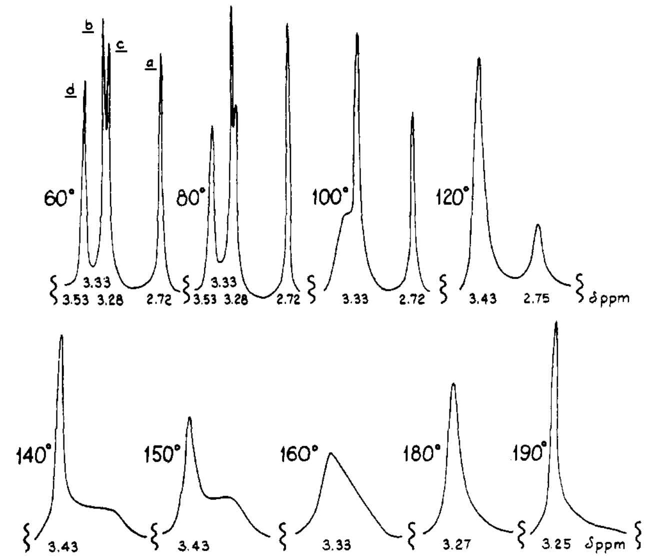

Figure 1. Nmr spectrum of 1,1,2,2,4,4,5,5-octamethyl-3-phenylbiguanide dichloride.

1,1,2,2,4,4,5,5-octamethyl-3-phenylbiguanide dichloride (II), colorless hygroscopic crystals, mp 281° dec.

The nmr spectrum[6] of II ($DOCD_2CD_2OD$), which at 60° exhibits four equally intense methyl singlets at δ 3.53, 3.33, 3.28, and 2.72 (Figure 1), provides considerable insight into the spatial configuration of the molecule. This spectrum is compatible only with a molecular geometry in which the biguanide system is planar, or nearly so,[7] and in which rotation about each skeletal bond (α, β, γ) is slow with respect to the nmr time scale. The highest field peak at δ 2.72 can be assigned to methyl groups a because of their proximity to the shielding π system of the benzene ring.[8] Because of the deshielding effect resulting from van der Waals compression,[9] the peak at δ 3.53 can be attributed to crowded methyl groups d. As the temperature of the nmr solution is raised, the signals at δ 3.53 and 3.28 broaden, then collapse, and by 120° reemerge as a single composite peak at δ 3.43. The coalescence of these peaks requires that they be associated with methyls on the same nitrogen atoms, and, since the δ 3.53 signal corresponds to methyls d, the δ 3.28 peak must be assigned to methyls c. By elimination, the δ 3.33 resonance represents methyls b. The appearance of the δ 3.43 composite peak indicates that the energy barrier to rotation about bond α has been overcome. At 100°, the δ 3.33 and 2.72 signals begin to broaden, and by 150° have virtually flattened; rotation about bond β has become rapid. Finally, as the temperature is raised to 190°, a single peak forms at δ 3.25; rotation about bond γ has also been freed, and all eight methyl groups have become magnetically equivalent.

The nmr spectrum (D_2O, 33°) of I consists of three peaks at δ 3.38 (1 CH_3, sharp), 3.28 (6 CH_3, broad), and 3.02 (2 CH_3, broad). The similarity of this spectrum to the 120° spectrum of II suggests that one bond (α) may be free to rotate, while the restricted rotation about the others (β, γ) is essentially unchanged.

The syntheses of other biguanide dications appropriate to a study of the influence of steric and electronic effects on the rotation process is in progress.

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[6] Nmr spectra were determined with a Varian Associates A-60 spectrometer with DSS as an internal standard.

[7] The severe steric interaction of the N-methyl groups d can be partially alleviated by either a modest deviation from planarity or deformation of the biguanide skeleton bond angles.

[8] K. Tori, K. Kitahonoki, H. Tanida, and T. Tsuji, *Tetrahedron Letters*, 559 (1964).

[9] W. Nagata, T. Terasawa, and K. Tori, *J. Am. Chem. Soc.*, **86**, 3764 (1964); R. W. Frank and K. Yanagi, *J. Org. Chem.*, **33**, 811 (1968).

Restricted Rotation in Guanidines

Sir:

The nmr spectrum of 1,1,2,2,4,4,5,5-octamethylbiguanide perchlorate (**1**) consists of a lone sharp singlet at δ 2.90.[1] This result was unexpected, since the presence of double bonds and severe steric crowding of methyl groups in the molecule should hinder rotation and, therefore, introduce methyl nonequivalence. A ready explanation for this phenomenon, as well as a new aspect of guanidine structure, was revealed by an examination of the spectra of several guanidine bases and cations.

