Acetylenedicarboxylate. A mixture of 1.58 g (3.96×10^{-3} mol) of the Reissert salt **4** (R = 1-naphthyl), 2.0 mL of dimethyl acetylenedicarboxylate, and 25 mL of anhydrous DMF was stirred at 100 °C for 22 h. The reaction mixture was concentrated and then poured into 130 mL of water. A light yellow-brown solid which formed was collected by suction filtration. This crude material (3.05 g) was chromatographed on a dry column,[20] with methylene chloride being used as eluent. A pale yellow solid (0.62 g, 38%) was eluted. Recrystallization of the solid, identified as dimethyl 3-(1-naphthyl)pyrrolo[2,1-*a*]isoquinoline-1,2-dicarboxylate (**22**), from methanol gave a pure product: mp 195.5–196.5 °C; IR ($CHCl_3$) 3030, 2960, 1715, 1600, 1515, 1450, 1405, 1360, 1300, 1215, 1095, 1055, 1005, 970, 940, 910, 760 cm^{-1}; NMR ($CDCl_3$) δ 3.50 (s, 3 H), 4.00 (s, 3 H), 6.55 (d, 1 H, J = 9.0 Hz), 6.95 (d, 1 H, J = 9.0 Hz), 7.40 (m, 8 H), 7.85 (m, 2 H), 8.55 (m, 1 H).

Anal. Calcd for $C_{26}H_{19}NO_4$: C, 76.27; H, 4.68; N, 3.42. Found: C, 75.96; H, 4.80; N, 3.26.

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Registry No.—**5,** 53778-23-7; **6,** 68001-15-0; **7,** 68001-16-1; **8,** 68001-17-2; **9,** 68001-18-3; **10,** 68001-19-4; **11,** 68001-20-7; **12,** 68001-21-8; **13,** 68001-22-9; **14,** 68001-23-0; **15,** 68001-24-1; **16,** 10425-52-2; **17,** 20958-81-0; **18,** 51039-56-6; **19,** 34977-08-7; **20,** 68001-39-8; **21,** 68001-40-1; **22,** 68001-41-2; 2-*p*-anisoyl-7,8-dimethoxy-1,2-dihydroisoquinaldonitrile, 68001-42-3; 2-*p*-anisoyl-5,6,7-trimethoxy-1,2-dihydroisoquinaldonitrile, 68001-43-4; 2-acetyl-1,2-dihydroisoquinaldonitrile, 29924-67-2; 2-isobutyryl-1,2-dihydroisoquinaldonitrile, 68001-44-5; 2-(cyclopropanecarbonyl)-1,2-dihydroisoquinaldonitrile, 68001-45-6; 2-(1-naphthoyl)-1,2-dihydroisoquinaldonitrile, 21259-46-1; 2-(α-bromobenzyl)-2-phenyl-1,3-dioxolane, 68001-46-7; potassium cyanide, 151-50-8; isoquinoline, 119-65-3; 1-naphthoyl chloride, 879-18-5; desyl bromide, 1484-50-0; ethylene glycol, 107-21-1; 1-benzylisoquinoline, 6907-59-1; phenyllithium, 591-51-5.

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Hindered Rotation in Hexasubstituted Guanidine Salts

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Proton NMR spectra of 2,2-dibenzyl-1,1,3,3-tetramethylguanidine chloride and 2,2-dixylyl-1,1,3,3-tetramethylguanidine chlorides were examined. All compounds exhibited temperature dependent resonances for both the $-N(CH_3)_2$ and $-N(CH_2Ar)_2$ protons. This temperature dependence is consistent with the view that restricted rotation exists for the three major C=N bonds of the guanidine nucleus. The results provide evidence for the existence of a nonplanar structure for hexasubstituted guanidine salts.

