Pro, 1.01. The crude product when rechromatographed on a PA-35 column or on a C-18 reverse phase column eluted with CH<sub>3</sub>CN-0.1% phosphoric acid gradient ( $0.4 \times 30$  cm) in LC showed a symmetrical peak (Figure 3). This product also eluted as a single peak in both systems when cochromatographed with standard, biologically active [Val5]angiotensin II.

Cyanide and photolytic cleavage gave 60 and 61% yields, respectively. When both products were further deprotected in HF and applied to the Dowex 50  $\times$  4 ion-exchange column, each showed a major peak at 309 min (86.2 and 89.5% of ninhydrin-positive materials) corresponding to angiotensin. The photolytic cleavage product gave a mixture of about 2:1 of angiotensinyl-OMPA and protected angiotensin, indicating an incomplete conversion of resin 11 to BrCH2-Pop-resin before the esterification step of Boc-Phe. This would account also for the low yield of the HF cleavage. All reactions were not optimized.

Reattachment of Boc-Leu-Ala-Gly-Val-OMPA and Boc-[Leu<sup>5</sup>]Enkephalin-OMPA to Aminomethyl-Resin. Boc-Leu-Ala-Gly-Val-OMPA and Boc-[Leu<sup>5</sup>]enkephalin-OMPA were each obtained from the photolysis of 200-mg resin samples of Boc-Leu-Ala-Gly-Val-OCH2-Pop-resin and Boc-[Leu<sup>5</sup>]enkephalin-OCH<sub>2</sub>-Pop-resin. After the evaporation of the photolysate DMF filtrate both samples were used for the reattachment experiments. After a single precipitation from EtOAc-hexane as slightly yellowish waxy solids, both samples gave one major ninhydrin-positive spot on TLC (CMA, CA). Boc-Leu-Ala-Gly-Val-OMPA (20 mg, 33

 $\mu$ mol) was activated by DCC (10 mg, 48  $\mu$ mol) and HOBt (7 mg, 48  $\mu$ mol) at 0 °C in 2 mL of CH<sub>2</sub>Cl<sub>2</sub>/DMF (1:1 v/v) for 1 h and followed by addition of aminomethyl resin<sup>41</sup> (200 mg, 0.25 mmol/g). The coupling was conducted for 1 day. The resin was then washed five times each with 5 mL of DMF and CH<sub>3</sub>CN, dried, and analyzed as follows. (1) Amino acid analysis (25 mg) gave 81% coupling yield based on

Leu  $(Leu_{1,00}Ala_{0.95}Gly_{1,07}Val_{0.98})$ .

(2) HF cleavage (70 mg) gave 84% yield of LAGV based on the chromatographic analysis of the product on a Beckman  $120B^{45}$  and the amino acid analysis of the resin. Similarly, Boc-[Leu5]enkephalin-OMPA (18 mg, 22 µmol) was coupled to aminomethyl-resin (200 mg, 0.25 mmol/g). Amino acid analysis (28 mg of resin) gave 95% coupling yield based on Tyr (Tyr<sub>1.00</sub>Gly<sub>2.18</sub>Phe<sub>0.98</sub>Leu<sub>0.95</sub>) and 82% yield based on amino acid analysis of the resulting resin, HF cleavage Boc-[Leu<sup>5</sup>]enkephalin-OCH<sub>2</sub>-Pam-resin.

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# 2,5-Diphenyl-2,5-norbornyl Dications<sup>1</sup>

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Abstract: Preparation and <sup>13</sup>C NMR spectroscopic study of the parent and a series of substituted 2,5-diphenyl-2,5-norbornyl dications 1-R with both electron-releasing and electron-withdrawing substituents were carried out to determine the effect of dipositive charge on the norbornyl skeleton. A plot of C-1 vs. C-3 carbon chemical shifts shows an excellent linear fit with a wide variety of substituents, indicating the regular phenylcarbenium ion nature of dications 1-R in contrast to 2-phenyl-2-norbornyl monocations 3-R, where significant deviation from linearity was observed in the case of electron-withdrawing substituents due to the onset of nonclassical  $\sigma$  delocalization. The observed behavior of dications can be rationalized by charge-charge repulsion resulting in increased charge delocalization into the phenyl rings.

