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RELATIONSHIP BETWEEN REACTIVITY AND ^{13}C CHEMICAL SHIFTS OF BENZOCYCLOBUTENES

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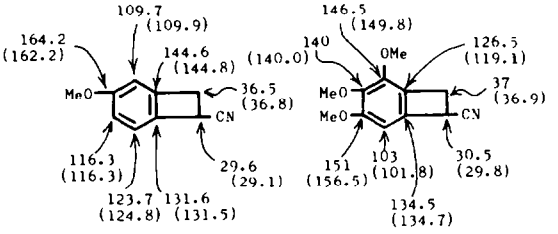
Abstract—^{13}C NMR spectra of benzocyclobutene derivatives have been investigated; substituent effects and the relationship between the chemical shifts and the reactivity of their cyclobutene ring are discussed.

Benzocyclobutenes have received considerable attention in both chemical reactivity studies[1] and spectroscopic investigations.[2-6] We have been utilizing the benzocyclobutenes as starting materials for the total synthesis of natural products, and synthesized many types of benzocyclubutene derivatives by treatment of 2- or 3-bromophenylpropiononitriles with sodium amide.[7] We have introduced several new substituents into the aromatic ring in benzocyclobutenes in order to obtain more effective precursors for the synthesis of natural products. Prior to this work, we have investigated the character of benzocyclobutenes, which would react more likely with dienophiles, by ^{13}C NMR spectroscopic method. Here we report these results.

Table 1 represents the ^{13}C chemical shifts observed for a number of the benzocyclobutene derivatives. The chemical shifts are assigned by taking into consideration of the substituent effect on the benzene ring by using of benzocyclobutene (**1**) as a standard compound. Nelson *et al.*[8] reported that the substituent effect by the OMe group on the benzene ring was +31·4 (ppm) at C-1 position, −14·4 at *ortho*-carbon, +1·0 at *meta*-carbon, and −7·7 at *para*-carbon, and in our case the substituent effect by OMe group showed +34 (ppm) at C-1, −12·4 at *ortho*-carbon, +1·5 at *meta*-carbon, and −7·3 at *para*-carbon. Thus, the substituent effect by the OMe group in the benzocyclobutene system having a large strain is in good accordance with that in the substituted benzenes. By using of the substituent effect observed by our experiment, the assignment of the chemical shift of 4-methoxybenzocyclobutene (**2**) and 4,5-dimethoxybenzocyclobutene (**7**) was proved correct.

Furthermore, the substituent effect of the substituent at C-1 position are listed in Table 2. The combination of both substituent effects of OMe and the substituent at C-1 position predicts the chemical shift of each carbon in all the compounds. The calculated values of the chemical shifts of 1 - cyano - 4 - methoxybenzocyclobutene (**4**) and those of 1 - cyano - 3,4,5 - trimethoxybenzocyclobutene (**12**) from parent benzocyclobutene (**1**) by use of additive parameters are shown in Scheme 1. This predicts chemical shifts to be closely similar to the observed data.

Benzocyclobutene (**1**) and methoxylated derivatives (**2** and **7**) have been reported to be stable and to react at higher temperatures than 200° to generate *o*-quinodimethane intermediates (**16**),[9] but 1-hydroxybenzocyclobutene (**15**) is easily converted into a ring-opened product. Moreover, benzocyclobutenes (**3**~**6**) and (**8**~**14**) having substituents on the cyclobutene ring form the *o*-quinodimethane intermediates at 150~170°

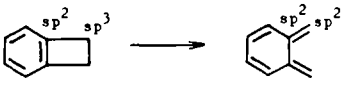


4 **12**

Predicted CMR Chemical Shifts

(The values in parenthesis are the observed data.)

Scheme 1.



1 **16**

Scheme 2.

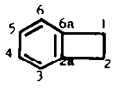
and the ring opening reaction of the compounds having more substituents on benzocyclobutene ring occurs easily than that of the less substituted ones.[7]

In the transformation of the benzocyclobutene into *o*-quinodimethane, sp^3-hybridized carbons change to sp^2 carbons. Therefore, this type of conversion may occur more easily, when the sp^2 character of C-1 and C-2 is increased: namely, the δ_c differences between C-1 and C-2, C-2a and C-6a become smaller. On this hypothesis, we calculated Δ values from the following equation, and also listed them in Table 1.

$$\Delta = \sum (\delta_{6a} + \delta_{2a}) - \sum (\delta_1 + \delta_2).$$

These data reveal that compounds **1**, **2** and **7** cleaving the benzocyclobutene ring at higher temperatures than 200° have the Δ values larger than 215 and compounds **3**~**6**, **9**, **10**, **12** and **14** reacting at a moderate temperature show the values around 200, but the Δ value of benzocyclobutenol (**15**)[10] cleaving at 110° is lower than 180, and this result is closely related to the reactivity of the benzocyclobutene ring reported. Thus, the calculation of the Δ value of benzocyclobutenes is suggested for predicting the reactivity of the cyclobutene ring.

