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^{13}C-NMR Study of the Application of the "Tools of Increasing Electron Demand" to the 8-Aryl-tricyclo[3.2.1.0^{2,7}]oct-8-yl Cations

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The ^{13}C-NMR shifts of a series of para-substituted 8-aryl-tricyclo[3.2.1.0^{2,7}]oct-8-yl and 9-aryl-tricyclo[3.3.1.0^{2,8}]-non-9-yl cations were measured in FSO_3H/SO_2ClF at $-90^{\circ}C$ in order to examine whether the ρ^{C+} values can be used as a measure of the geometric influence on the charge delocalization resulting from σ conjugation in rigid tricyclopropylcarbinyl cations. Plot of the $\Delta\delta^{C+}$ shifts against the σ^{C+} constants revealed excellent linear correlation. The 8-aryl tricyclooctyl systems yielded a ρ^{C+} value of -5.00 with $r=0.9962$. Previous investigation of the 9-aryl-tricyclononyl systems gave a correlation coefficient of $r=0.9948$ with a slope of $\rho^{C+}=-4.95$. A fair parallelism exists between the results of ^{19}F-NMR studies and the change of ρ^{C+} value in these cations. Consequently, it is established that the ρ^{C+} value can be used to explain the mechanism of charge stabilization of the rigid cyclopropylcarbinyl cation such as tricyclo[3.2.1.0^{2,7}] oct-8-yl cation.

Introduction

For many years solvolysis rates have been utilized to arrive at an understanding of the factors influencing the stability of carbonium ions. A remarkably consistent body of knowledge has been built up in this way. One possible difficulty has been the necessity of comparing the rate with a suitable model system. Occasionally this can lead to ambiguities. The tool of increasing electron demand appears to minimize such ambiguities.[1]

Although this tool combined with the ^{13}C-NMR method should give similar unambiguous answers about the structural effect on stability of the carbocation in superacid media, often conflicting interpretation has been made.[2] The ^{13}C-NMR chemical shifts for the corresponding carbon in carbocation may be taken as a measure of the charge delocalization into the molecular structure.

Accordingly, numerous attempts seeking to correlate the ^{13}C NMR chemical shifts for the cationic centers of the substituted benzylic carbocations with Hammett-Brown σ^{+} constants have been reported.[3]

Application of the tool of increasing electron demand to the study of fully formed cations in superacids requires the plotting of the ^{13}C chemical shifts against some quantitative measure of electron demand. The use of electrophilic substitutent constant σ^{C-} has been shown to be inappropriate for this purpose.

Therefore, Brown and coworkers developed the following modified Hammett-Brown equation of the from

$$\Delta\delta^{C+}=\rho^{C-}\cdot\sigma^{C+}$$

where $\Delta\delta^{C+}$ is the difference between the cationic carbon chemical shift for the unsubstituted benzylic carbocation and that for the substituted carbocationic species, *i.e.*, $\Delta\delta^{C+}=$

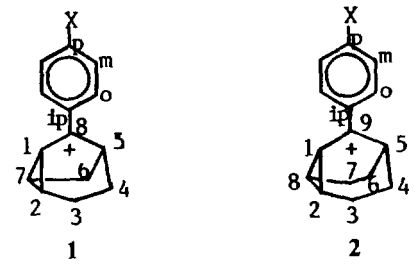


Figure 1.