### Introduction

Experimental and theoretical studies on carbodications are extremely sparse as compared to those on carbomonocations.<sup>2</sup> In the early 1960s the first carbodications were reported by Hart<sup>3</sup> and subsequently by Volz.<sup>4</sup> In these studies the two carbocation centers were stabilized by conjugation with aromatic rings. The first aliphatic carbodications were reported by Olah et al.,<sup>5</sup> who showed that these ions can be formed only if the carbocation centers are separated by at least two carbon atoms. Since then a limited number of carbodications such as Hückeloid cyclic dications,<sup>6</sup> including cyclobutadiene and cyclooctatetraene dications, Hogeveen's pyramidal dication,<sup>7</sup> rigid bridgehead bicyclo[2.2.2]octyl<sup>8</sup> and bicyclo[3.3.3]undecyl<sup>9</sup> dications, and alkyl/aryl substituted acyclic dications,<sup>10</sup> have been studied. In our continuing studies on carbodications we now report the preparation and <sup>13</sup>C NMR spectroscopic study of the parent and a series of substituted 2,5-diphenyl-2,5-norbornyl dications (1-R).



Introduction of two electron-deficient centers into the norbornyl skeleton and the effect of substituted phenyl rings on the system are of particular interest in view of the extensive studies<sup>11</sup> on the

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Table I. <sup>13</sup>C NMR Chemical Shifts<sup>a</sup> of Observed Carbodications in FSO<sub>3</sub>H-SbF<sub>5</sub>-SO<sub>2</sub>ClF or SbF<sub>5</sub>-SO<sub>2</sub>ClF Solution at -70 °C<sup>a</sup>

dictation	C-1	C-2	C-3	C-4	C-5	C-6	C-7	others
$1-4-C_6H_4(OCH_3)$	49.3	213.6	42.5	49.3	213.6	42.5	42.1	OCH <sub>3</sub> 60.7, C <sub>p</sub> 184.6, C <sub>o</sub> 149.0, 146.3, C <sub>m</sub> 124.5, 117.2, C <sub>i</sub> 129.9
$1-4-C_{6}H_{4}(CH_{3})$	52.2	234.3	45.3	52.2	234.3	45.3	42.8	CH <sub>3</sub> 26.20, C <sub>p</sub> 180.5, C <sub>o</sub> 145.0, C <sub>m</sub> 135.0, C <sub>i</sub> 134.1
1-C, H,	54.3	245.1	46.9	54.3	245.1	46.9	44.0	C <sub>p</sub> 161.1, C <sub>o</sub> 146.3, C <sub>i</sub> 136.5, C <sub>m</sub> 134.3
$1-4-C_6H_4(CF_3)$	56.9	254.4	49.1	56.9	254.4	49.1	44.2	$C_p^{c}$ 156.6 ( $J_{C-C-F} = 37.5 \text{ Hz}$ ), $C_o^{c}$ 147.7, $C_i$ 138.3, $C_m$ 131.3, $CF_3$ 122.5 ( $J_{C-F} = 276.0 \text{ Hz}$ )
$1-3,5-C_6H_3(CF_3)_2$	58.0	258.2	50.0	58.0	258.2	50.0	45.10	$C_p$ 152.2, $C_o$ 145.3, $C_m$ 138.0 ( $J_{C-C-F}$ = 35.5 Hz), $C_i$ 136.8, $CF_1$ 122.1 ( $J_{C-F}$ = 272.7 Hz)
1-C <sub>6</sub> F <sub>5</sub>	58.2	241.1	52.1	58.2	241.1	52.1	47.1	$C_p \ 165.1 \ (J_{C-F} = 303.7 \ Hz), C_0 \ 155.2 \ (J_{C-F} = 301.0 \ Hz), C_m \ 140.9 \ (J_{C-F} = 268.9 \ Hz), C_i \ 118.2$
1-OH	51.0	242.3	41.2	51.0	242.3	41.2	40.9	
6-C <sub>6</sub> H <sub>5</sub>	247.9	37.2	37.2	247.9	37.2	37.2		C <sub>p</sub> 160.1, C <sub>o</sub> 142.8, C <sub>m</sub> 134.1, C <sub>i</sub> 139.1
$6-4-C_6H_4(CH_3)$	237.4	35.7	35.7	237.4	35.7	35.7		$C_p$ 178.9, $C_m$ 134.9, $C_o$ 142.1, $C_i$ 137.1
9	39.8	32.8	32.8	32.8	32.8	39.8		C <sup>4</sup> 333.2, CH <sub>2</sub> 69.7, CH <sub>3</sub> 46.7

<sup>a</sup> Chemical shifts are in parts per million from external capillary tetramethylsilane.

mode of charge delocalization in the parent 2-norbornyl cation. The application of the "tool of increasing electron demand" has been carried out previously on 2-phenyl-2-norbornyl cations 3-R,<sup>12,13</sup> and the study gave unambiguous evidence for the onset of nonclassical  $\sigma$  delocalization in cations 3-R with strongly electron-withdrawing substituents.