Syn–anti isomerization of double-bonded nitrogen in free guanidines has been observed[1-4] by their temperature dependent NMR spectra. Kessler and co-workers[1,2] have shown convincingly that this syn–anti conversion is a true inversion process involving an sp hybridized nitrogen atom in the transition state. A similar NMR temperature dependence has been observed for the salts of 2-aryl-1,1,3,3-tetramethylguanidine.[1] Two mechanisms which have been proposed are rotation about the C=N bond or deprotonation to the free guanidine followed by inversion and protonation. The authors considered rotation about the C=N bond to be more likely for three reasons. First, in tetramethyl-2-alkylguanidine salts[5] vicinal coupling of the NH protons with the α protons of the alkyl group occurs at room temperature while simultaneously the signal of the dimethylamino protons appears as a sharp singlet. Secondly, the free energy of activation of proton exchange was shown to be larger than the free energy of activation for the syn–anti conversion. Finally, they reported finding similar free energy of activation barriers for pentamethylarylguanidine iodine salts.[6]

In our study of 2,2-dibenzyl- and 2,2-dixylyl-1,1,3,3-tetramethylguanidine salts similar rotation barriers were found. In this report we present the results of NMR studies and their implications concerning a new aspect of the structure of highly substituted guanidine salts.

Results and Discussion

The synthesis of the hexasubstituted guanidine halides is outlined in Scheme I. The reaction carried out in benzene is quite exothermic and goes essentially to completion without heating of the reaction mixture. Under these conditions the guanidine salts precipitate from the reaction mixture as fine needles. If the reaction is carried out with equal molar quantities of tetramethylguanidine (TMG, **1**) and benzyl halide,

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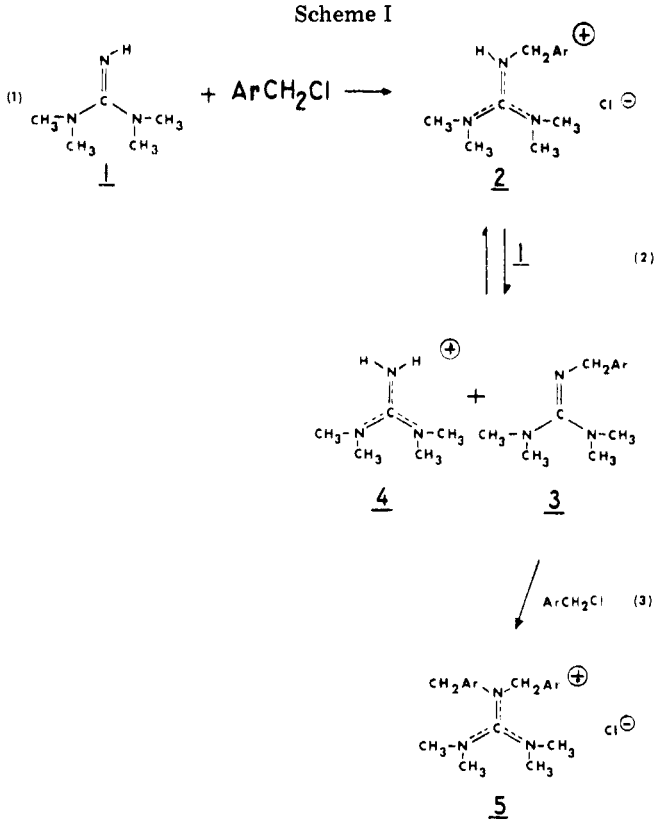
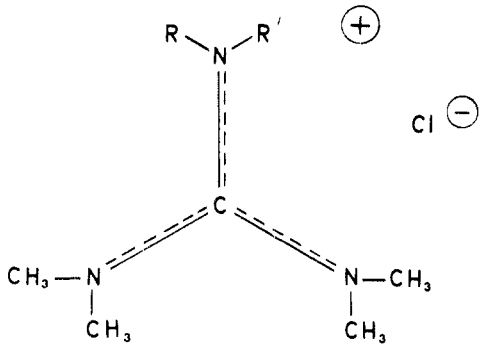
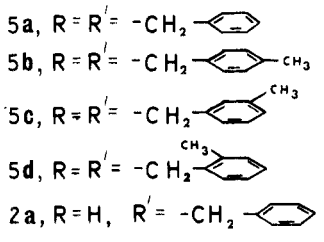
Scheme I



the precipitate consists of an approximately equal mixture of **5** and **4**. Molar ratios of TMG/benzyl halide greater than 1 yield a crystalline mixture of **5**, **4**, and **2**, from which **2** can be isolated by fractional crystallization. Although a detailed study of the reaction was not carried out, presumably the predominance of product **5** over that of **2** is due to reaction 3 being essentially irreversible and more rapid than reaction 1. Increasing the concentration of TMG would tend to favor the formation of **2** by increasing the rate of reaction 1 relative to reaction 2.

