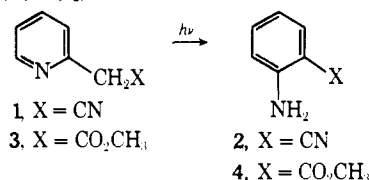


**Table I.** Solvent Dependence of Product Formation for the Isomerization of 2-Pyridylacetonitrile (1)<sup>a</sup>

Solvent	% conversion of 1	% formation of 2
Ethyl ether	55.3	8.3
Ethyl ether- <i>t</i> -BuOH (1:1 v/v)	38.0	36.8
Acetonitrile	42.7	3.0
Benzene	10.9	22.9
Methanol	65.2	5.2

<sup>a</sup> Pyridylacetonitrile concentrations were  $3\text{--}7 \times 10^{-4}$  M. Irradiation conditions are described in ref 2.

Moreover, irradiation<sup>8</sup> of methyl 2-pyridylacetate (3) ( $1.7 \times 10^{-2}$  M) in ethyl ether-*tert*-butyl alcohol gave a product which was identified as methyl *o*-amino-benzoate (4) (31 %).<sup>9</sup>



A plot of changes in the absorption spectrum of 1 on irradiation shows the gradual disappearance of 1 with simultaneous increase in absorbance at 248 and 324 nm. The final product, 2 ( $\lambda_{\text{max}}$  248 and 324 nm), is photochemically stable under these conditions. Further, the absence of isosbestic points and the increase of another absorption maximum at *ca.* 280 nm implies the possibility of another pathway to other products.<sup>10</sup>

Unsubstituted  $\alpha$ -picoline is known to undergo photolytic valence isomerization to  $\gamma$ -picoline in a poor yield *via* the prismane<sup>13</sup> but not to aniline; hence an electron-attracting group X in the side chain may be necessary for this photoisomerization.

A tentative mechanism for the formation of 2 from 1 is presented in Scheme I. Initial photochemical isomerization of the pyridine ring to a 2,5-bonded Dewar isomer (*e.g.*, 5) is well known.<sup>11,14</sup> An alternative tautomeric isomer of 5 (*e.g.*, 7) may be expected from valence isomerization of the methide 6.

The photolysis of 1 (or 3) (or their methides, 6<sup>15</sup>) may initially proceed to the 3-substituted 2-azabicyclo-[2.2.0]hexa-2,5-diene (5) (or 7), which is then converted

(8) Irradiation conditions are the same with ref 2 except for an irradiation time of 12 hr. *Ca.* 360 mg of the starting material was recovered. Methyl 2-pyridylacetate (3):  $\lambda_{\text{max}}^{\text{MeOH}}$  267 nm ( $\epsilon$  2250), 261 ( $\epsilon$  3000), 255 ( $\epsilon$  2320); nmr (CCl<sub>4</sub>)  $\delta$  8.34 (m, 1 H), 7.25 (m, 3 H), 3.67 (s, 2 H), 3.59 (s, 3 H).

(9) 4 (a colorless liquid): mass spectrum (*m/e*), 151 (M<sup>+</sup>);  $\lambda_{\text{max}}^{\text{MeOH}}$  248 nm ( $\epsilon$  6640), 337 ( $\epsilon$  4600); ir (cm<sup>-1</sup>) (liquid film) 3460, 3360, 2930, 1690, 1620, 750; nmr (CCl<sub>4</sub>)  $\delta$  7.65 (m, 1 H), 7.1 (m, 1 H), 6.5 (m, 2 H), 4.67 (s, 2 H, exchangeable with D<sub>2</sub>O), 3.75 (s, 3 H).

(10) The possibility of accumulation of Dewar-type pyridine (5) is less plausible in the respect that Dewar pyridine shows the end absorption at 220 nm alone.<sup>11</sup> The promotion of 1 to the methide form (6)<sup>12</sup> by uv light may occur, but this remains to be confirmed.

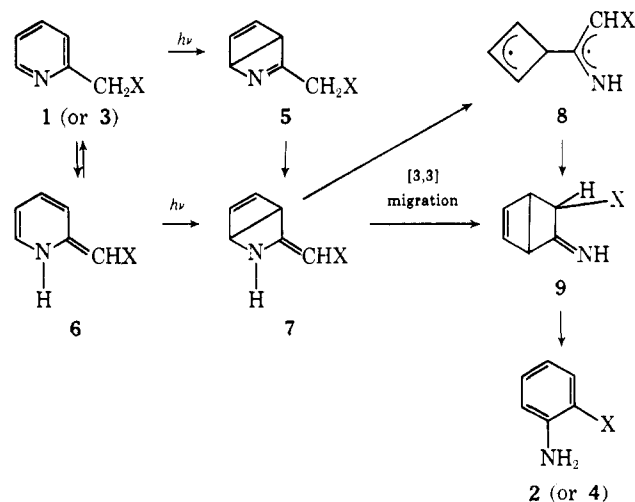
(11) K. E. Wilzbach and D. J. Rausch, *J. Amer. Chem. Soc.*, **92**, 2178 (1970).