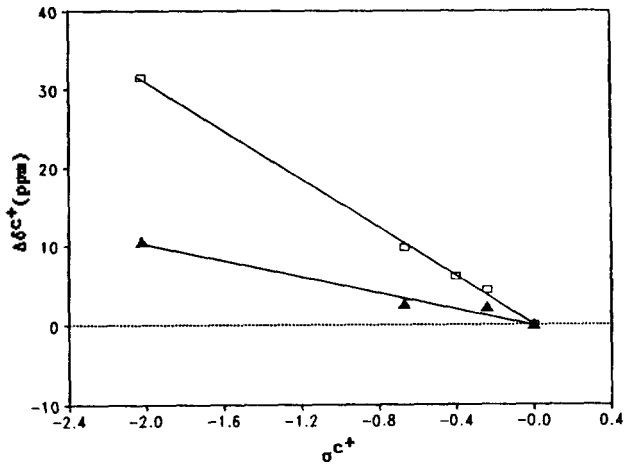


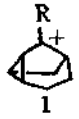
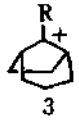
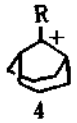
Figure 2. A plot of $\Delta\delta^{C+}$ values against σ^{C+} for ion 1(Δ) (slope $\rho^{C+}=-5.00$, correlation coefficient $r=0.9962$) and for ion 3(□) (slope $\rho^{C+}=-15.48$, correlation coefficient $r=0.993$).

$\delta^{C+}{}_H-\delta^{C+}{}_Z$, and σ^{C+} is the enhanced new substituent constant.[4] When applied to a range of acyclic, cyclic, and polycyclic aryldialkylcarbocation systems, these new σ^{C+} constants give excellent linear correlation for the cationic carbon chemical shifts ($\Delta\delta^{C+}$).[5]

In the previous ^{13}C-NMR studies[6], we confirmed the validity and usefulness of the σ^{C+} constants to examine the structural effect on the relative stability of rigid cyclopropylcarbinyl cations.

We now wish to report the utility of these new σ^{C+} constants to explain the mechanism for stabilization of the geometrically rigid cyclopropylcarbinyl cations such as 8-aryl-tricyclo[3.2.1.0^{2,7}]oct-8-yl cations. For comparision of the results,

Table 2. Comarison of ρ^{C+} Values and ^{19}F Chemical Shifts for Cation 1, 2, 3 and 4 in FSO_3H/SO_2ClF at −90℃

Compound	δ^{19}F	ρ^{C+}	Compound	δ^{19}F	ρ^{C+}
 1	−81.4	−5.00 (0.9962)	 2	−86.2	−4.95 (0.9948)
 3	−67.1	−15.48 (0.9993)	 4	−64.8	−18.31 (0.9998)
$\Delta\delta^{19}F=14.3$		$\Delta\rho^{C+}=10.4$	$\Delta\delta^{19}F=21.4$		$\Delta\rho^{C+}=13.3$

[a] ^{19}F chemical shift are in ppm from external CCl_3F. [b] Correlation coefficient r is indicated in parenthese. [c] R denotes para-substituted phenyl group. [d] Data for ion 2 and ion 4 were taken from ref 6.

we have also studied these cation by ^{19}F-NMR spectroscopy.

Results and Discussion

8-Aryl-tricyclo[3.2.1.0^{2,7}]octan-8-ol derivatives were prepared by the addition of the ketone to the Grignard reagents prepared from the corresponding bromobenzenes. The cations were prepared by adding a measured quantity of the alcohols to the FSO_3H/SO_2ClF solution at −100℃. The ^{13}C chemical shifts were then measured at −80 ℃. The ^{13}C chemical shifts of the these cations are summarized in Table 1 with those of the corresponding alcohols.

A plot of $\Delta\delta^{C+}$ value against the σ^{C+} constant for cation 1 (Figure 2) revealed an excellent correlation with $r=0.9962$ and $\rho^{C+}=-5.00$ (Table 2).