#### Results

Precursor alcohols 4-R were prepared by the addition of corresponding organomagnesium or -lithium reagents to the diketone  $2.^{14}$  The parent diol 4-H was obtained by the reported<sup>14</sup> hydroboration-oxidation procedure. To prepare a series of substituted cyclohexyl dications 6 for comparison, we also synthesized the precursor cyclohexyl derivatives by literature procedures.<sup>15</sup> The aryl-substituted dications 1-R and 6-R were prepared by



ionizing the corresponding diols 4-R and 5-R in  $FSO_3H-SbF_5$  or  $SbF_5/SO_2CIF$  solution at -78 °C. The diketone 2 was diprotonated in  $FSO_3H-SO_2CIF$  media. The parent or alkyl-substituted dications 1-R and 6-R (R = H or alkyl) were either not stable or found to rearrange even at -140 °C.

The <sup>13</sup>C NMR spectroscopic data of observed dications are summarized in Table I. The chemical-shift assignments were made by off-resonance decoupling experiments. Figure 1 shows a plot of the C-1 vs. C-3 carbon chemical shifts of dications 1-R. Figure 2 exhibits the plot of the carbocation center shift of dications 1-R against those of substituted 1-phenyl-1-cyclopentyl cations.<sup>13</sup> In both plots excellent linear fit was observed.

#### Discussion

Attempts to prepare the parent disecondary dication 1-H or the ditertiary dimethyl substituted analogue 1-CH<sub>3</sub> by ionizing the corresponding diols 4-H and 4-CH<sub>3</sub> under a variety of superacidic conditions at -78 or -140 °C were unsuccessful and gave



Figure 1. A plot of <sup>13</sup>C NMR chemical shifts of C-1 vs. C-3 in 2,5-diphenyl-2,5-norbornyl dications.

only unidentifiable polymeric species. The diketone **2**, however, underwent facile protonation to the corresponding dioxonium ion in FSO<sub>3</sub>H–SO<sub>2</sub>ClF. In the <sup>13</sup>C NMR spectrum the carbonyl carbon absorbs at  $\delta^{13}$ C 242.3, which is about 28 ppm deshielded over that in the neutral precursor **2**.<sup>16a</sup> Similar deshielding effects are also observed in the case of protonated 2-norbornanone.<sup>16b</sup> This demonstrates that there is very little contribution of 2,5-di-hydroxy-2,5-norbornyl dication structure **1**-OH to the overall protonated diketone structure.

The phenyl-substituted dication  $1-C_6H_5$  was found to be re-



markably stable, permitting a detailed study. The stability of  $1-C_6H_5$  can be explained by its ability to accommodate the di-

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Figure 2. A plot of the <sup>13</sup>C NMR chemical shifts of cationic centers in 2,5-diphenyl-2,5-norbornyl dications against those in 1-phenyl-1-cyclopentyl cations.

positive charge via delocalization into phenyl rings (involving the ortho and para resonance forms), thus minimizing charge-charge replusion effects. No such stabilization is possible for either 1-H or  $1-CH_3$ .

For comparison, the 1,4-diphenyl-1,4-cyclohexyl dications 6- $C_6H_5$  and 6-4- $C_6H_4(CH_3)$  were also prepared. Again, their stability reflects the delocalizing ability of phenyl groups, which decrease charge-charge repulsions. The chemical-shift data in Table I show that carbocation centers in dications 1- $C_6H_5$ , 6- $C_6H_5$ , and 6-4- $C_6H_4(CH_3)$  are observed at  $\delta^{13}C$  245.1, 247.9, and 237.4, respectively. The carbocation centers are thus shielded by almost 15 ppm as compared to those in the analogous monocations.<sup>12,17</sup> The positive charge is increasingly delocalized into the phenyl rings in both dications resulting in increased deshielding of the ortho and para carbon chemical shifts ( $\simeq 4$  and  $\simeq 6$  ppm, respectively) relative to those in analogous monopositive systems.