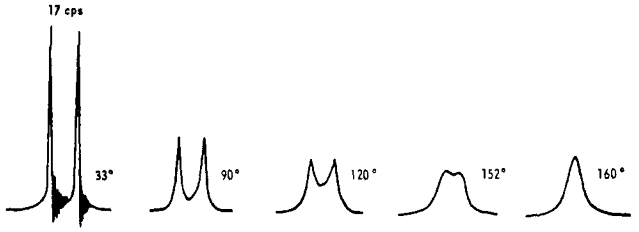

Figure 1. Nmr spectrum of 2-methoxy-1,1,3,3-tetramethylguanidine (**2b**): $N(CH_3)_2$ signals.

The nmr spectrum[2] ($CDCl_3$, 33°) of 1,1,2,3,3-pentamethylguanidine (**2a**)[3] consists of three singlets at δ 2.93, 2.77, and 2.67 of relative intensity 1:2:2. In this compound, rotation about the C=N bond must be restricted, while rotation about each C—N bond is rapid with respect to the nmr time scale.[4] The $N(CH_3)_2$ methyls appear at different chemical shifts because of their "*syn–anti*" relationships to the imine methyl. In contrast, the nmr spectrum (D_2O, 33°) of 1,1,2,2,3,3-hexamethylguanidine perchlorate (**3a**), mp not below 320°, the product of reaction[5] between tetramethylchloroformamidine chloride[1,6] and dimethylamine, is a sharp singlet at δ 2.92. This simplicity is a necessary result of the complete molecular symmetry of **3a**.

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(1) V. J. Bauer and S. R. Safir, *J. Med. Chem.*, **9**, 980 (1966).

(2) Nmr spectra at 33° were determined with a Varian Associates A-60 spectrometer with TMS or DSS as an internal standard. High-temperature nmr spectra were determined by Dr. J. E. Lancaster, American Cyanamid Co., Stamford, Conn., with a Varian Associates HA-100 spectrometer.

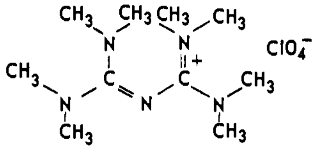
(3) H. Lecher and F. Graf, *Ber.*, **56**, 1326 (1923).

(4) (a) H. Kessler [*Tetrahedron Lett.*, 2041 (1968)] has described restricted rotation in aryltetramethylguanidines. (b) An alternative explanation, free rotation about the C=N bond and restricted rotation about each C—N bond, would also accommodate the observed spectrum, but is unlikely. This possibility is under investigation.

(5) *Cf.* C. Jutz and E. Müller, *Angew. Chem.*, **5**, 724 (1966).

(6) H. Eilingsfeld, G. Nebauer, M. Seefelder, and H. Weidinger, *Ber.*, **97**, 1232 (1964).

More informative are the nmr spectra of 2-methoxy-1,1,3,3-tetramethylguanidine (**2b**, bp 55–56° (19 mm) and 2-methoxy-1,1,2,3,3-pentamethylguanidine perchlorate (**3b**, mp 181°), the reaction products of tetramethylchloroformamidine chloride and methoxyamine and O,N-dimethylhydroxylamine, respectively. As in the case of **2a**, the spectrum ($CDCl_3$, 33°) of **2b** consists of three singlets at δ 3.65, 2.80, and 2.65 with a relative intensity of 1:2:2. Here the "*syn-anti*" relationships of the $N(CH_3)_2$ groups to the imine methoxyl, a result of restricted rotation about the C=N bond, cause nonequivalence of the methyl groups. The nmr spectrum (D_2O, 33°) of **3b** exhibits singlets at δ 3.67, 3.23, and 2.95 with a relative intensity of 1:1:4. Now the four $N(CH_3)_2$ methyls have become equivalent, and restricted rotation is no longer observed.[7]



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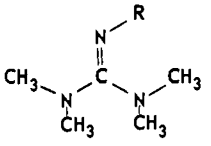
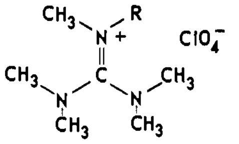


2a, R = CH_3
b, R = OCH_3



3a, R = CH_3
b, R = OCH_3

The nmr spectra (o-$Cl_2C_6H_4$) of **2a** and **2b** display the anticipated temperature-dependent coalescence of the $N(CH_3)_2$ signals. Thus, for **2b** (Figure 1) a coalescence temperature of 152° is observed; this, when substituted into the Eyring equation,[8] permits an estimate of 22.1 kcal/mol for the free energy of activation for rotation. A similar determination for **2a** provides a coalescence temperature of 78°, which corresponds to an energy barrier of 18.8 kcal/mol.

