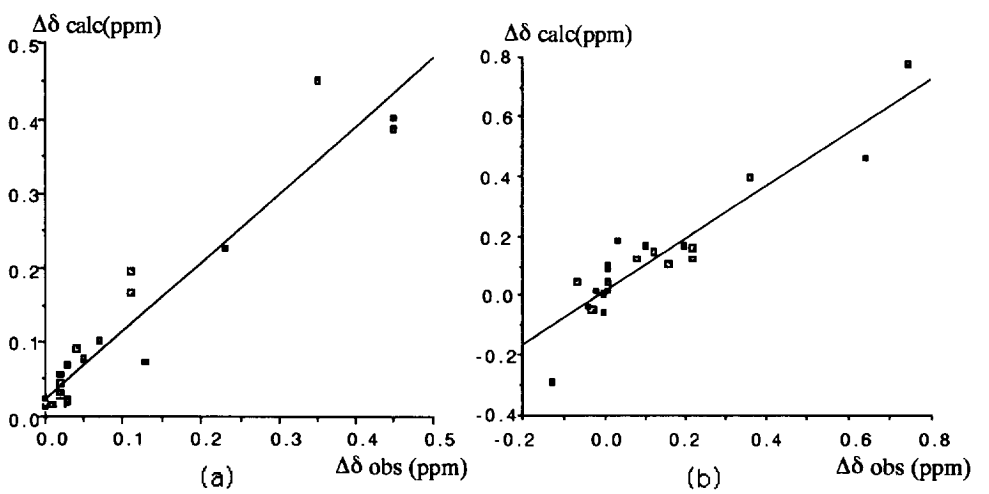


Figure 4. Observed and calculated SIS (a) in 5α-androstan-3-one and (b) in 5α-androstan-11-one.

With the new NMR shielding parameters, we calculated the SIS values for all the protons of 5α-androstan-3- and 11-one and compared with those reported.[23] In Table 2, the observed and calculated induced shifts for all the protons of the ketosteroids are listed. Again, excellent correlation of these data is obtained in a linear regression analysis, where the data of protons vicinal to the carbonyl group are omitted because of the close proximity to the carbonyl group.[25] [for 5αH-androstan-3-one, a set of 22 data (range of the observed data -0.07 ~ 0.36 ppm) $\Delta\delta_{calc} = a \cdot \Delta\delta_{obs} + b$; a = 0.914, b = 0.025, R = 0.956; for 5αH-androstan-11-one, a set of 23 data (range of the observed data -0.13 ~ 0.74 ppm) $\Delta\delta_{calc} = a \cdot \Delta\delta_{obs} + b$; a = 0.890, b = 0.016, R = 0.924 (Figure 4); for 5αH-androstan-3-one and 5αH-androstan-11-one, a set of 45 data (range of the observed data -0.13 ~ 0.74 ppm) $\Delta\delta_{calc} = a \cdot \Delta\delta_{obs} + b$; a = 0.895, b = 0.016, R = 0.934].

Calculation of Induced Shift of the Aromatic Protons

The observed incremental shift of the individual aromatic proton of **2** was obtained from the difference between the chemical shift of **2** and its reference compound, 1-(3,3-dimethylbutyl)-3-(1,1-dimethylpropyl)-benzene (**3**) in $CDCl_3$. The calculated incremental shift of the individual aromatic proton of each conformer can be estimated by addition of the increments caused by the benzene ring and the carbonyl groups. We earlier developed a method to estimate induced shift value due to the ring current of the nearby benzene ring by line current approximation.[4] Chemical shift increments caused by the carbonyl group can be estimated by our new parameters. In Table 3 are listed the observed and calculated induced shifts of the four aromatic protons of all the possible conformers. Conformer **a1** is calculated to be the most stable of the five anti structures by MM3, but all the syn structures are predicted to be more stable than **a1**. Comparison of the observed and calculated chemical shifts, however, suggests that **a1** should be the main conformer in solution.