(12) S.-O. Chua, M. J. Cook, and A. R. Katritzky, *J. Chem. Soc., Perkin Trans. 2*, 2111 (1973).

(13) S. Caplain and A. Lablache-Combiere, *Chem. Commun.*, 1247 (1970).

(14) (a) K. L. Wierzchowski, D. Shugar, and A. R. Katritzky, *J. Amer. Chem. Soc.*, **85**, 827 (1963). (b) M. G. Barlow, J. G. Dingwall and R. N. Haszeldine, *Chem. Commun.*, 1580 (1970).

(15) While the equilibrium constant for reaction between 1 (or 3) and 6 is unavailable, the proton exchanges of side-chain methylene with D<sub>2</sub>O (excess) proceed in yields of 34 and 55% for 1 and 3, respectively, at ambient temperature for 1 day. For X = H and Ph, logarithms of the constant, log *K*, are estimated to be 13.28 and 11.88, respectively.<sup>12</sup>

**Scheme I**

to a biradical intermediate (8) followed by ring closure and then rearomatization to 2 (or 4).

Alternatively, Dewar pyridine methide (7) is in a concerted manner subject to a thermally allowed [3,3] sigmatropic migration to 9 followed by rearomatization to 2 (or 4).<sup>16</sup>

Precursor 7 to the 3-substituted 2-iminobicyclo-[2.2.0]hex-5-ene (9) may be formed directly from 6, since *N*-methyl-2-pyridone, similar to the methide 6, affords photo-*N*-methyl-2-pyridone (Dewar type) which can be isolated in 20% yield.<sup>17</sup>

Finally, quantum yields for the rearrangement of 1 to 2 vary from 0.02 in acetonitrile to 0.08 in *tert*-butyl alcohol.<sup>18</sup> The rearrangement could not be quenched by piperylene nor could it be caused to occur by a triplet sensitizer such as acetophenone or propiophenone. This suggests that the rearrangement involves a singlet excited state.

(16) The photoinduced cleavage between the C and N bond of 6 followed by the recyclization to substituted cyclohexadiene, a precursor of 2 (or 4), may be also envisaged, but the pathway seems to be less feasible on the basis of the necessity of the high energy of the bond (sp<sup>2</sup>) compared to the bond (sp<sup>3</sup>) of 7.

(17) (a) E. J. Corey and J. Streith, *J. Amer. Chem. Soc.*, **86**, 950 (1964); (b) R. C. DeSels and W. R. Schleigh, *Tetrahedron Lett.*, 3563 (1972); (c) H. Furrer, *Chem. Ber.*, **105**, 2780 (1972).

(18) The values have the same order as the quantum efficiency of photovalence isomerization of pyridine to Dewar pyridine (quantum yield 0.05).<sup>11</sup>

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## Solution Conformation of Acetylcholine and Choline

Sir:

Acetylcholine (ACh) and a large number of its biologically active analogs are known to be important in the transmission of nerve impulses.<sup>1-3</sup> Since the action of biologically active small molecules may depend on conformational changes upon attachment to macromolecular receptors, information about the rotational

(1) D. Nachmanson, *Handb. Sens. Physiol.*, **1**, 18 (1971), and references cited therein.

(2) R. B. Barlow, "Introduction to Chemical Pharmacology," 3rd ed, Methuen, London, 1964.

(3) M. Martin-Smith, G. Smail, and J. B. Stenlak, *J. Pharm. Pharmacol.*, **19**, 561 (1967).

barriers in these molecules is significant for a better understanding of their biological activity. For this reason the conformation of ACh and its analogs has been studied extensively both experimentally<sup>4-11</sup> and theoretically.<sup>12-15</sup>

On the basis of various X-ray<sup>9-11</sup> and nmr<sup>4-8</sup> studies, it has been concluded that the predominant conformation of the O-CH<sub>2</sub>-CH<sub>2</sub>-N linkage is gauche for both choline (Ch) and ACh in aqueous solution as well as in the crystalline state. Conclusions regarding the conformation in solution have principally been based on pmr data, specifically on the analysis of the AA'BB' multiplet using the well-established empirical relationships<sup>16,17</sup> between the vicinal H-H coupling constants in disubstituted ethanes and the electronegativities of the substituents.<sup>18</sup> The spectral parameters  $N$  and  $L$  (the sum and difference of the vicinal coupling constants) can be calculated for the pure trans ( $N_t$ ,  $L_t$ ) and gauche ( $N_g$ ,  $L_g$ ) conformers using the empirical relationships.