Compounds **2a**, **5a**, **5b**, **5c**, and **5d** were prepared. Their

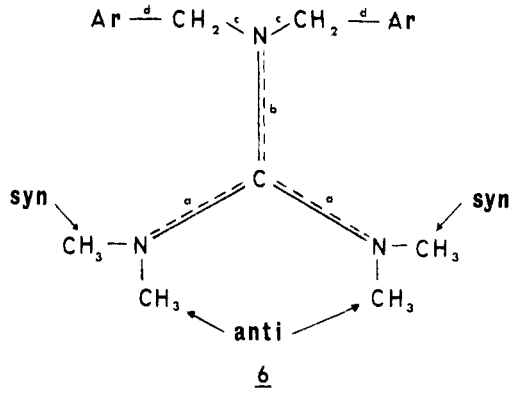




NMR spectra were determined at various temperatures in $CDCl_3$ in order to detect restricted rotation and simultaneously to determine the associated free energy of activation ($\Delta G^{\ddagger}$). In all cases, two temperature dependent peaks were found, one corresponding to the benzyl hydrogens $-N(CH_2Ar)_2$ and the other to the $-N(CH_3)_2$ hydrogens. The benzyl hydrogens show a somewhat broadened singlet at higher temperatures and a broad AB pattern at lower temperatures. The $-N(CH_3)_2$ hydrogens, however, exhibit a sharp singlet at high temperatures which becomes two overlapping singlets at lower temperatures. Compound **2a**, an exception, shows only a broadening of the $-N(CH_3)_2$ hydrogens at the lowest temperature achievable in our experiment, but otherwise still exhibits a typical AB pattern at lower temperatures for the benzyl hydrogens.

The coalescence temperatures, chemical shift differences, coupling constants, and $\Delta G^{\ddagger}$ values are summarized in Table I. Figure 1 shows two typical NMR spectra at room temperature and the temperature dependence of both the $-N(CH_2Ar)_2$ and $-N(CH_3)_2$ resonances. Assignment of the resonances is based on their relative areas and their chemical shifts with respect to $(CH_3)_4Si$. The free energies of activation were calculated by standard methods.[7] See footnote *a* in Table I.

At low temperatures the $-N(CH_3)_2$ resonances appear at different chemical shifts due to their "syn–anti" relationship with respect to the $-N(CH_2Ar)_2$ groups in the apparent planar structure **6**. As suggested by Kessler,[1] the interconversion of



the syn–anti methyls at higher temperatures must obviously involve a rotation about the a bonds. For the guanidinium ion the free energy of activation of bond rotation has been recently deduced.[8] This value ($\Delta G^{\ddagger} \leq 13$ kcal/mol, 300 K) is close to that found by Kessler[1] for tetramethylarylguanidine salts particularly with respect to that C=N bond which is least affected by steric crowding.[9] Furthermore, it compares favorably with the recent results of ab initio calculations for the rotational barriers in the guanidinium ion.[10] It should be noted that our free energy of activation barriers are of the same magnitude as those found by Kessler for tetramethylaryl- and pentamethylarylguanidine salts.[1,5,6]

More interesting is the temperature dependence of the benzyl hydrogen resonance. There are three possible interpretations of this behavior. (1) Restricted rotation about bond c is capable of creating an asymmetric environment which renders the benzyl hydrogens nonequivalent. (2) Restricted rotation about bond d could lead to the same type of nonequivalence. (3) Rotation about bond b is resticted, and the $-N(CH_2Ar)_2$ group is not in, nor perpendicular to, the plane of the guanidine nucleus. If such is the case, regardless of rapid rotation about bonds c and d, the benzyl hydrogens will not be equivalent and a single AB spectrum should arise. The third interpretation seems most likely for several reasons. Dreiding models indicate that there would be little if any steric interference to rotations about bonds c and d. If so, one would expect the barriers about bonds c and d to be of the same order of magnitude as barriers for rotation about sp^2–sp^3 σ bonds. Generally the free energy of activation barriers for sp^2–sp^3 bonds range from approximately 1–3 kcal/mol,[11] which are