At one time, the high reactivity of cyclopropylcarbinyl derivatives in carbonium ion reactions was attributed to the formation of a stabilized species involving a σ bridge or σ conjugation between the cationic carbon and one or both of the distant carbon atoms of the cyclopropane ring.[7] From the results of many experimental studies and theoretical calculation, it is clear that the bisected conformation of a cyclopropylcarbinyl cation is energetically favored over the perpendicular conformation.[8]

Table 1. ^{13}C NMR-Shifts of Ion 1 in FSO_3H/SO_2ClF at −90℃

Ion	Substituent	Chemical Shift											
		C_β	C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_{ip}	C_o	C_m	C_p
I	*p*-OCH_3	232.7	48.8	54.2	30.7	19.1	43.1	40.5	67.6	127.6	141.5	118.6	175.6
		(81.2)	(18.6)	(15.3)	(23.6)	(28.9)	(41.3)	(25.3)	(16.1)	(140.2)	(126.9)	(113.5)	(158.6)
	p-F	240.7	59.6	65.8	31.3	20.4	44.8	43.3	85.5	130.1	140.6	120.1	173.5
		(81.2)	(18.7)	(15.3)	(13.9)	(20.4)	(44.8)	(43.3)	(85.4)	(143.3)	(127.4)	(114.6)	(161.8)
	p-Cl	241.1	61.5	67.5	31.3	20.6	44.8	43.6	88.5	131.4	137.3	131.7	152.6
		(81.6)	(18.7)	(15.2)	(23.3)	(28.6)	(41.2)	(24.7)	(15.7)	(132.5)	(128.1)	(127.2)	(146.1)
	p-H	243.2	60.7	66.7	31.1	20.4	44.5	43.4	87.4	132.8	135.1	131.2	144.8
		(81.5)	(18.8)	(15.3)	(23.6)	(28.8)	(41.3)	(24.9)	(16.1)	(147.7)	(128.1)	(125.8)	(126.8)

[a] ^{13}C Chemical shifts the corresponding alcohols are given in parentheses. [b] Chemical shifts are ± 0.1 ppm from external Me_4Si. [c] C_β is cationic carbon for ion 1. [d] Assignment may be interchanged.

Indeed, an examination of the molecular geometries shows that the cyclopropane moiety in ion 2 is situated in a favored bisected conformation toward the vacant *p* orbital at the cationic carbon for the charge delocalization while the cyclopropane moiety in ion 1 does not maintain favored bisected orientation (Figure 1).

The ρ^{C+} value of ion 1(−5.00) is very similar to ρ^{C+} for 2(−4.95). This indicates that the electronic contribution from the cyclopropane moiety is very similar in the two systems, in spite of the small difference in molecular geometries.

The Gassman-Fentiman approach[9] provides an alternative means of evaluating the deficiency of the developing cationic center in a system undergoing ionization. The greater the electron deficiency at the developing cationic center, the greater should be the demand on the substituted phenyl ring for electronic stabilization. Thus we may expect that the ρ^{C+} value for ion 2 would clearly reveal a less negative value. However, the structural effect on charge delocalization by adjacent cyclopropane moiety in ion 1 can not be directly compared with that of ion 2 using the ρ^{C+} value because of the difference in the ring size of the two carbocation systems. It should, therefore, be more reasonable to compare the structural effect on charge delocalization in these cationic systems using $\Delta\rho^{C+}$ values. The $\Delta\rho^{C+}$ is the difference between the ρ^{C+} value for cyclopropylcarbinyl cation and that of the cation with the identical ring size but devoid of cyclopropane moiety.

Comparison of the $\Delta\rho^{C+}$ for ion 1(10.48) with that of ion 2 (13.36) (Table 2) implies that ion 1 is more sensitive to the variation of electron supply from the substituent of phenyl ring than ion 2. In other words, the results indicate that the cyclopropane ring in ion 2 is situated in a favored bisected conformation toward the vacant *p* orbital at cationic carbon for the maximum charge delocalization.

In our previous NMR studies on relative stability of carbocationic species, the results of ^{19}F chemical shifts were in accordance with the result of solvolytic studies. Thus we have also prepared 8-*p*-fluoropheny substituted cation 1 and model cation 3 with the identical ring size but devoid of cyclopropane ring. ^{19}F chemical shift of these cations recorded at −70℃, and their ^{19}F-NMR data as well as Δδ value are summarized in Table 2, along with some previously recorded data.