Attempted generation of the parent 1,4-cyclohexyl dication 6-H and the 1,4-dimethyl-1,4-cyclohexyl dication 6-CH<sub>3</sub> starting from the corresponding alcohol precursors resulted only in rearranged allylic cations 7 and 8, respectively. Their formation can be rationalized by an ionization–elimination mechanism.<sup>18</sup>



Ionization of 1,4-di-*n*-butyl-1,4-cyclohexanediol ( $5-C_4H_9$ ) in SbF<sub>5</sub>-SO<sub>2</sub>ClF either at -78 or -140 °C gave only the rearranged dication **9** (single isomer), in which the carbocation centers are separated by six carbon atoms. The rearrangement occurs through a series of H and CH<sub>3</sub> shifts to the more stable dication **9**, resulting



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in minimized charge-charge repulsion. The <sup>13</sup>C NMR chemical shift of the carbocation centers in dication **9** is observed at  $\delta^{13}$ C 333.2, which is comparable to that of the monopositive *tert*-butyl cation<sup>19</sup> found at  $\delta^{13}$ C 335.2.

Tool of Increasing Electron Demand. In order to further explore the effect of dipositive charge on the norbornyl skeleton, we prepared a series of 2,5-diphenyl-2,5-norbornyl dications 1-R with both electron-releasing and electron-withdrawing substituents on the phenyl rings. The <sup>13</sup>C NMR chemical shifts of the carbocation centers range from  $\delta^{13}$ C 213.6 for the 4-OCH<sub>3</sub> substituent to  $\delta^{13}$ C 258.2 for the 3,5-bis(trifluoromethyl) groups (a range of  $\simeq 45$ ppm). A comparison with the related 2-phenyl-2-norbornyl cations  $3-R^{12}$  reveals a range of 238.3-264.5 ppm (a much narrower spread of  $\simeq 27$  ppm). Figure 1 shows the plot of the C-1 vs. C-3 carbon chemical shifts of dications 1-R. An excellent linear relationship is observed (correlation coefficient = 0.999). Such a linear fit demonstrates similar neighboring group deshielding effects experienced by the C-1 and C-3 carbons as the substituents on the phenyl ring are changed from electron-releasing to electron-withdrawing groups. A similar plot in the case of substituted 2-phenyl-2-norbornyl cations 3-R,<sup>12</sup> however, shows significant deviation for electron-withdrawing substituents, indicating the onset of nonclassical  $\sigma$  delocalization due to decreased chargedelocalizing ability of the deactivated phenyl ring. No such  $C_1 - C_6$ or  $C_2$ - $C_5$  bond interaction with the electron-deficient centers at  $C_2$  and  $C_5$  positions is occurring in the case of dications 1-R. The lack of any onset of  $\sigma$ -bond delocalization in 1-R can be understood based on electronic effects. The charge-charge repulsion is rather significant, and this renders the whole norbornyl skeleton electron deficient. However, this effect is partly relieved by the dispersal of charge into the aryl groups. The charge delocalization into the aryl ring even in the case of electron-withdrawing substituents such as  $4-CF_3$ ,  $3,5-(CF_3)_2$ , and pentafluoro groups is evidenced by the significant deshielding of ortho and para carbon chemical shifts and shielding of carbocationic centers (Table I) as compared to those in the monopositive analogues. The regular phenylcarbenium ion nature of 2,5-diphenyl-2-5-norbornyl dications 1-R is also evident from the plot of carbocation center shifts with those of substituted 1-phenyl-1-cyclopentyl cations<sup>13</sup> (Figure 2). A linear

<sup>(19)</sup> Olah, G. A.; Donovan, D. J. J. Am. Chem. Soc. 1977, 99, 5026-5039.

fit (r = 0.999) similar to the plot in Figure 1 is also observed.

Brown and his co-workers in a recent paper<sup>20</sup> questioned the previous <sup>13</sup>C NMR spectroscopic conclusions<sup>12,13</sup> on the onset of nonclassical  $\sigma$  delocalization in 2-phenyl-2-norbornyl cations 3-R with electron-withdrawing substituents. They argued that they have observed high exo/endo rate ratios in most tertiary derivatives including systems such as 10 and  $11^{21}$  with a wide variety of



substituents on the aryl ring. We reiterate our view that the "tool of increasing electron demand" as applied to solvolytic studies is too coarse to fully detect changes in the electron demand of a system unless the magnitude of such a demand is indeed large. Even negatively substituted phenyl rings are  $6\pi$  systems capable of significant charge delocalization; thus, the residual  $\sigma$ -bond delocalization effect should be small in 2-phenyl-2-norbornyl cations. Moreover, the observation of high exo/endo rate ratios in tertiary norbornyl systems does not provide any diagnostic test for the presence or absence of nonclassical  $\sigma$  delocalization. As pointed out by Brown in many of his works, 11b,21 such an effect may be of steric origin. Our present <sup>13</sup>C NMR spectroscopic study demonstrates the regular phenylcarbenium ion nature of 2,5-di-