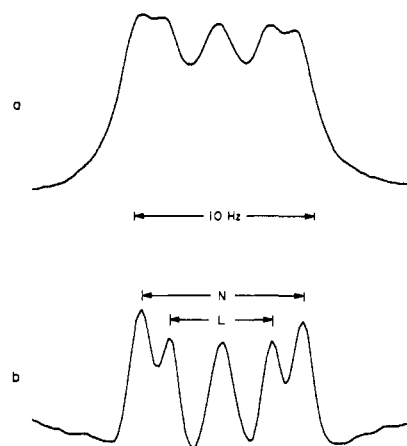
The experimental  $N$  and  $L$  values for Ch and ACh as well as the calculated parameters for the gauche and trans conformers are summarized in Table I. A comparison of these data with the calculated spectral parameters indicates that the gauche form predominates for both Ch and ACh. Thus  $L$  may be taken to be

**Table I.** Spectral Parameters<sup>a</sup> and Conformational Results for Choline and Acetylcholine Chloride

	Ch	ACh
Calculated $N_g$		9.63
Calculated $N_t$		17.78
Calculated $L_g$		4.04
Calculated $L_t$		-6.83
$N$ , room temp <sup>b,d</sup>	9.51	9.72
$L$ , room temp <sup>b,d</sup>	2.99	4.70
$N$ , -60° <sup>d</sup>	8.90	9.00
$L$ , -60° <sup>d</sup>	4.30	5.80
% gauche at room temp		
Based on $N$	94 (93) <sup>c</sup>	91
Based on $L$	88 (78) <sup>c</sup>	91
$\Delta G^\circ$ (room temp)		
kcal/mol	0.8-1.2 (0.3-1.1) <sup>c</sup>	1.0

<sup>a</sup> All spectral parameters are given in hertz. <sup>b</sup> Calculated from values given for the room temperature vicinal coupling constants in ref 6. <sup>c</sup>  $N_g$  and  $L_g$  approximated by  $N$  and  $L$  of ACh measured at -60°. <sup>d</sup> Errors in these spectral parameters are estimated to be less than 0.2 Hz.

- (4) C. C. J. Culvenor and N. S. Ham, *Chem. Commun.*, 537 (1966).  
 (5) E. Shefter, "Colinergic Ligand Interactions," D. J. Triggle, Ed., Academic Press, New York, N. Y., 1971, p 83, and references cited therein.  
 (6) R. J. Cushley and H. G. Mautner, *Tetrahedron*, **26**, 2151 (1970).  
 (7) A. Makriyannis, R. F. Sullivan, and H. G. Mautner, *Proc. Nat. Acad. Sci. U. S.*, **69**, 3416 (1972).  
 (8) J.-P. Behr and J.-M. Lehn, *Biochem. Biophys. Res. Commun.*, **49**, 1573 (1972).  
 (9) P. Pauling, Vth Jerusalem Symposium, 1973, p 505.  
 (10) J. Herdklotz and R. Sass, *Biochem. Biophys. Res. Commun.*, **40**, 523 (1970).  
 (11) F. P. Canepa, P. Pauling, and H. Sörm, *Nature (London)*, **210**, 907 (1966).  
 (12) L. B. Kier, *Mol. Pharmacol.*, **3**, 487 (1967).  
 (13) A. M. Liquori, A. Damiani, and J. L. De Coen, *J. Mol. Biol.*, **33**, 445 (1968).  
 (14) D. W. Genson and R. F. Christofferson, *J. Amer. Chem. Soc.*, **95**, 362 (1973).  
 (15) G. N. J. Port and A. Pullman, *J. Amer. Chem. Soc.*, **95**, 4059 (1973), and references cited therein.  
 (16) R. J. Abraham and K. G. R. Pachler, *Mol. Phys.*, **7**, 165 (1963).  
 (17) R. J. Abraham and G. Gatti, *J. Chem. Soc. B*, 961 (1969).  
 (18) M. L. Huggins, *J. Amer. Chem. Soc.*, **75**, 4123 (1953).