When a positive charge is dispersed into an adjacent *p*-fluorophenyl ring, the chemical shift of the fluorine atom on the phenyl ring moves downfield compared to that of uncharged species. Thus, the ^{19}F chemical shift can provide information on the degree of charge delocalization through neighboring group participation.

The chemical shift of fluorine atom in ion 1 appears at −81.4 ppm and that in ion 2 at −86.2 ppm. The signal of the fluorine atom in ion 1 was shifted considerably downfied (4.8 ppm) compaared to that of ion 2. However, the ^{19}F chemical shift of ion 1 can not be directly compared with that of ion 2 because the ring size of cationic systems may influence the chemical shifts. The difference of ^{19}F chemical shift between ion 1 and ion 3 was 14.3 ppm, and the corresponding value between ion 2 and ion 4 was 21.4 ppm., respectively. This means that the signal of the fluorine atom in ion 1 was shifted considerably downfield (ΔΔδ, 7.1) compared to that the in ion 2. This indicates that the stabilization provided by σ-conjugation of *p*-orbital of the carbonium carbon with the cyclopropane ring is greatly deminished in ion 1.

In our previous NMR studies on relative stability of carbocation, the ^{19}F-NMR data were agreed with the results of relayed solvolysis studies.

In the present ^{13}C-NMR study, we confirm the conclusion that the ρ^{C+} value can be used as a measure of the geometric influence for the charge stabilization resulting from σ conjugation of rigid cyclopropylcarbinyl cationic systems such as ion 1 and ion 2.

Experimental Section

NMR Spectra. The ^{13}C-NMR spectra were recorded at −90℃ on a Bruker AC 80 spectrometer operating at 20.1 MHz in the FT mode in 10 mm tube. Data were accumulated by using 32768 data point, spectral widths of 5000 or 6000 Hz, and pulse angles of 60°. Chemical shifts are reported in ppm from internal $(CH_3)_4$ Si. Assignment was based on DEPT-AU progam.

Carbocations. Each cation was prepared by slow addition of a solution of the respective alcohols in dichlorometan-d_2 to a rapidly stirred solution of FSO_3H/SO_2ClF at −110 ℃ using an ion generating apparatus. The concentration of the ion based on the precursor added was in the range 0.3-0.5 M and were generally colored yellow-brown.

Synthesis of Alcohols. A substituted 8-aryl-tricyclo [3.2.1.0^{2,7}] octan-8-ol was synthesized by the reaction of the ketone precursor with the Grignard reagent prepared from the corresponding bromobenzene, and was purified by column chromatography. All of the alcohols gave satisfactory ^{1}H and ^{13}C-NMR spectra, and their ^{13}C chemical shifts are summarized in Table 1.

Synthesis of Ketone. Tricyclo[3.2.1.0^{2,7}]octa-8-one. 3-Cyclohexene-1-carboxylic acid was prepared by Diels-Alder reaction from butadiene and ethyl acrylate devised by Doering *et al*[10]. The azoketone, which was obtained from the corresponding acid chloride in the usual way, was converted to the tricyclic ketone by treatment with copper powder. ^{1}H-NMR ($CDCl_3$); δ 1.8(m, 2H), 2.0(bs, 5H), 2.2(m, 3H). ^{13}C-NMR ($CDCl_3$); δ 184.7, 41.0, 30.7, 28.9, 27.3, 25.2, 16.2. IR (CCl_4) (cm^{-1}); 3040(*w*), 3010(*w*), 2940(*s*), 2870(*s*), 1720(*s*), 1645(*w*), 1445(*w*), 1320(*m*), 1330(*m*), 1210(*w*), 1190(*m*), 1090(*s*), 950(*m*), 920(*m*), 860(*m*).