phenyl-2,5-norbornyl dications 1-R, even with strong electronwithdrawing substituents, in contrast to 2-phenyl-2-norbornyl cations 3-R, where the onset of  $\sigma$  delocalization is observed with electron-withdrawing substituents. This study is in accord with the structure and stability of the parent 2-norbornyl cation based on a variety of spectroscopic<sup>11,22</sup> and calorimetric studies<sup>23</sup> in the condensed phase.

#### **Experimental Section**

The exo, exo diols 4-R were prepared by the addition of organomagnesium or organolithium reagents to the diketone  $2.1^{4}$  exo, exo-2, 5-Norbornanediol (4-H) was prepared by the reported "hydroboration-oxidation" of norbornadiene.<sup>14</sup> The diols 5-R (mixture of cis and trans) were prepared from the commercially available cyclohexane-1,4-dione.<sup>11</sup> All the new diols showed satisfactory spectroscopic and analytical data.

Preparation of Dications. Freshly distilled SbF5 and FSO3H were used. To the appropriate superacid dissolved in about a twofold amount of SO<sub>2</sub>ClF at dry ice-acetone (ca. -78 °C) or petroleum ether-liquid nitrogen slush temperature (-140 °C) was slowly added, with vigorous stirring, a cooled slurry or solution of the corresponding diol precursor in  $SO_2ClF$ , resulting in an approximately 10-15% solution of the ion.

<sup>13</sup>C NMR Spectra were obtained by using a Varian Associates Model FT-80 spectrometer, equipped with a multinuclei broad band variable temperature probe. The chemical shifts were referenced from external capillary tetramethylsilane.

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# Crystal Structure and Spectroscopic Properties of Violet Glutathione-Copper(II) Complex with Axial Sulfur Coordination and Two Copper Sites via a Disulfide Bridge

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Abstract: The violet glutathione-Cu(II) complex, [Cu<sup>II</sup>GSSGCu<sup>II</sup>]Na<sub>4</sub>·6H<sub>2</sub>O, was firstly isolated as a single crystal. The X-ray crystallographic analysis of the binuclear complex showed that each Cu(II) atom is in a distorted square-pyramidal configuration and the Cu(II)-Cu(II) distance is 5.21 Å. The coordination of Cu(1) involved the two deprotonated peptide nitrogens, N(1) and N(2), the glutamic amine nitrogen, N(3), and the glycinyl terminal carboxylate oxygen, O(1), in an approximate planar coordination while the cysteinyl sulfur, S(1), is bonded apically to form a square pyramid. The Cu(51)ion is similarly coordinated to N(51), N(52), N(53), O(51), and S(51). The apical Cu(II)-S mean distance is 3.22 Å and a direction of this bond is bent by 22° from the perpendicular  $C_{4v}$  axis of the square-planar basal plane. Of special interest is the Cu(II) coordination by the sulfur atoms of the disulfide bridge. The Cu(II) complex was also characterized by magnetic susceptibility and electron spin resonance (ESR), electronic, circular dichroism, and X-ray photoelectron spectra (X-ray PES). The magnetic susceptibility and ESR spectra showed that the internuclear Cu(II)-Cu(II) interaction is negligibly small. The ESR parameters and X-ray PES binding energies determined were as follows:  $g_{zz} = 2.251$ ,  $g_{xx} = 2.047$ ,  $g_{yy} = 2.038$ ,  $A_{zz} = 177.2$ ,  $A_{xx} = 43.8$ , and  $A_{yy} = 36.0$  G (ESR); Cu  $2p_{3/2} = 933.1$  and 943.9, S 2p = 163.4 and 167.5, N 1s = 399.4, O 1s = 531.2, and Na 1s = 1071.1 eV (X-ray PES). The present results provide valuable information for biologically significant glutathione-Cu(II) complexes.

#### Introduction

Glutathione-Cu(II) complexes are of biological and chemical interest. Marzullo and Friedhoff<sup>2a</sup> identified an inhibitor of opiate receptor binding as a glutathione-Cu(II) complex from human red blood cells and from rabbit brain. It has been reported that the Cu(II) complex is involved in rheumatoid arthritis and that the inhibitory activity is due to a complex of oxidized glutathione

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