From these observations two conclusions may be drawn. First, in guanidine bases electron localization imparts enough double bond character to the C=N unit to establish restricted rotation. Secondly, stabilization of a guanidinium cation by charge delocalization distributes the double bond character more uniformly to a point where no bond possesses sufficient rigidity to impede rotation relative to the nmr time scale. The great base strength of guanidines is generally considered to be a reflection of the high resonance stabilization of the planar cation.[9] It is thus paradoxical that charge delocalization lowers the energy level of the planar cation and at the same time increases the rate at which rotation from the planar conformation occurs.

From these observations, an explanation for the simple nmr spectrum of **1** may be extrapolated. Charge delocalization over the five nitrogen atoms of **1** results in a distribution of the multiple bond orders so that rotation is not restricted, and complete methyl equivalence is therefore observed.

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[7] The possibility that accidental equivalence can account for this observation is remote, particularly since the same phenomenon has been observed in a number of related compounds (to be published).

[8] A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," John Wiley & Sons, Inc., New York, N. Y., 1953, p 89.

[9] L. Pauling, "The Nature of the Chemical Bond," 3rd ed, Cornell University Press, Ithaca, N. Y., 1960, p 286; G. W. Wheland, "Resonance in Organic Chemistry," John Wiley & Sons, Inc., New York, N. Y., 1955, p 357.

Direct Formylation of a Methyl Group in the "Oxo" Reaction. The Formation of (*R*)-3-Ethylhexanal in the Hydroformylation of (+)-(*S*)-3-Methyl-1-hexene

Sir:

In the hydroformylation of (+)-(*S*)-3-methyl-1-pentene, 4% of 3-ethylpentanal is obtained even under reaction conditions wherein practically no double bond migration occurs.[1] In order to clarify the mechanism of formation of this aldehyde, the products of hydroformylation of (+)-(*S*)-3-methyl-1-hexene (I) under similar conditions were examined.

I, optical purity 9.8% (see Table I), was prepared from the racemic compound using *cis*-dichloro-[(*S*)-α-phenylethylamine](ethylene)platinum as previously described.[2]

The hydroformylation of I (35 g, 0.357 mol) was carried out in the presence of $Co_2(CO)_8$ (0.300 g) at 110°, p_{CO} 100 atm and p_{H_2} 100 atm using benzene (40 g) as solvent.

The reaction mixture containing three major reaction products in the ratio 93.0:3.4:3.6 was oxidized with silver oxide and the mixture of acids thus obtained was esterified by an excess of CH_2N_2.

The mixture of the esters (41.6 g, 0.285 mol; ratio between the three major products, corresponding to about 99% of the total products, 93.8:3.1:3.1 (Perkin-Elmer vapor fractometer F 11, polypropylene glycol on Chromosorb W (15:85), 4 ft, 120°)) was separated by vapor phase chromatography (Perkin-Elmer fractometer F 21, butanediol succinate polyester (LAC-6-R-860) on Chromosorb A (20:80), 10 ft, 140°).

Three fractions were obtained which were shown to be respectively methyl (+)-(*S*)-4-methylheptanoate (II) (35 g), a mixture of diastereoisomeric methyl 2,3-dimethylhexanoates (III) (0.700 g), and methyl (+)-(*R*)-3-ethylhexanoate (IV) (0.690 g).

II has been identified by reduction ($LiAlH_4$) as (+)-(*S*)-4-methyl-1-heptanol,[3] bp 95° (20 mm), n^{22}D 1.4290.

The structure of III was demonstrated by comparing its infrared and nmr spectra with those of an authentic sample of a diastereoisomeric mixture of racemic methyl 2,3-dimethylhexanoates, prepared as previously described.[4]

Finally, IV (n^{25}D 1.4164) has been identified as methyl (+)-(*R*)-3-ethylhexanoate by comparing its infrared and nmr spectra with those of an authentic

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[1] P. Pino, S. Pucci, and F. Piacenti, *Chem. Ind.* (London), 294 (1963).

[2] R. Lazzaroni, P. Salvadori, and P. Pino, *Tetrahedron Lett.*, 2507 (1968).

[3] S. Julia, M. Julia, S. Tchen, and P. Graffin, *Bull. Soc. Chim. Fr.*, 3207 (1964).

[4] M. S. Kondakowa and M. M. Katznelson, *C. R. Acad. Sci. URSS*, **18**, 271 (1938); *Chem. Zentr.*, **109**, 4444 (1938).