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NUCLEOPHILIC DISPLACEMENT OF N-BENZYL GROUPS: EFFECT OF PYRIDINIUM ON RATES AND MECHANISM

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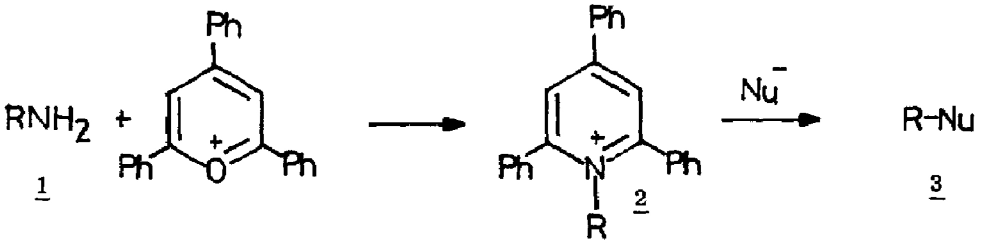
Summary Steric acceleration by α-substituents in pyridine leaving groups is quantitatively assessed. Constraint of α-phenyls to near planarity forms superior leaving groups for S_N2 displacements. α-t-Butyl groups significantly increase S_N1 dissociation.

The displacement of N-alkyl and N-benzyl substituents from 2,4,6-triphenylpyridinium cations (2) by a variety of nucleophiles converts primary amines (1) into a wide variety of functionalities (3), including halides, and O-, S-, N- and C-linked groups. These reactions are of considerable synthetic potential and have already led to several novel transformations.[1] To attain such reactions under mild conditions, we studied the effect of C-substituents in the pyridinium ring on the kinetic rates for transfer of an N-benzyl group to piperidine. Previous studies[2] indicated that N-substituents could be displaced nucleophilically from 2,4,6-triphenylpyridiniums by S_N1 or S_N2 mechanisms.



Reactions were followed spectrophotometrically in chlorobenzene solution. In all cases, the observed rate was a linear function of the piperidine concentration. The rate variations could be interpreted in terms of either pure S_N2 reaction or a combination of S_N1 and S_N2 mechanisms: values of k_1 and k_2 are given in the Table.

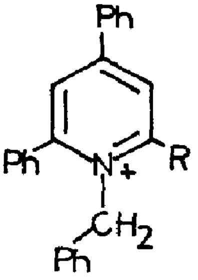
Considering N-benzyl compounds: 2,4,6-triphenylpyridine as leaving group is displaced essentially completely via the S_N2 mechanism:[2] replacement of the 2-phenyl in 4 by a 2-methyl (5) or 2-t-butyl (6) reduces the S_N2 rate constant by factors of ca. 40 and 5, respectively. However, appreciable S_N1 reactivity now appears, at least for the t-butyl derivative (6). Replacement of the 2-phenyl in 4 by a 2,3-fused cyclopentano (7) or cyclohexano ring (8) also reduces the S_N2 rate constants by factors of ca. 20 and 10, respectively; the higher rate for 8 as compared to 7 is a clear indication of greater steric repulsions in the ground state of 8.

TABLE. FIRST AND SECOND ORDER RATE CONSTANTS

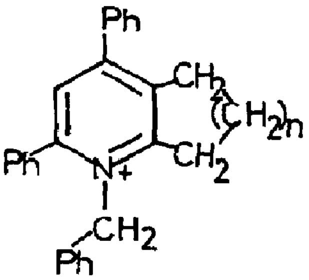
Cpd no.	C-Substituents					T (°C)	$10^5 \times k_1$ (sec^{-1})[a,b]	$10^3 \times k_2$[b] (l mol^{-1} sec^{-1})	Relative S_N2 rates
	2	3	4	5	6				
4	Ph	-	Ph	-	Ph	100	(0.2±1.4)	4.94 ± 0.13	1
5	Me	-	Ph	-	Ph	100	(0.3±0.6)	0.117± 0.020	0.024
6	t-Bu	-	Ph	-	Ph	100	8.0±2.2	1.07 ± 0.08	0.20
7	$(CH_2)_3$		Ph	-	Ph	100	(0.9±2.4)	0.22 ± 0.08	0.045
8	$(CH_2)_4$		Ph	-	Ph	100	5.1±0.3	0.43 ± 0.010	0.087
9	di-H-naphtho		Ph	-	Ph	60	(0.4±2.0)	20.6 ± 2.2	65.4[c]
10	di-H-naphtho		Ph	-	t-Bu	60	6.8±0.5	31.0 ± 3.0	395.6[c]
11	di-H-naphtho		Ph	indeno		100	31.7±8.3	223 ±45	45.1
12	di-H-naphtho		Ph	di-H-naphtho		30	(0.4±0.8)	105 ± 4	900 [c]
13	Ph	Me	Ph	-	Ph	100	(-2.5±7.5)	0.82 ± 0.23	0.16

[a] Values in brackets not significantly different from zero. [b] 90% c.l.