Table 1. ^{13}C chemical shift of benzocyclobutenes, δ_c



	Substituent						Position								$\Sigma(\delta_{6a}+\delta_{2a}) - \Sigma(\delta_1+\delta_2)$
	1	2	3	4	5	6	1	2	2a	3	4	5	6	6a	
1*	H_2	H_2	H	H	H	H	29.6	29.6	145.6	122.1	126.6	126.6	122.1	145.6	232.0
2	H_2	H_2	H	OMe	H	H	29.8	30.0	147.4	109.7	160.5	114.3	124.4	138.3	228.0
3	H CN	H_2	H	H	OMe	H	29.4	36.7	135.5	125.8	118.0	161.5	108.9	140.5	209.9
4	H CN	H_2	H	OMe	H	H	29.1	36.8	144.8	109.9	162.2	116.3	124.8	131.5	210.4
5	H CO_2H	H_2	H	H	OMe	H	44.9	33.1	135.4	124.0	115.6	159.7	108.1	142.5	199.9
6	H $CONH_2$	H_2	H	H	OMe	H	47.3	33.5	136.9	125.0	115.5	160.4	109.5	146.5	202.7
7	H_2	H_2	H	OMe	OMe	H	30.0	30.0	137.9	108.5	150.6	150.6	108.5	137.9	215.8
8	H CN	H_2	H	OMe	OMe	H	28.7	36.2	134.9	107.8	152.1	151.1	107.0	130.5	200.5
9	H CO_2H	H_2	H	OMe	OMe	H	45.8	34.3	136.2	108.2	151.6	151.0	107.8	134.0	189.7
10	Me CN	H_2	H	OMe	OMe	H	38.3	44.9	133.3	108.9	151.6	152.6	106.1	136.8	186.9
11	Me CO_2H	H_2	H	OMe	OMe	H	52.5	42.5	134.5	108.8	150.9	151.7	106.7	139.8	179.3
12	H CN	H_2	OMe	OMe	OMe	H	29.8	36.9	119.1	149.8	140.0	156.5	101.8	134.7	187.1
13	H CO_2H	H_2	OMe	OMe	OMe	H	46.2	34.5	119.7	149.3	139.2	155.7	101.9	137.9	176.9
14	H CN	H_2	H	OMe	OCH_2Ph	H	29.3	36.7	136.3	110.4	150.8	153.3	108.9	130.9	201.2
15	H OH	H_2	H	H	H	H	71.6	43.1	140.3	123.3	128.2	130.4	124.56	148.9	174.5

* This result is those reported by Adcock and coworkers.[5]

Table 2. Substituent effects on δ_c (positive values indicate downfield shifts in ppm)

Substituent at C-1	C-6a	C-2a, C-6	C-3, C-5	C-4	C-1	C-2
CN	-6.7	-0.1 ~ -0.28	+1 ~ +1.5	+3.7	-0.4	+6.7
CO_2H	-4.9	-1.7 ~ -2.9	-0.5 ~ -0.8	+1.3	+14.9	+3.3
Me	+6.3	-0.9 ~ -1.5	+1.5 ~ +1.7	+0.4	+9.6	+12.7

EXPERIMENTAL

The ^{13}C FT NMR spectra were obtained by a JEOL-PFT-100 spectrometer operating at 25·15 Hz by using TMS as an internal standard. $CDCl_3$ was used as an internal standard in **8** and **9**, and **13**, and data were converted to TMS scale by $\delta_c = 78{\cdot}10 + \delta_{ext}CDCl_3$. All benzocyclobutenes, except **6**, were dissolved in $CDCl_3$ to yield 0·5 to 1·0 M solutions, (**6**) was dissolved in DMSO-d_6.

3-Methoxybenzocyclobutene (**2**). Commercial anhyd liquid ammonia (*ca.* 1 liter) was added to a 2 liter 3-necked round-bottomed flask equipped with a mercury-sealed stirrer and a reflux condenser connected to a KOH drying tube. To the above liquid ammonia a solution of **3** (19·0 g) and dry isopropanol (14·4 g) in dry ether (60 ml) was added at −40 ~ −45°. Li (1·5 g) freshly cut was then added to the above mixture during 1 hr and the reaction was continued until no cyano-absorption had been shown by IR spectral inspection. Ammonium chloride (15 g) was added while the temp. was kept below the b.p. of ammonia in a dry ice-acetone bath. The excess of ammonia was allowed to evaporate at room temp. and water (250 ml) was then added cautiously to the resulting residue and the organic material was extracted 3 times with ether (200 ml). The extract was washed with 3N HCl (100 ml), satd $NaHCO_3$ aq (200 ml) and satd NaCl aq (200 ml), and dried over Na_2SO_4. After concentration, distillation of the residue *in vacuo* afforded 3-methoxybenzocyclobutene (12·0 g, 76·2%), b.p. 92 ~ 93°/19 mmHg (Found: C, 80·03; H, 7·67. $C_9H_{10}O$ requires: C, 80·56; H, 7·51%), NMR ($CDCl_3$) δ 3·07 (4H, s, 2 × CH_2), 3·71 (3H, s, OMe), 6·59 ~ 6·97 (3H, m, 3 × Ar-H), mass (*m/e*) 134 (M^+), 119 ($M^+ - 15$).

3,4-Dimethoxybenzocyclobutene (**7**). A mixture of **8** (5·0 g), dry isopropanol (3 g) and dry ether (20 ml) was dissolved in liquid ammonia (300 ml) in a Dewar vessel, to a soln of which Li (1·5 g) freshly cut was added with occasional stirring in 3 portions during 30 min. The reaction was continued for 2 hr. After ammonium chloride (5 g) had been added carefully to the above mixture, the excess of ammonia was evaporated and the product was extracted with ether. The extract was washed with water, 5% HCl, sat $NaHCO_3$ aq and sat NaCl aq, and dried over Na_2SO_4. The solvent was removed by evaporation to give crystals, which were purified by alumina chromatography using n-hexane–ether (10:1) as an eluant to give **7** as crystals (1·5 g, 33%). Recrystallisation from n-hexane gave colourless needles, m.p. 98·5–100° (Found: C, 73·21; H, 7·33. $C_{10}H_{12}O_2$ requires: C, 73·14; H, 7·37%), NMR (CCl_4) δ 3·04 (4H, s, 2 × CH_2), 3·72 (6H, s, 2 × OMe), 6·51 (2H, s, 2 × Ar-H), mass (*m/e*) 164 (M^+), 149 ($M^+ - 15$).

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