Table 3. Observed and Calculated Induced Shifts of the Aromatic Protons and Steric Energies (MM3) of the Conformers.

			Δδ (ppm)							
	obs.		calc.[a]							
			s1	**s2**	**s3**	**a1**	**a2**	**a3**	**a5**	**a6**
Ha		Ar[b]	0.296	0.368	0.385	1.280	1.932	1.996	1.478	1.504
		CO[c]	-0.004	-0.247	-0.459	0.097	-0.254	-0.276	0.059	-0.035
	1.296	total	0.292	0.121	-0.074	1.377	1.678	1.720	1.537	1.469
Hb		Ar[b]	0.558	0.581	0.564	-0.073	-0.040	-0.037	-0.052	-0.061
		CO[c]	-0.267	-0.223	-0.153	-0.479	-0.281	-0.187	-0.193	-0.189
	-0.546	total	0.291	0.358	0.411	-0.552	-0.321	-0.224	-0.245	-0.250
Hc		Ar[b]	0.569	0.567	0.566	-0.059	-0.055	-0.046	-0.039	-0.056
		CO[c]	-0.196	-0.115	-0.035	-0.118	-0.132	-0.132	-0.106	-0.108
	-0.161	total	0.373	0.452	0.531	-0.177	-0.187	-0.178	-0.145	-0.164
Hd		Ar[b]	0.505	0.480	0.513	-0.068	-0.055	-0.049	-0.055	-0.065
		CO[c]	-0.262	-0.179	-0.109	-0.192	-0.221	-0.219	-0.181	-0.464
	-0.155	total	0.243	0.301	0.404	-0.260	-0.276	-0.268	-0.236	-0.529

[a] A minus sign denotes down field shift. [b] Values are due to the facing benzene ring. [c] Values are due to the two carbonyl groups.

Conformational Dynamic Process

Conformational dynamic processes of **2** were analyzed by temperature dependent ^{1}H NMR spectra (Figure 5). When the temperature was lowered the sharp methyl singlet became broad and decoalesced at -65°C, then split into two singlets at -80°C, indicating that flipping of the benzene rings is slowed down below -65°C. The free energy of activation for the flipping process is obtained to be 9.8 kcal/mol. On the other hand, all the signals due to the aromatic protons remain essentially unchanged, and no minor signal could be detected even at the lowest temperature. The observed temperature dependent signal behavior can be explained by the interconversion of a main conformer to its mirror image by the flipping of the benzene rings. Such a flipping mechanism has been proven operative in [3.3]metacyclophanes.[4a,26]