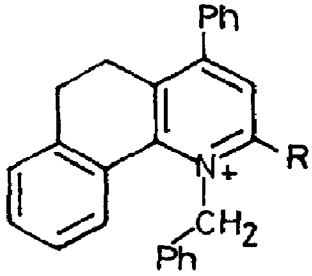
[c] Extrapolated to 100°.



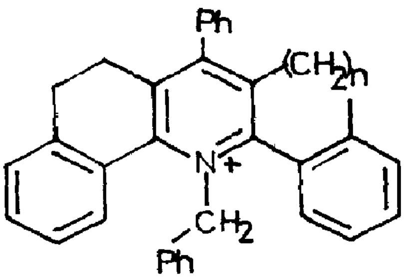
4 R = Ph
5 R = Me
6 R = t-Bu



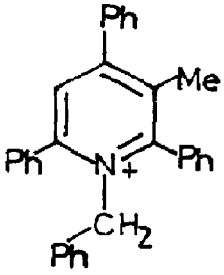
7 n = 1
8 n = 2



9 R = Ph
10 R = t-Bu



11 n = 1
12 n = 2



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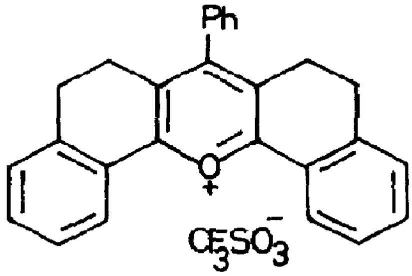

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Constraining the 2- and 6-phenyl groups in 4 to near-planarity by the introduction of one (in 9) or two (in 12) bridging CH_2CH_2 groups greatly increases the S_N2 rate constants: extrapolation of these to 100° indicates factors of *ca.* 65 and 900 respectively, at 100°. For compounds 9 and 12 the S_N1 rates remain very low. However, in the t-butyl derivative 10, although the S_N2 rate is little changed as compared to the phenyl analogue (9), the S_N1 rate becomes very significant indeed for (10).

The subtle nature of the steric interactions involved is shown by a comparison of the compound sets 4, 13, 9 and 9, 11, 12. The first of these trios clearly indicates that simple buttressing as in 13 actually *decreases* the S_N2 rate of 4 by a factor of *ca.* 6 in contrast to the strong acceleration found in 9 over 4. Consideration of the second trio demonstrates that S_N2 rates do not increase simply with increasing co-planarity of the α-phenyl groups: the S_N2 rate for 11 is less by a factor of 20 than that for 12; however the five-membered ring in 11 now induces an S_N1 rate which is much greater than those for 9 or 12.

The above results indicate that tricyclic and pentacyclic pyridiniums of type 9 and 12 should be desirable intermediates for the conversion of amino groups by S_N2 processes into other functionality. We recently utilised the superior reactivity of N-aryl tricyclic pyridiniums (*cf.* 9) in a new synthesis of aryl thiocyanates,[3] and preliminary results indicate that many reactions previously realised at 150-200 °C under pyrolysis conditions with 2, 4, 6-triphenylpyridine as leaving group, can be achieved in solution at $\leqslant$ 100 °C where systems of type 9 or 12 are utilised.[4,5] Furthermore, there is evidence that reactions which previously failed with systems of type 4 can succeed with 9 or 12. The pentacyclic pyrylium 14 is readily available from 1-tetralone and 2-benzylidene-1-tetralone in 51% yield and reacts readily with a variety of primary amines at 20° to give the corresponding pyridiniums in yields averaging 80%.[6]

This work clearly indicates the inadequacy of any single "steric parameter" for a given substituent. It points the way to the specific design of leaving groups for special purposes in organic synthesis and increases our understanding of nucleophilic displacement mechanisms.

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