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Development of New Protecting Groups for Guanine Residue in Oligodeoxyribonucleotide Synthesis

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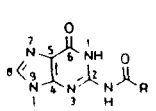
Attempts were made to develop new protecting groups for 1,6-lactam function of 2-N-acyl guanine in oligodeoxyribonucleotide synthesis. Several acyl groups, aryl groups, and carbamoyl groups were tested. Dimethylcarbamoyl and phenylacetyl groups are shown to be a good combination for guanine residue. 6-O-Di-methylcarbamoyl-2-N-pheylacetyl-2'-deoxyguanosine have been successfully used in the synthesis of d[AAGCTT], which is Hind III recognition sequence.

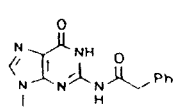
Introduction

In the most common oligonucleotide synthetic route, the phosphotriester method,[1,2] the choice is to block each reactive center because of the poor selectivity of the reagents used, the need for high yield and purity, and the difficult separations often encountered. Since Khorana and his coworker[3] introduced the use of N^2-isobutyryl group for guanine residue [as in (1)], almost every worker followed Khorana's original initiative. But it is well known that 2-N-acyl guanine is susceptible to side rections during oligonucleotide synthesis,[4,5] Therefore, attemts were made to develop new protecting groups for 1,6-lactam function of 2-N-acyl guanine and the number of different protecting groups were introduced by several workers.[6-9] Despite several protecting groups were introduced, because of unsatisfactory yield of preparation of building block, relatively long time or strong reaction condition for deprotection, or depurination, we still need to develop better protecting groups for guanine residue in oligodeoxyribonucleotide synthesis.

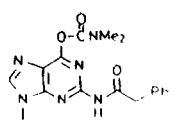
Recently, diphenylcarbamoyl (DPC) group was introduced by Hata and his coworkers for the O^6-amide group of guanine residue in the ribo-series[10] and in the deoxyriboseries.[11] They applied DPC group in combination with propionyl group for protecting the 2-amino group.



(1)



(2)



(3)

We favor the use of phenylacetyl group for protection of the 2-amino group [as in (2)], since the group is stable under all the reaction conditions used in the synthesis of oligodeoxyribonucleotide and is more base labile than conventional isobutyryl or isopropyl group. When we used DPC group with phenylacetyl group, we found quite a lot of depurination through the preparation of protected deoxyguanosine. To find out the appropriate protecting group of the O^6-amide group of 2-N-phenylacetyl-2'-deoxyguanosine, we investigated several acyl groups, aryl groups, and carbamoyl groups.

In this paper, we have shown that dimethylcarbamoyl (DMC) group is the most promising group for protection of O^6-amide group of 2-N-phenylacetyl-2'-deoxyguanosine [as in (3)]. We applied this protecting group for the synthesis of d[AAGCTT], which is Hind III recognition sequence.

Results and Discussion

We first investigated introduction of acyl and carbamoyl groups on the guanine residue of deoxyguanosine (Figure 1) by using modification of the reported procedure.[11] Without protection of 3',5'-hydroxyl group, 2-N-phenylacetyl-2'-deoxyguanosine was allowed to react with acyl chlorides or carbamoyl chlorides to give 6-O-acyl or 6-O-carbamoyl-2-N-phenylacetyl-2'-deoxyguanosine. As shown in Table 1, most of the chlorides gave reasonably good yield. DMC group was introduced in very good yield. When we introduced DPC group on the guanine residue of deoxyguanosine, we found that depurination occurred in substantial amount. Especially when DPC group was first introduced on 3'-5'-Di-O-methoxyacetyl-2-N-phenylacetyl-2'-deoxyguanosine followed deproection of dimethoxyacetyl groups with 4M-methanolic ammonia, the depurinated compound 6-O-diphenylcarbamoyl-2-N-phenylacetylguanine was isolated as major product.

Some acyl groups were also tested. We undertook synthesis of 6-O-trimethylbenzoyl-2-N-phenylacetyl-2'-deoxyguanosine