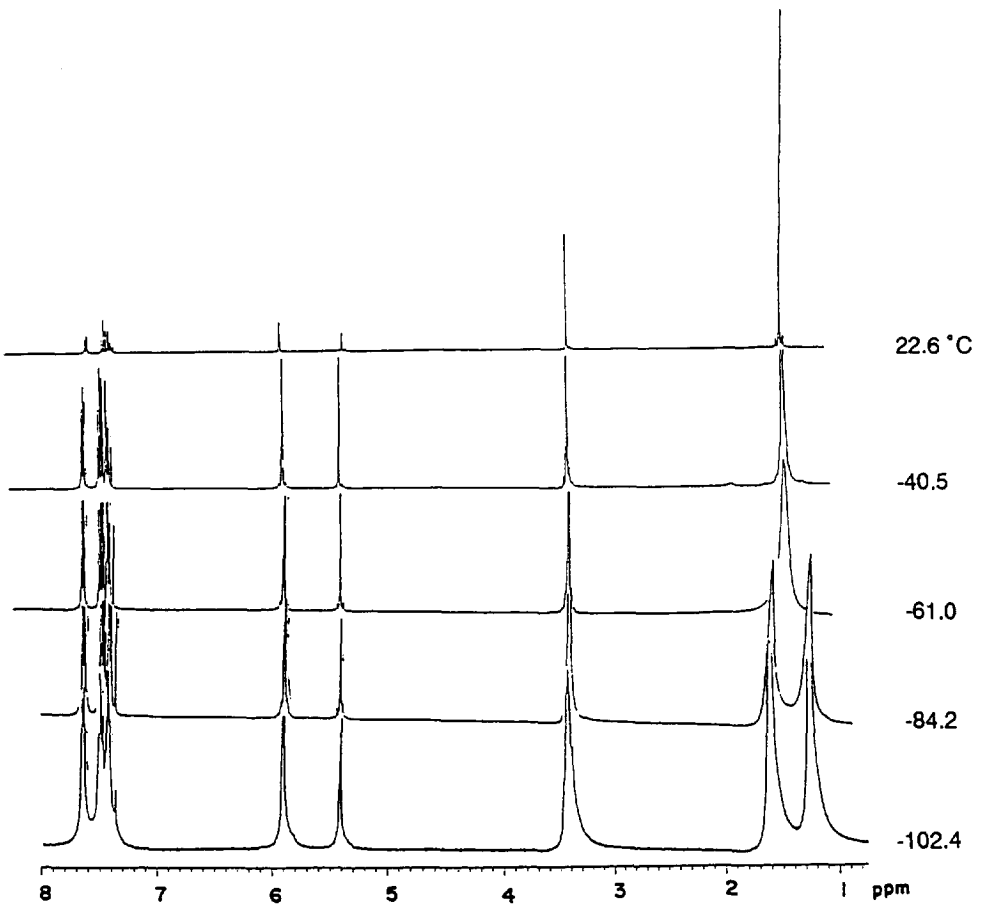


Figure 5. Temperature dependent ^{1}H NMR spectra of **2**.

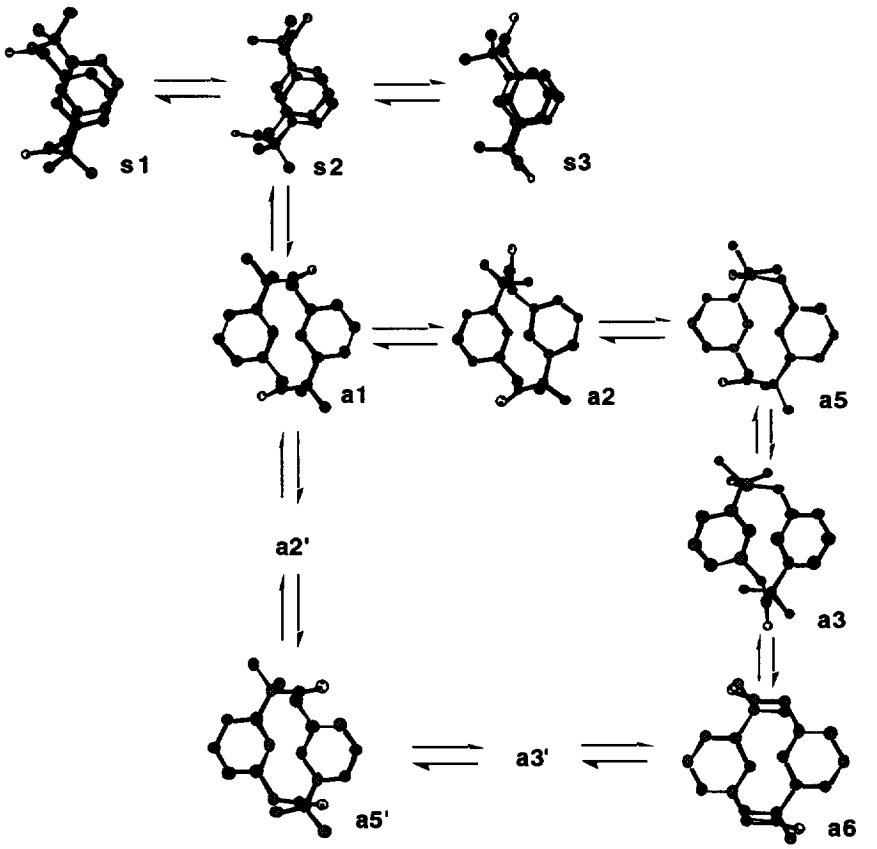


Figure 6. Conformational dynamic processes of **2**.

