

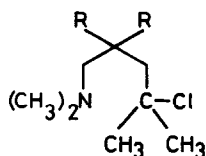
NUCLEOPHILIC DISPLACEMENT AT TERTIARY CARBON

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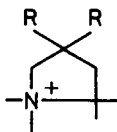
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With few exceptions <sup>1)</sup> nucleophilic substitution at tertiary carbon occurs by the limiting <sup>2)</sup> S<sub>N</sub>1 mechanism which involves a cationic intermediate. This also applies to intramolecular nucleophilic substitution as in the cyclization of simple δ-amino-tertiary chlorides. Thus, reaction of N,N-dimethyl-4-chloro-4-methyl-pentylamine (1a) <sup>3)</sup> in 80 % ethanol leads to 16 % of the pyrrolidinium salt 2a besides 47 % substitution (alcohol and ether) and 37 % elimination (Δ<sup>3-</sup> and Δ<sup>4-</sup>olefin) products, respectively. 1a reacts only 0.89 times as fast as the homomorphous tertiary alkyl chloride 3a. This shows that the nitrogen atom does not participate in the rate determining step. The cationic intermediate 4 is therefore indicated.



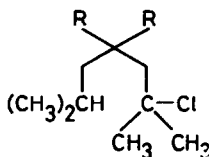
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a) R = H



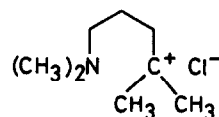
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b) R = CH<sub>3</sub>



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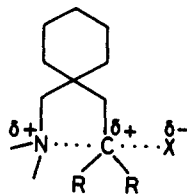
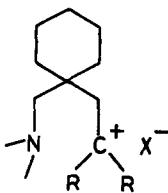
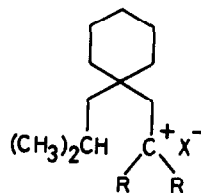
c) R = (CH<sub>2</sub>)<sub>5</sub>



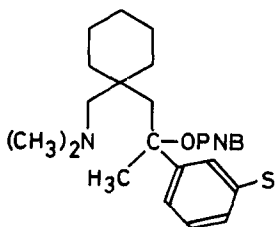
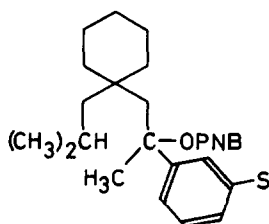
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A striking change takes place when geminal alkyl groups are introduced on C2 of 1a. Thus, the dimethyl derivative 1b reacts 7.2 times as fast as the corresponding homomorph 3b to yield 77 % of the pyrrolidinium salt 2b besides 14 % and 8 % of elimination and substitution products, respectively.

Introduction of a spiro-pentamethylene group, as in 1c, produces an acceleration with respect to the homomorph 3c by a factor of 70, the pyroli-  
dinium salt 2c being formed quantitatively.

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This marked acceleration can be explained by nucleophilic nitrogen participation in the transition state 5. Alternatively, the ion pair "S<sub>N</sub>2" mechanism recently observed by Bordwell <sup>1)</sup> for bimolecular substitution at a tertiary allylic carbon atom could account for the rate difference between 1c and 3c. In this case the ion pair 6 would be reversibly formed as an intermediate. Since the latter, due to cyclization, should be more rapidly consumed than the ion pair 7 derived from the homomorph 3c a rate difference could result. The two mechanisms differ with respect to the magnitude of the positive charge at the tertiary carbon atom in the transition state. It should be small in the transition state 5 of the displacement mechanism and large in the one leading to the ion pair 6.

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	S =	k/k <sub>h</sub>
a)	CH <sub>3</sub>	25
b)	H	39
c)	OCH <sub>3</sub>	43
d)	F	384

A decision was reached by comparing the meta substituted  $\alpha$ -aryl p-nitrobenzoates 8a - 8d with their homomorphs 9a - 9d. The rate constants k in 80

vol.% ethanol for the amines, which underwent practically quantitative cyclization, were larger than those for the homomorphs ( $k_h$ ) as shown by the above ratio of  $k/k_h$ . A plot of  $\log k_h$  for 9a - 9d against Brown's  $\sigma_m^+$  constants <sup>4)</sup> ( $r = 0.9999$ ) led to a reaction constant  $\rho$  of - 4.33 which is in good agreement with a cationic intermediate of type 7 <sup>4b)</sup>.

The  $\log k$  values for the amines 8a - 8d, however, gave a better correlation with Hammett's  $\sigma_m$  constants ( $r = 0.9987$ ) and gave  $\rho = 1.91$ . The magnitude of this value indicates that a much smaller albeit substantial positive charge is developed at the tertiary carbon atom in the transition state for the amines. Furthermore, a plot of  $\log k$  for the cyclization of the amine 8b in ethanol-water mixtures against solvent ionizing power (Y values of Grunwald and Winstein <sup>5)</sup>) led to a solvent sensitivity factor  $m$  of 0.236. This is much smaller than expected for the formation of the ion pair 6 and corresponds to a nucleophilic transition state <sup>2)</sup>.

These results are best explained by the "loose" nucleophilic ( $S_N2$ ) transition state 5 in which a substantial positive charge has developed at the tertiary carbon atom because both the entering and leaving group are less tightly bound than in the "tight" transition states characteristic of normal  $S_N2$  reactions <sup>6)</sup>. Although bond making and breaking are concerted they are not necessarily synchronous and equal. The cyclization reaction therefore appears to be an example of the much discussed intermediate or  $S_N1$ - $S_N2$  borderline mechanism of nucleophilic substitution <sup>7)</sup>. The role of geminal alkyl groups or of the spiro-pentamethylene substituent is clearly to increase the population of the quasi cyclic conformation leading to the transition state 5.

## References

- 1) F.C. Bordwell and T.G. Mecca, *J. Amer. chem. Soc.* 94, 2119 (1972).
- 2) S. Winstein, E. Grunwald and H.W. Jones, *ibid.* 73, 2700 (1951).
- 3) D. Currell, C.A. Grob and S.W. Tam, *Helv. chim. acta* 50, 349 (1967).
- 4) a) H.C. Brown and Y. Okamoto, *J. Amer. chem. Soc.* 79, 1913 (1957).  
b) *ibid.* 80, 4979 (1958).
- 5) E. Grunwald and S. Winstein, *ibid.* 70, 846 (1948); A.H. Fainberg and S. Winstein, *ibid.* 78, 2770 (1956).
- 6) for a discussion see G.J. Frisone and E.R. Thornton, *ibid.* 90, 1211 (1968).
- 7) e.g. D.J. Raber and J.M. Harris, *J. chem. Educ.* 49, 60 (1972).