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An Investigation of the Interaction of 4-Membered Rings with Adjacent Carbanion Centers

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A series of cyclobutylcarbinyl phenyl ketones was prepared and the rates of base catalyzed hydrogen-deuterium exchange of α-hydrogen atoms were compared with those of appropriate model compounds, to test the validity of an earlier finding, which suggested that a four-membered ring, like the three-membered ring, has the ability to stabilize an adjacent carbanion center. In this study, unlike the cyclopropyl group, no clearly defined stabilization of the adjacent carbanion center was detected by the 1-phenyl- and 1-*p*-nitrophenyl- substituted cyclobutyl groups and only a very slight rate enhancement by the 3-phenylcyclobutyl group was detected. Attempts to detect a stabilization of the carbanion center by a cyclobutyl-substituted methyl group (homoconjugative interaction) also failed.

Key Words: Carbanions, cyclobutylcarbinyl, cyclopropylcarbinyl, strained molecules

Introduction

Literature about the olefinic properties of small rings is abundant with data concerning the behavior of the cyclopropyl group[1]. Similar data on the olefinic behavior of the cyclobutane rings is scarce[2]. In contrast to the abundancy of the literature on the stabilization of the cyclopropylcarbinyl cation by the bisected conformation of the three-membered ring[1], only a limited number of studies have been performed on the interaction of the four-membered ring with an adjacent carbenium ion center[3]. In comparison to only two experimental studies on the stabilization afforded by the three-membered rings on adjacent carbanion centers[4,5], there is no extensive experimental data available on the stability of cyclobutylcarbinyl anions, except one[6] that compares the ability of the cyclobutyl group to stabilize an adjacent carbanion center with those of cyclopropyl, isopropyl, and vinyl groups by studying the kinetic effect of these groups on base catalyzed exchange of hydrogen on adjacent carbon. It has been concluded that the cyclobutyl group has the ability to stabilize an adjacent carbanion center but this stabilization is to a much lesser extent compared to those afforded by vinyl and cyclopropyl groups. As a continuation of these previous studies[4−6], the effect of the four-membered ring is investigated in more detail, by extending the series of compounds (Table 1)

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comprising the cyclopropyl- and cyclobutylcarbinyl phenyl ketones, their derivatives and the suitable model compounds.

Experimental

General

^{1}H-NMR spectra were recorded in $CDCl_3$ on a Bruker AC 80 MHz, and ^{13}C-NMR spectra on a Bruker AC 20 MHz FT spectrometer, using TMS as the internal reference. For the kinetic experiments, a Varian T-60A NMR spectrometer was used. IR spectra were determined on a Philips model PU9700 spectrometer. Elemental analyses were carried out by HT-185 C, H, N, Analyzer.

Pyridine for the kinetic runs was allowed to stand on sodium hydroxide, and then were distilled and kept on molecular sieves.

1-Phenyl-2-(1-phenylcyclobutyl)ethanone (4b)

1-Phenylcyclobutanecarbonitrile was prepared from benzyl cyanide (70.2 g, 0.6 mol) and 1,3-dibromopropane (133.2 g, 0.66 mol) according to the procedure described by Roberts[11] to yield the nitrile (23.7 g 25%) bp·100° (0.3 mm). This nitrile was then hydrolyzed into 1-phenycyclobutane-1-carboxylic acid (90%) according to a previously described procedure[11]. This acid was then homologated[4] through its chloride[12] into 1-phenylcyclobutylacetic acid and its chloride[13]. 1-Phenylcyclobutylacetyl chloride was used to prepare **4b** as follows. The acid chloride (3 g, 0.02 mol) was added to a stirred suspension of diphenylcadmium (from 4.4 g bromobenzene) in dry benzene (40 ml). The mixture was stirred at room temperature for 15 min, and then at reflux for 12 h. The mixture was then hydrolyzed with dilute HCl, the organic layer was washed with Na_2CO_3 solution and with water, and dried ($CaCl_2$). Removal of the solvent left an oily residue, which was crystallized several times from hexane to yield **4b** as a colorless solid (1.8 g, 51.4%). Mp 57-58°C; IR (KBr): 1697 cm^{-1} (C=O). ^{1}H-NMR: δ 2.0-3.0 (complex m, 6H cyclobutyl), 3.4 (s, 2H, CH_2), 7.0-8.0 (complex m, 10H, aromatic). ^{13}C-NMR: δ 16.051, 33.238, 45.374 (cyclobutyl), 49.332 (CH_2), 125.300, 125.832, 127.742, 128.001, 132.288, 137.800, 148.999 (aromatic), 198.859 (C=O). Anal calc for $C_{18}H_{18}O$: C, 86.40; H, 7.20. Found: C, 86.16; H, 7.32.