The details of the conformational dynamic processes can be learned from the MM3 calculations and the results are shown in Figure 6. The calculated thermodynamic parameters are listed in Table 4. The activation free energies to the bridge wobble motions of the syn conformers, which resulted in interconversions among the three syn conformers, are predicted to be 9.90 kcal/mol at 25°C. Almost the same energy (9.71 kcal/mol at the coalescence temperature, -65°C) is calculated for the interconversion process between **s 2** and **a1** conformers by flipping of a benzene ring. The highest calculated free energy of activation for the interconversion between **a1** and **a6** (through **a2**, **a5**, **a3**) is 7.7 kcal/mol at -80°C. Thus, the interconversion process between **a1** and **a6** must be rapid even at -102°C,[27] suggesting that these conformers could not be observed separately even if these conformers have detectable populations. Negligible contribution of the four conformers, **a2**, **a3**, **a5**, and **a6** can

be proven by a population analysis based on the chemical shifts of the aromatic protons (*vide infra*). From these calculations it is found that the free energies of activation for the bridge wobble motion and aromatic ring flipping are almost equal. It is also found that all the conformational dynamic processes are rapid at room temperature.

Table 4. Calculated Thermodynamic Parameters.

structure	steric energy [a]	enthalpy [a]	entropy [b]	free energy [a,c]
s 1	21.78	284.50	150.27	239.72
TS(s 1-s 2)	31.62	293.73	148.01	249.62
s 2	22.38	285.16	151.54	240.00
TS(s 2-s 3)	31.61	293.73	148.09	249.60
TS(s 2-a1)	32.30	294.24	148.51	249.98
s 3	22.99	285.81	148.77	241.48
a 1	23.50	285.84	152.81	240.30
TS(a1-a2)	24.76	286.68	148.02	242.57
a2	24.09	286.71	153.26	241.04
TS(a2-a5)	29.83	292.03	148.58	247.75
a5	27.25	289.94	153.00	244.35
TS(a5-a3)	28.66	290.90	147.49	246.95
a3	25.92	288.84	151.72	243.63
TS(a3-a6)	30.07	292.41	147.47	248.55
a6	29.53	292.56	151.93	247.29

[a] These values are in kcal•mol^{-1}. [b] These values are in cal•mol^{-1}•K^{-1}. [c] These values are at 298 K.

Population of Conformers

At room temperature, all the conformational dynamic processes are rapid, hence the observed chemical shifts are the weighted average of all the contributing conformers in the equilibrium. In order to find out the population of conformers actually contributing for the dynamic processes, we compared the observed and calculated chemical shifts for the aromatic protons by changing the probability of all the conformers. The best fit was obtained with four equilibrating conformers, **a1**, **s 1**, **s2** and **s 3**, with the composite ratio of 93, 2, 2 and 3 %, respectively. Calculation of the induced shifts of the aromatic protons using the four equilibrating conformers of the above population reproduced the observed values quite satisfactorily [Ha, 1.287 (1.296); Hb, -0.488 (-0.546); Hc, -0.132 (-0.161); Hd, -0.219 (-0.155); (ppm; where a minus sign denotes down-field shift, and observed values are shown in parentheses)]. Small population of the three syn conformers could not be detected by the dynamic NMR analysis, however their contribution is prominent when the temperature dependent chemical shift behavior of the aromatic protons is scrutinized. The chemical shift behavior of Ha is especially suggestive of the small contribution of the syn conformers. Ha showed very small but gradual upfield shift with temperature decrease down to -60°C (0.06 ppm), and it did not shift any more with further cooling (Figure 7). Since the induced upfield shift of the proton for these syn conformers are small compared to that of **a1** conformer, decrease of the contribution of the syn conformers result in a small upfield shift of the proton. Moreover, below -65°C the syn conformers freeze out from the conformational equilibrium and **a1** is the only one conformer left, hence, the chemical shift of the proton did not show any temperature dependency. The behavior of the temperature dependent NMR signals can thus be explained by the single anti conformer with very small contribution of the syn conformers. The population of the conformers estimated with the forcefield calculations is quite different to