**Figure 1.** CH<sub>2</sub>-N portion of the AA'BB' methylene multiplet of ACh at 220 MHz at -60°: (a) Fourier transform spectrum, (b) Fourier transform spectrum after enhanced resolution by deconvolution.

positive definite. In principle, it is possible to translate these spectral parameters into population ratios for the gauche ( $n_g$ ) and trans ( $n_t$ ) forms, since

$$\frac{n_g}{n_t} = \frac{N_t - N}{N - N_g} = \frac{L - L_t}{L_g - L}$$

Thus the room temperature population of the trans conformer can be calculated to be ~1% for ACh using the " $N$ " equality and ~9% for Ch using the " $L$ " equality above. Unfortunately this analysis yields meaningless conclusions ( $n_g/n_t < 0!$ ) if the  $L$  values are used for ACh and the  $N$  values are used for Ch. This dilemma is clearly a consequence of incorrect spectral parameters for the pure conformers. In particular the conditions  $N_g \leq N$  and  $L_g \geq L$ , which must always be fulfilled, are not met for the  $L$  values of ACh and the  $N$  values of Ch. Thus, although these data have previously been interpreted to mean a negligible trans population for ACh,<sup>7</sup> this conclusion is somewhat doubtful in view of these difficulties with the above analysis.

This communication reports a conformational analysis of Ch and ACh which is based on experimentally determined approximations for  $N_g$  and  $L_g$ . In this connection we note that since the gauche conformer predominates for both Ch and ACh, the ratio  $n_g/n_t$  is not very sensitive to errors in  $N_t$  and  $L_t$ . However,  $n_g/n_t$  is extremely sensitive to the correct values for  $N_g$  and  $L_g$ . An approximation to these limiting spectral parameters may be obtained *via* low temperature experiments.

We have found that the cooling of aqueous solutions of both Ch and ACh (from 25 to 5°) is accompanied by changes in  $N$  and  $L$ , indicating conformational changes. Moreover, in methanol<sup>19</sup> these spectral parameters are further changed upon cooling below 5°. The observed changes are much larger than one would expect from the temperature dependence of the coupling constants of the pure rotamers.<sup>20</sup> We therefore interpret these observations as indicative of further changes in the rotamer populations. The spectra recorded at -60° (Figure 1, Table I), we feel, yield reasonable limits for

(19) At room temperature, the  $N$  and  $L$  values for ACh in methanol are similar to those obtained in aqueous solutions.

(20) J. C. Schug, P. E. McMahon, and H. S. Gutowsky, *J. Chem. Phys.*, **33**, 843 (1960).

the spectral parameters of the pure gauche conformer. Using these parameters as an approximation for those of the gauche conformers, we obtained the room temperature trans-gauche populations summarized in Table I. The agreement between the trans-gauche populations calculated using both the  $N$  and  $L$  parameters supports the supposition that the low temperature spectral parameters are good approximations to those of the pure gauche rotamer.

On the basis of the available data it is difficult to ascertain whether or not the spectral parameters of the pure gauche forms of Ch and ACh are the same. However, we can conclude that for both Ch and ACh the free energy difference between the rotamers ( $\Delta G^\circ = -RT \ln n_g/2n_t$ ) is no more than 1 kcal/mol, and for Ch it may in fact be lower. This conclusion is in accord with the theoretical predictions presented by some investigators<sup>12,13</sup> and with the recent <sup>13</sup>C studies of Behr and Lehn,<sup>8</sup> but it is in disagreement with a number of more recent MO calculations.<sup>14,15</sup> However, one should not necessarily expect the results of this study to be in full agreement with the theoretical studies, where account of environmental and other possibly important effects are not included. Also, the experimental results refer to  $\Delta G^\circ$  and the theoretical results refer to  $\Delta E^\circ$ , further complicating any comparisons.

The significant difference, at least in the case of ACh, between the experimental limiting spectral parameters and those predicted for the pure rotamers by the empirical relationships would seem to undermine their usefulness. For the present case, however, it seems reasonable to attribute the departure in terms of conformational deviations of the "gauche" conformer from pure gauche as a result of some steric interactions. If one assumes that the Karplus<sup>21</sup> equation is applicable here, and moreover that the empirical spectral parameters are in fact correct for the pure gauche form, the limiting  $N$  and  $L$  values at  $-60^\circ$  may be taken to infer gauche rotamers with dihedral angles of  $\sim 65^\circ$  and  $\sim 69^\circ$ , respectively. These deductions are in satisfactory agreement with the solid state structure.<sup>10</sup> Whether similar structural deviations occur for the "gauche" rotamer of Ch cannot be inferred at this time.