Table I. Coalescence Temperatures (T_c), Chemical Shift Differences ($\Delta\nu$), and $\Delta G^{\ddagger}$ Values

	$-N(CH_3)_2$			$-N(CH_AH_BAr)_2$			
compd	T_c, K	$\Delta\nu$, Hz	$\Delta G^{\ddagger}$,[a] kcal/mol	T_c, K	$\Delta\nu$, Hz	J_{AB}, Hz	$\Delta G^{\ddagger}$,[a] kcal/mol
5a	276.0 ± 3	3.0	14.6 ± 0.2	290.0 ± 3	22.3	15.6	13.8 ± 0.2
5b	298.7 ± 3	4.0	15.7 ± 0.2	312.0 ± 3	17.2	10.2	15.2 ± 0.2
5c	298.0 ± 3	3.5	15.7 ± 0.2	307.0 ± 3	19.2	14.4	14.8 ± 0.2
5d	297.0 ± 3	9.0	15.1 ± 0.2	302.5 ± 3	18.6	13.0	14.6 ± 0.2
2a				285.0 ± 3	16.4	11.8	13.8 ± 0.2

[a] The rate constants k_c were calculated using the expression $k_c = (\pi/\sqrt{2})\Delta\nu$ for the $-N(CH_3)_2$ group and $k_c = (\pi/\sqrt{2})[(\Delta\nu)^2 + 6J^2]^{1/2}$ for the $-N(CH_AH_BAr)_2$ group. $\Delta G^{\ddagger}$ was calculated from the Eyring expression $k_c = (\kappa kT/h)[\exp(-\Delta G^{\ddagger}/RT)]$ with the transmission coefficient $\kappa = 0.5$; see ref 7. For the method of evaluating $\Delta\nu$, see A. J. Gordon and R. A. Ford, "The Chemist's Companion", Wiley, New York, 1972, p 309.

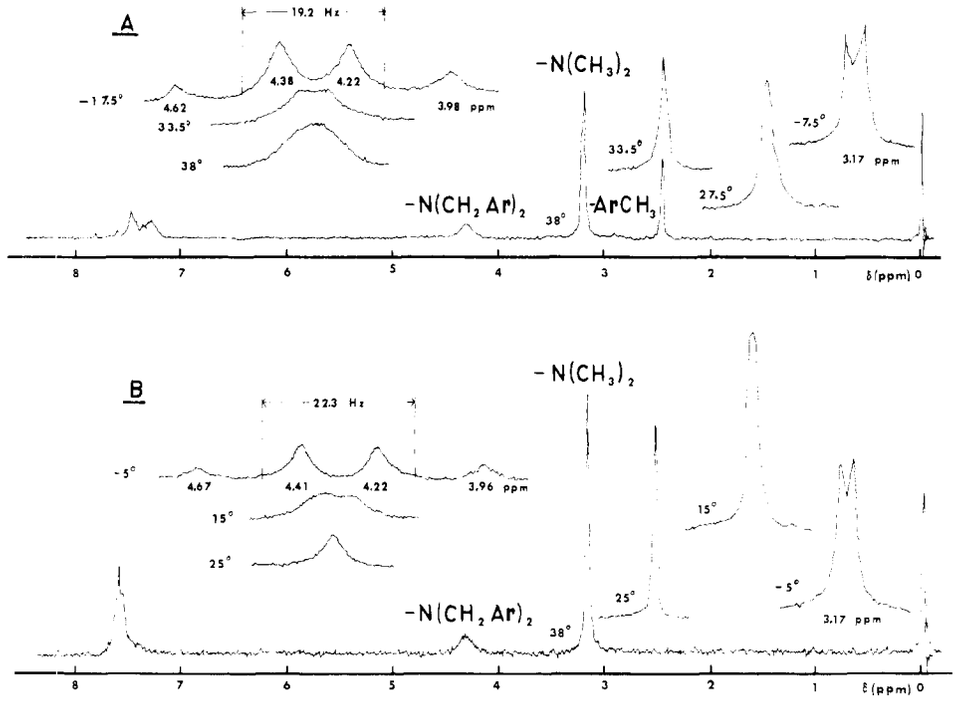


Figure 1. NMR spectra of 2,2-di-*m*-xylyl-1,1,3,3-tetramethylguanidine chloride (A) and 2,2-dibenzyl-1,1,3,3-tetramethylguanidine chloride (B).