2-[1-(4-Nitrophenyl)cyclobutyl]-1-phenylethanone (4c)

The ketone **4b** (0.41 g, 0.002 mol) in acetic anhydride (2.5 ml) was added portionwise to a nitrating mixture at -20° made up of fuming HNO_3 (0.82 ml) in acetic anhydride (2.5 ml). The mixture was then added to boiling water, extracted with ether, washed with Na_2CO_3 and dried (Na_2SO_4). Removal of the solvent under reduced pressure yielded an oily residue. Preparative TLC (Kieselguhr GF_{254}, hexane/EtOAc, 16:1) afforded two fractions. The upper fraction was identified as the *2-[1-(2-nitrophenyl)cyclobutyl]-1-phenylethanone* (0.11 g, 19% , mp. 95-7°) and the lower layer (0.3g, 51% , mp.76°) as the desired **4c**.

For o-*isomer*: IR (KBr): 1690 cm^{-1} (C=O). ^{1}H-NMR: δ 1.6-2.7 (complex m, 6H cyclobutyl), 3.8 (s, 2H, CH_2),7.0-8.0 (complex m, 9H, aromatic). Anal calc for $C_{18}H_{17}NO_3$: C, 73.22; H, 5.76; N, 4.74. Found: C, 74.36; H, 5.46; N, 4.82.

For p-*isomer* (**4c**): IR (KBr): 1690 cm^{-1} (C=O). ^{1}H-NMR: δ 1.6-2.6 (complex m, 6H cyclobutyl), 3.6 (s, 2H, CH_2),7.2-8.2 (complex m, 9H, aromatic, distinguishable AA'BB' pattern for 4-nitrophenyl moiety).

^{13}C-NMR: δ 16.192, 33.523, 45.202 (cyclobutyl), 49.016 (CH_2), 123.106, 127.149, 127.759, 128.422, 132.975, 137.800, 148.586, 156.000 (aromatic), 197.616 (C=O).

Anal calc for $C_{18}H_{17}NO_3$: C, 73.22; H, 5.76; N, 4.74. Found: C, 73.13; H, 5.37; N, 4.69.

trans-1-Phenyl-2-(3-phenylcyclobutyl)ethanone (5)

trans-3-phenylcyclobutanecarboxylic acid was prepared starting from diethyl phenylmalonate according to a procedure described by Beard and Burger[14]. Diphenylcadmium, prepared from bromobenzene (1.2 g) and anhydrous $CdCl_2$ (1.04 g, 0.01 mol) was reacted with 3-phenylcyclobutylacetyl chloride as in the case of **4b**. The product was purified by column chromatography (silicagel, hexane-EtOAc) to yield **5** (0.7 g, 73%). Mp. 30-31°; IR (KBr): 1685 cm^{-1} (C=O). ^{1}H-NMR: δ 1.8-4.2 (complex m, 6H cyclobutyl), 3.4 (d, 2H, CH_2), 7.2-8.3 (complex m, 10H, aromatic). ^{13}C-NMR: δ 27.362, 34.069, 36.169, 45.367 (cyclobutyl), 44.437 (CH_2), 125.560, 126.192, 127.878, 128.098, 128.374, 128.422, 132.750, 136.946, 148.586, 145.736 (aromatic), 199.318 (C=O). Anal calc for $C_{18}H_{18}O$: C, 86.40; H, 7.20. Found: C, 85.56; H, 7.19.

3-Cyclobutyl-1-phenyl-1- propanone (6)

Cyclobutylacetyl chloride [6] was homologated into 3-cyclobutylpropanoyl chloride via Arndt-Eistert homologation followed by treatment with thionyl chloride. The acid chloride (0.1g, 0.001 mol) was added dropwise to dry benzene (2 ml) containing anhydrous $AlCl_3$ (0.1g, 0.001 mol). The reaction mixture was refluxed (30 min), hydrolyzed with cold water, extracted with ether, washed (Na_2CO_3) and dried ($MgSO_4$). The solvent was removed and the residue was chromatographed (prep TLC, silicagel, hexane/EtOAc 16:1) to yield **6** as an oil (0.05g, 36%).

IR (neat): 1680 cm^{-1} (C=O). ^{1}H-NMR: δ 1.5-2.5 (complex m, 8H cyclobutyl and CH_2), 3.4 (d, 2H, CH_2CO), 7.2-8.3 (complex m, 5H, aromatic). ^{13}C-NMR: δ 18.354, 28.107, 31.596, 35.000, 36.348 (aliphatic), 128.104, 128.550, 132.856, 137.800 (aromatic), 202.000 (C=O).