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(21) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

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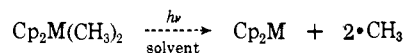
### Photochemical Reactions of Dimethyl Derivatives of Titanocene, Zirconocene, and Hafnocene

Sir:

Photochemical reactions involving metal carbonyls have been extensively investigated in recent years since the pioneering work of Strohmeier and others in this

area,<sup>1</sup> and photochemically induced substitution reactions have proved to be an elegant way to prepare new metal carbonyls containing other  $\pi$ -bonded ligands. At the present time, however, no systematic studies concerning photochemical reactions of  $\sigma$ -bonded organic derivatives of the transition metals have been described, except for certain  $\sigma$ -alkylcobalt complexes of the cobaloxime and related types.<sup>2,3</sup>

We now wish to report that dimethyl derivatives of titanocene, zirconocene, and hafnocene<sup>4</sup> readily undergo photolysis with homolytic cleavage of the methyl-metal bond. By this process, the metal is reduced to a lower oxidation state and the methyl radicals so produced



M = Ti, Zr, Hf

undergo further reactions. These photolytic reactions are solvent dependent. In pentane, for example, photolysis of group IVb metallocene dimethyl compounds results in formation of the corresponding metallocenes and the generation of methane. Infrared spectra (Nujol) of the organometallic products from each reaction are virtually identical and exhibit only absorptions which are characteristic of  $\pi$ -cyclopentadienyl-metal complexes.<sup>5,6</sup> It is important to note that titanocene prepared by our photochemical method does *not* show any absorption frequencies in the vicinity of  $1230\text{ cm}^{-1}$  which have previously been attributed to bridging metal-hydrogen-metal bonds in the "so-called" titanocene prepared by other methods.<sup>7</sup> Furthermore, the carbon-hydrogen bending vibrations at  $800$  and  $1015\text{ cm}^{-1}$  for our titanocene appear as sharp, unsplit bands and give strong evidence for only  $\pi$ -bonded cyclopentadienyl rings being present.<sup>7,8</sup> ESR studies in tetrahydrofuran solution at low temperatures combined with proton nmr studies<sup>9</sup> give evidence that these metallocenes are diamagnetic under the conditions measured. The elemental analyses of these organometallic products are in agreement with the empirical formulas  $\text{C}_{10}\text{H}_{10}\text{M}$  in each case. Preliminary mass spectral studies indicate that photochemically produced titanocene is not as volatile as is titanocene prepared by other methods.<sup>7</sup> At  $180^\circ$ , however, a spectrum can be obtained which is similar to that of the previously reported titanocene.<sup>7</sup> The most intense titanium-containing peak at  $m/e$  178 can represent either  $[\text{C}_{10}\text{H}_{10}\text{Ti}]^+$  or a doubly charged dimer ion. Additional molecular weight studies are in progress.

(1) (a) W. Strohmeier and K. Gerlach, *Z. Naturforsch. B*, **15**, 413, 622 (1960); *Chem. Ber.*, **93**, 2087 (1960); (b) G. N. Schrauzer, *J. Amer. Chem. Soc.*, **81**, 5307 (1959); (c) H. P. Kögler and E. O. Fischer, *Z. Naturforsch. B*, **15**, 676 (1960).

(2) G. Costa, G. Mestroni, and G. Pellizer, *J. Organometal. Chem.*, **15**, 187 (1968).

(3) G. N. Schrauzer, L. P. Lee, and J. W. Sibert, *J. Amer. Chem. Soc.*, **92**, 2997 (1970).

(4) E. Samuel and M. D. Rausch, *J. Amer. Chem. Soc.*, **95**, 6263 (1973).

(5) G. W. Watt and F. O. Drummond, Jr., *J. Amer. Chem. Soc.*, **92**, 826 (1970).

(6) E. R. Lippincott and R. D. Nelson, *Spectrochim. Acta*, **10**, 207 (1958).

(7) H. H. Brintzinger and J. E. Bercaw, *J. Amer. Chem. Soc.*, **92**, 6182 (1970).

(8) J. E. Bercaw, R. H. Marvich, L. G. Bell, and H. H. Brintzinger, *J. Amer. Chem. Soc.*, **94**, 1219 (1972).

(9) The proton nmr spectra of all three metallocenes in  $\text{C}_6\text{D}_6$  solution at room temperature exhibit broad absorptions due to cyclopentadienyl protons between  $\tau$  4-5 ppm. Temperature-dependent nmr studies are in progress and will be reported later.