the observed. This difference may be caused by ignorance of solvent effect or by some defects of the energetic parameters of the force constants for carbonyl group.

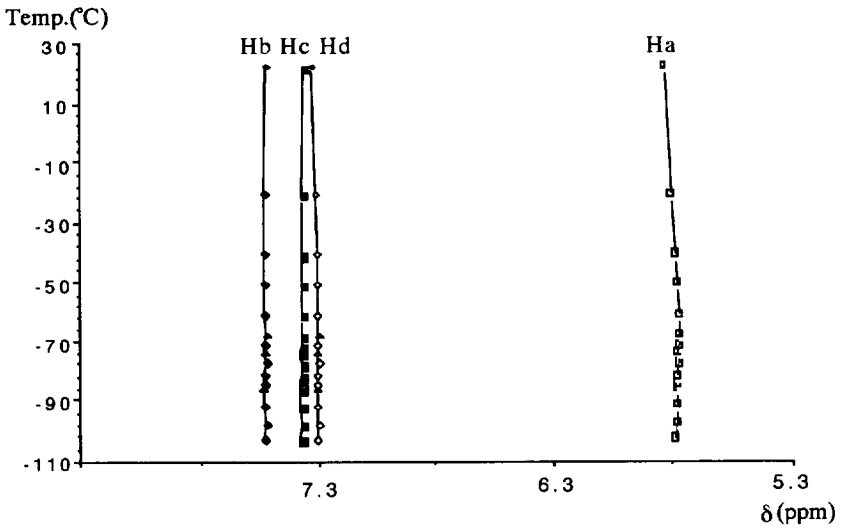


Figure 7. Change of chemical shifts of aromatic protons of **2** with temperatures.

CONCLUSIONS

The molecular geometry of the main conformer of the title compound in solution was obtained to be the C_i symmetric anti form **a1** by use of our newly developed chemical shift simulation method. The structure of the main conformer is identical to that found in crystal. Our method of the conformational analysis consists of three stages: the creation of all the plausible structures, estimation of the chemical shifts of these structures by induced shift caused by the aromatic ring and carbonyl group in the molecule, and selection of the most probable ones by comparison of the observed and calculated shifts. In the first stage of the analysis, structures of conformer **a1** were generated by the three different methods. Comparison of the calculated structures to the observed one disclosed that MM3 calculation gave the almost identical geometry though the relative stability of the conformer is not correct. AM1 calculation on the other hand correctly predicted the most stable conformer, however, the molecular geometry of that is not satisfactory for this analysis. PM3 calculation gave the least reliable result. In the second stage, estimation of the chemical shift can be successfully carried out by our new shielding parameters of the carbonyl group. Throughout this analysis, we found that whether this method can give the correct answer or not is highly dependent on the reliability of the molecular geometries of the plausible conformers. We found that the MM3 calculation gave the most satisfactory result, and conclude that the method we employed can be useful for the analysis of a multiple conformation problem.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were measured in $CDCl_3$ (0.05~0.1 M sample concentration) with a JEOL-270GSX NMR spectrometer, operating at 270 MHz and 67.8 MHz, respectively, and the mass spectra were taken with a JEOL JMS-SX 102A high-resolution double-focusing mass spectrometer at the Instrument Center for Chemical Analysis, Hiroshima University.