Anal calc for $C_{13}H_{16}O$: C, 82.98; H, 8.51. Found: C, 82.56; H, 8.77.

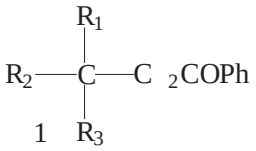
Results and Discussion

The relative rates of base-catalyzed hydrogen-deuterium exchange in these ketones **1a-6** were compared using the same methods employed previously[4–6]. The relative kinetic acidities of compounds **1a**, **1c**, **1e**, **1f**, **1g**, **2a**, **3a**, **3b**, and **3g**[4], and that of compound **4a**[6] are already known. Among the currently added compounds in this study, 1-phenyl-1-propanone (**1b**), 1-phenyl-2-methyl-1-propanone (**2b**), and acetophenone (**2c**) were commercially available. The ketones **1d**, **1h**, **1i**, **4b**, **4c**, **5**, and **6** were prepared by conventional means.

Thus, 3,3-dimethyl-1-phenyl-1-butanone (**1d**)[7], 4-methyl-1-phenyl-1-pentanone (**1i**)[7], and 3-cyclobutyl-1-phenyl-1-propanone (**6**) was obtained by the acylation of benzene with appropriate acid chlorides. The acid chlorides used in the preparations of **1i** and **6** were in turn prepared by the homologation of isobutyric and cyclobutylacetic acids[6]. Diethyl phenylmalonate was the starting material in the synthesis of *trans*-1-phenyl-2-(3-phenylcyclobutyl)ethanone (**5**). The starting material was reduced into the 1,3-diol with $LiAlH_4$;

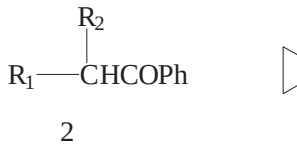
treatment of the tosylate of this diol with sodium diethyl malonate, followed by saponification, yielded 3-phenylcyclobutane-1,1-dicarboxylic acid, which was decarboxylated and the product was chromatographed to isolate *trans*-3-phenylcyclobutanecarboxylic acid. Homologation of this acid and treatment of its chloride with diphenylcadmium yielded (**5**). The synthesis of 1-phenyl-2-(1-phenylcyclobutyl)ethanone (**4b**) was started with phenylacetonitrile, which was converted into 1-phenylcyclobutanecarboxylic acid via reaction with sodium hydride and 1,3-dibromopropane, followed by hydrolysis. This acid was homologated and the reaction of its chloride with diphenylcadmium gave **4b**. 2-[1-(4-nitrophenyl)cyclobutyl]-1-phenylethanone (**4c**) was prepared by controlled nitration of **4b**. The preparation of 1-phenylpent-4-ene-1-one (**1h**)[9] was accomplished via alkylation of acetophenone with allyl bromide in the presence of lithium diisopropylamide.

Table 1



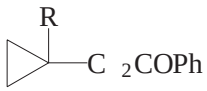
1

a: R_1=H, R_2=R_3=Me
b: R_1=R_2=R_3=H
c: R_1=R_2=H, R_3=Me
d: R_1=R_2=R3=Me
e: R_1=R_2=Me, R_3=Ph
f: R_1=R_2=H, R_3=4-NO_2Ph
g:R_1=R_2=H, R_3=PhCH2
h: R_1=R_2=H, R_3=vinyl
i: R_1=R_2=H, R_3=i-Pr



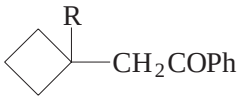
2

a: R_1=H, R_2=vinyl
b: R_1=R_2=Me
c: R_1=R_2=H



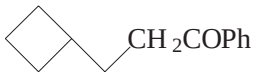
3

a: R=H
b: R=Ph
c: 4-NO_2Ph



4

5



6

a: R=H
b: R=Ph
c: 4-No$_2$Ph

The base catalyzed rate of enolization was followed by ^{1}H-NMR spectroscopy as in previous studies[4,6], at a probe temperature of 33°, where pyridine-D_2O-NaOD mixtures had been used as the medium of enolization. Relative rates were determined using pairs of ketones, which were chosen so that differences in the chemical shifts of their exchanging enolizable protons permitted observations of each exchange separately. 3-Methyl-1-phenyl-1-butanone (**1a**) was chosen as a standard with an arbitrary rate of unity. Table 2 lists the relative rates for the compounds **1a-6** at a constant concentration of base.