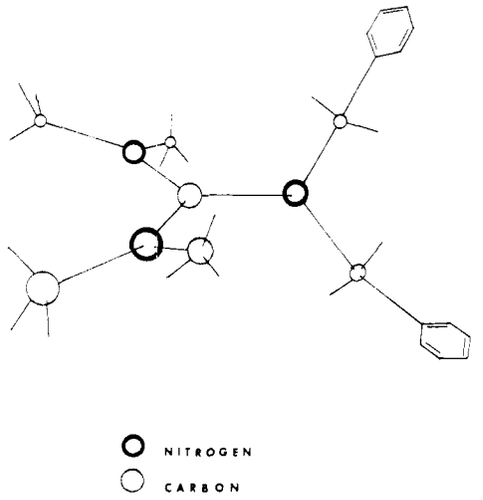


Figure 2. Conformation of 2,2-dibenzyl-1,1,3,3-tetramethylguanidine cation.

lower than the measured values for the guanidine salts. Secondly, if interpretation 1 or 2 is operative, substitution in the ortho position would significantly change the free energy of activation. Such changes are not realized as evidenced by the fact that no significant differences in the $\Delta G^{\ddagger}$ values were found for the ortho (**5d**), meta (**5c**), and para (**5b**) 2,2-dixylyl-1,1,3,3-tetramethylguanidine cations. In addition, interpretation 1 seems unlikely since both 2-benzyl-1,1,3,3-tetramethylguanidine chloride (**2a**) and 2,2-dibenzyl-1,1,3,3-tetramethylguanidine chloride (**5a**) have the same $\Delta G^{\ddagger}$ values, which is unexpected on steric grounds.

Dreiding models on the other hand suggest significant steric crowding in the planar structure which can be relieved by a slight rotation about bonds a and b. Small rotations about these bonds would not, however, significantly reduce the delocalization energy of the guanidine structure. We are therefore led to the conclusion that a propeller-like stable conformation must exist for these cations (Figure 2). This conclusion is supported by INDO[12] calculations of the hexamethylguanidine cation which indicate that the $-N(CH_3)_2$ groups are twisted approximately 5° out of the plane of the guanidine nucleus. On the basis of such a model, one would expect little if any difference in the $\Delta G^{\ddagger}$ values for the $-N(CH_3)_2$ and $-N(CH_2Ar)_2$ groups. An examination of Table I shows that such is the case for the compounds studied.

We therefore conclude that highly substituted guanidine cations are nonplanar and probably exist at low temperatures in an asymmetric propeller-like conformation. Furthermore, unless steric interference between substituents bound to ni-

trogen is large, stabilization due to electron delocalization should still be substantial.

Experimental Section

General. NMR spectra were obtained with a Varian A60A spectrometer equipped with a variable temperature probe. $CDCl_3$ was used as solvent and $(CH_3)_4Si$ as internal standard. The temperature of each spectrum was determined from the separation between methyl and hydroxyl resonances of methanol. The standard methanol sample supplied by Varian was utilized. The temperature was determined both before and after each spectrum was obtained. The same methanol sample was used for all spectral measurements, which were consistently reproducible.

Preparation of 2,2-Dibenzyl-1,1,3,3-tetramethylguanidine Chlorides (5a–d). In 150 mL of benzene was dissolved 0.1 mol of benzyl chloride ($ArCH_2X$). (The source of benzyl chlorides was Aldrich Chemical Co.) To this solution was added 0.1 mol of TMG, and the flask was stoppered and allowed to stand at room temperature for approximately 24 h. The crystalline precipitate (P_1) was filtered off and the filtrate evaporated down to approximately 10 mL on a rotary evaporator. The crystalline solid (P_2) formed on evaporation was filtered from the remaining liquid and washed with a small quantity of cold benzene. Both P_1 and P_2 were then subjected to fractional recrystallization from *o*-dichlorobenzene. The products P_1 and P_2 were combined and recrystallized from *o*-dichlorobenzene. This final product was then vacuum-dried with warming for 24 h.