Synthetic Procedures

Synthesis of the [3.3]metacyclophanedione (**2**) was carried out by the method reported.[10]

1-(3,3-Dimethyl-2-oxobutyl)-3-(1,1-dimethyl-2-oxopropyl)benzene (5). To a solution of 1-bromo-3-(1,1-dimethyl-2-oxopropyl)benzene (**4**, 1021 mg, 4.23 mmol) and pinacolon (3.2 mL, 26 mmol) in 400 mL of liquid ammonia was added potassium *tert*-butoxide (3.4 g, 30 mmol). The mixture was then irradiated by high-pressure mercury lamp for 1 h. Resulting yellow solution was poured onto ammonium chloride (5 g) and the ammonia was allowed to evaporate at room temperature. The residue was diluted with water (20 mL) and extracted with ethyl acetate (15 mL × 3). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated and the crude yellow oil was purified by column chromatography on silica gel (10% AcOEt in hexane) to give **5** as a colorless oil (735 mg, 67 %); IR (neat) 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (s, 9H), 1.47 (s, 6H), 1.92 (s, 3H), 3.80 (s, 2H), 7.04 (d, J=2.0 Hz, 1H), 7.07 (bd, J=7.8 Hz, 1H), 7.14 (dt, J=2.0, 7.8 Hz, 1H), 7.29 (t, J=7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 25.05, 25.51, 26.38, 43.26, 52.36, 124.12, 127.45, 128.03, 128.71, 135.37, 144.05, 211.18, 212.54; HRMS calcd for $C_{17}H_{24}O_2$: 260.1776, found: 260.1783.

1-(3,3-Dimethylbutyl)-3-(1,1-dimethylpropyl)benzene (3). A solution of **5** (495 mg, 1.90 mmol), hydrazine monohydrate (100%, 5.0 mL), and potassium hydroxide (2.5 g) in diethyleneglycol (15 mL) was heated at 120 °C for 2 h and then at 210 °C for 5 h under a slow stream of nitrogen. The mixture was cooled to room temperature, diluted with water (40 mL), and extracted with hexane (15 mL × 3). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated and the crude product was purified by short pass chromatography on silica gel (hexane) to give **3** as a colorless oil (427 mg, 97 %); ^1H NMR ($CDCl_3$) δ 0.69 (t, J=7.3 Hz, 3H), 0.96 (s, 9H), 1.27 (s, 6H), 1.50 (m, 2H), 1.63 (q, J=7.3 Hz, 2H), 2.56 (m, 2H), 6.99 (bd, J=7.3 Hz, 1H), 7.11-7.14 (m, 2H), 7.20 (t, J=7.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 9.18, 28.46, 29.39, 30.57, 31.53, 36.89, 37.79, 46.44, 123.13, 125.21, 125.99, 127.82; HRMS calcd for $C_{17}H_{28}$: 232.2191, found: 232.2177.

Calculation of Structures

All the calculations were carried out on a UNIX work station: INDY SC R4000. The semi-empirical calculations were performed with the MOPAC 6.0 program system and SPARTAN V4.0 program package. Empirical forcefield calculations ("molecular mechanics") were carried out using the MM3 force field.

The generation of the plausible geometries were done by our program MMRS: the procedure for geometry generation is as follows. Starting from the first three atoms, the fourth atom can be given by knowing three variables (bond distance, angle and torsion angle). Changing the torsion angle by a certain increment generates

some sets of coordinates of the first four atoms. Remaining atoms can be generated by repeating the process until to reach the terminal atom. Any chain which has a reasonable bonding distance between the two termini was assumed to be a possible cyclic starting geometry. All the remaining geometries which satisfy the criterion were subjected to the geometry optimization process with MM3 program. Energy optimization was carried out using a full matrix Newton-Raphson method. Conformational dynamic processes of the bridge wobble motion and the flipping of the benzene rings were analyzed using the torsion drive options. All the transition structures were obtained by the full matrix Newton-Raphson optimization starting from the respective maximum energy structures between the two minima for these drive option calculations. Transition structures were fully characterized through harmonic vibrational frequency analysis and comparison of the structures with their respective two minima. The free energy of activation of these conformational dynamic processes were estimated by the values of enthalpy and entropy for these stationary points (two minima and saddle point).