It is already known[4] that the allylic ketone **2a** exchanges too fast for its rate to be compared with those of the reference (**1a**), cyclopropylcarbinyl- (**3a**), or cyclobutylcarbinyl- (**4a**) phenyl ketones by the method employed in this work. It has already been established[6] that the rates of exchanges of **1a**, **3a**, and **4a** reveal a distinct rate enhancement of the four-membered ring (compared to the isopropyl group of

1a). This rate enhancement due to the cyclobutyl group is 2.5 times smaller than that observed for the three-membered ring[4], although it is not easy to estimate the steric retardation imposed by the larger four-membered ring. This steric (and inductive) retardation can clearly be seen when one compares the rates of exchange of acetophenone (**2c**), 1-phenyl-1-propanone (**1b**), 1-phenyl-1-butanone (**1c**), and the reference ketone (**1a**). The rates are nearly the same for **1b** and **1c**, where there is only one β-methyl substitution in **1c**. However, this rate decreases by a factor of 2.9 times upon a second β-methyl substitution (**1a**), and by a factor of 5.9 times upon a third β-methyl substitution (see **1d**) on **1b** were observed.

Table 2. Relative rates for base-catalyzed exchange of the ketones at 33°

Compound	Rel. rate	Compound	Rel. rate
1a	1.0	2b	0.49
1b	2.9	2c	3.2
1c	2.9*	3a	4.8*
1d	0.49	3b	7.9*
1e	1.0*	3c	36*
1f	20.0*	4a	2.0**
1g	4.2*	4b	0.96
1h	2.8	4c	4.3
li	1.8	5	3.2
2a	fast*	6	1.2

*) ref. 4
**) ref. 6

An α-methyl substitution on **1b** decreases its rate 5.9 times, equivalent to a tri β-methyl substitution on **1a** (cf. compound **1d**). **1a** is thought to be a better reference ketone than **1c** and **1b** for **3a** and **4a**, respectively, because of the steric and inductive retardation due to β-methyl substituents. This kind of retardation in compound **4a** can be approximated to be at least as much as that present in the reference ketone **1a**.

Comparison of the rates of exchange of 1,3-diphenyl-3-methyl-1-butanone (**1e**) and **4b** reveals, on the other hand, no detectable increase in the rate of exchange due to 1-phenyl-substituted cyclobutyl group. In contrast, an 8-fold increase due to 1-phenylcyclopropyl group had been observed[4] when the relative rates of **1e** and **3b** were compared. A nitro group, substituted at the para position of the 1-phenyl group in **4b** (compound **4c**) increases the rate of exchange of **4b** by 4.4 fold. Relative rate increases of 4.6 and 4.8 had also been observed[4] upon comparisons of the rates of exchange of **3c** with that of **3b**, **1f**, with that of **1g**, where the effect of the p- nitro substitution had been diagnosed only to be inductive[4]. Since the same is also observed when the effects of 1-phenylcyclobutyl in compound **4b** and 1-(p-nitrophenylcyclobutyl) groups in compound **4c** are compared, any possibility of the transmission of the resonance effect of the nitro group by the four-membered ring is excluded.

A 1.4-fold increase of the rate of exchange is detected[4] upon a 4-phenyl substitution on **1c**, when the rates of exchange of **1c** and **1g** are compared. Comparison of this 1.4-fold increase with the 1.6-fold increase when the rates of **5** and of **4a** are compared, the existence of perhaps a very weak conjugative effect of the four-membered ring is conceivable.

The rates of exchange of 1-phenylpent-4-ene-1-one (**1h**), 4-methyl-1-phenyl-1-pentanone (**1i**), and 3-cyclobutyl-1-phenyl-1-propanone (**6**) were also compared in order to see whether or not there was any

homoconjugative stabilizing effect of the four-membered ring. Although an effect was detected for the vinyl moiety, no rate enhancement was seen for the cyclobutyl group.

A net increase in the rate of exchange due to the cyclobutyl had been reported earlier[6] in compound **4a**, when its rate was compared to that of **1a**. In the same study, as a result of a theoretical approach using semi-empirical MNDO calculations on the acidities of isobutane, propene, methylcyclopropane and methylcyclobutane, it is claimed that the cyclobutyl group has the ability to stabilize an adjacent carbanion center, similar to vinyl and cyclopropyl groups, although to a lesser extent. In the present study, however, the reasons for the ineffectiveness of the cyclobutyl group in the rate enhancement upon 1-phenyl substitution on **4a** (compound **4b**) are not well understood. The complex interplay of steric, conformational, and electronic effects, does not warrant a detailed discussion.

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