Preparation of 2-Benzyl-1,1,3,3-tetramethylguanidine Chloride (2a). In 100 mL of benzene was dissolved 0.2 mol of TMG. To this was added slowly a solution of 0.1 mol of benzyl chloride in 50 mL of benzene, and the flask was stoppered and allowed to stand for 24 h. The separation procedure was as described above.

Satisfactory analytical data (±0.2% for C, H, and N) were reported for all compounds (Ed.).

Registry No.—**2a,** 68051-05-8; **5a,** 68081-52-7; **5b,** 68081-53-8; **5c,** 68081-54-9; **5d,** 68081-55-0; benzyl chloride, 25168-05-2; TMG, 80-70-6.

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Reaction of *p*-Quinones with Thioamides

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Reaction of thioacetamide with 1,4-benzoquinone produced 3a-hydroxy-2-methyl-1,3-benzothiazol-6(3a*H*)-one (**1**), mercaptohydroquinone (**3**), and its disulfide **4** as the main sulfur-containing products. The yield of **1**, **3**, and **4** varied depending on reactant ratio and solvent. The chemistry of **1** as well as of its precursor, iminothioacetylhydroquinone (**8**), is characterized by the tendency to eliminate acetonitrile. This was found in three separate reactions as well as in the fragmentation observed by mass spectrometry. Methyl-1,4-benzoquinone behaved similarly to 1,4-benzoquinone and thiobenzamide similarly to thioacetamide. 2,5-Di-*tert*-butyl-1,4-benzoquinone and 2-methyl-1,4-naphthoquinone with thioacetamide produced S_8 and the respective hydroquinone. A new nonoxidative disulfide formation (from compound **1** and a thiol **3**) is described.

Reactions of bidentate nucleophiles with *p*-quinones represent common synthetic routes to many heterocycles, either nonaromatic, as exemplified by reactions of β-amino alcohols[1] or cysteine,[2] or aromatic, represented by Nenitzescu synthesis of 5-hydroxyindoles.[3] Many of the above reactions involve oxidation of the primary product with a second quinone molecule. The formation of a substituted quinone enables the cyclization step.

In this paper the results of reactions of *p*-quinones with bidentate thioamides and the chemistry of the respective products are reported. In the past certain compounds with thioamide structure yielded only Michael addition products with *p*-benzoquinone,[4] whereas others such as thiourea produced a benzothiazole derivative.[5a] In all of the examples shown above, the primary nucleophilic attack resulted from the sulfur atom. However, no reaction of *p*-quinones with simple thioamides has been documented in the literature. In the studies reported in this paper, reaction of 1,4-benzoquinone with thioacetamide was examined in some detail. The studies were further extended to other quinones (methyl-1,4-benzoquinone, 2,5-di-*tert*-butyl-1,4-benzoquinone, and 2-methyl-1,4-naphthoquinone) and to another simple thioamide (thiobenzamide).

Discussion

Reactions between thioamides and 1,4-benzoquinone showed rapid darkening in early stages of the process and produced generally variable quantities of tarry products. This made determination of the mass balance of the reaction virtually impossible. The reaction of thioacetamide with 1,4-benzoquinone was examined using different solvents and varying the ratio of reactants from 1:1 to 1:2. The results of the reaction were evaluated in either preparative fashion or by gas chromatographic analysis after acetylation using authentic samples as standards (Table I). Small differences were observed when the results from preparative and analytical types of experiments were compared. The following compounds were identified as the reaction products: 3a-hydroxy-2-methyl-1,3-benzothiazol-6(3a*H*)-one (**1**), hydroquinone (**2**), mercaptohydroquinone (**3**), dithiobis[hydroquinone] (**4**), 2,6-(or 2,5-)bis(2,5-dihydroxyphenylmercapto)hydroquinone (**5**), and their acetyl derivatives. The structure of compound

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