Estimation of Probability of Conformers

We have compared the observed and calculated induced shift values of the aromatic protons and evaluated the discrepancy factor (R) defined by

$$R = \frac{\sum_i \left| \Delta\delta H^i_{obsd} - \Delta\delta H^i_{calcd} \right|}{\sum_i \left| \Delta\delta H^i_{obsd} \right|}$$

where $\Delta\delta H^i_{obsd}$ and $\Delta\delta H^i_{calcd}$ are the observed and calculated induced shift of H^i. The latter is defined by

$$\Delta\delta H^i_{calcd} = \sum_j \Delta\delta H^i_j w_j$$

where $\Delta\delta H^i_j$ is the predicted induced shift of H^i and w_j is the probability of the j-th conformer. The probability of each conformer was systematically changed by the increment of 2 % with our computer program until the minimum discrepancy factor was obtained. When the width of the discrepancy factor was expanded by the amount of 0.01 from the minimum value, a large number of sets of the probability for each conformer were obtained. There are 98 sets and the deviation of the probability for each conformer within these sets are as follows: **s 1**, 0 - 8 %; **s 2**, 0 - 6 %; **s 3**, 0 - 6 %; **a1**, 90 - 98 %; **a2**, 0 - 4 %; **a3**, 0 - 4 %; **a5**, 0 - 4 %; **a6**, 0 - 2 %. The probabilities of these conformers were obtained by the weighted average of their histograms, and they are as follows: **s 1**, 1.6 %; **s 2**, 1.6 %; **s 3**, 2.5 %; **a1**, 92.3 %; **a2**, 0.6 %; **a3**, 0.4 %; **a5**, 0.7 %; **a6**, 0.4 %. The conformers having the probability less than 1 % can be neglected. It is thus obtained four conformers, **s 1**, **s 2**, **s 3**, and **a1**, with the probabilities of 2, 2, 3 and 93 %, respectively. This set gives the discrepancy factor of 0.074 and the calculated induced shift of the aromatic protons are Ha, 1.287 (1.296); Hb, -0.488 (-0.546); Hc, -0.132 (-0.161); Hd, -0.219 (-0.155) (ppm ; where a minus sign denotes down-field shift, and observed values are shown in parentheses). Thus the preferred conformation of **2** in solution is determined unequivocally to be the structure **a1**.

Single-Crystal X-ray Diffraction Analysis of 2

The crystal data for **2** are as follows: Monoclinic; space group $P2_1/n$ with a = 9.762 (2), b = 13.822 (2), c = 6.578 (1) Å, β = 99.56 (1)°, V = 875.3 (2) Å^3, and Z = 2. The empirical formula is $C_{22}H_{24}O_2$, molecular weight is 320.4, and calculated density is 1.22 g/cm^3. The three-dimensional X-ray data were collected by the use of graphite-monochromated Mo Kα radiation (λ=0.71073 Å) on a Mac Science MXC3 automatic four-circle diffractometer up to a maximum 2θ of 55.0°. Of 2009 total unique reflections, 1231 were considered observed at the level of $|Fo|>3.0\sigma|Fo|$. Data were corrected for Lorentz and polarization effect by usual way but not for absorption as linear absorption coefficient is small enough [λ(Mo Kα)=0.41 cm^{-1}]. The structure was solved by the direct method (SHELXS78). All non-hydrogen atoms were located on the initial E synthesis. Hydrogen atoms were found from the difference fourier map and included in the further calculations. Full-matrix least squares refinements with anisotropic 12 non-hydrogen atoms and 12 isotropic hydrogens have converged to a conventional R factor of 0.062.

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