A Novel S_N1 Displacement: The Reaction of Tertiary Amines with Acetic Anhydride

R. P. MARIELLA AND K. H. BROWN[1,2]

Department of Chemistry, Loyola University, Chicago, Illinois 60626

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The action of acetic anhydride on tertiary amines at reflux may cause the displacement of one of the R groups from the amine. The groups which are displaced are benzyl, *t*-butyl, benzhydryl, trityl, and cinnamyl; the groups which are not displaced are methyl, ethyl, *n*-butyl, phenyl, α-naphthyl, *iso*-propyl, allyl, and propargyl. An S_N1 mechanism with special steric requirements is consistent with the experimental results.

L'action de l'anhydride acétique sur les amines tertiaires à reflux, peut provoquer le déplacement de l'un des groupes R de l'amine. Les groupes qui sont déplacés sont benzyle, *t*-butyle, benzhydryle, trityle, et cinnamyle; les groupes qui ne sont pas déplacés sont méthyle, éthyle, *n*-butyle, phényle, α-naphtyle, *iso*-propyle, allyle, et propargyle. Un mécanisme S_N1 avec des conditions stériques spéciales est consistant avec les résultats expérimentaux.

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In the course of studying the acetylation of amines (1) we have examined the reaction of several tertiary amines with acetic anhydride. It was found that certain special tertiary amines underwent displacement of one of the groups attached to nitrogen by the acetic anhydride, while other tertiary amines were inert.

$$[1]\quad RR'R''N + (CH_3CO)_2O \xrightarrow{\text{Reflux}} RR'NCCH_3 + CH_3C{-}OR''$$

Table 1 shows the results of the reaction of the various tertiary amines with acetic anhydride at reflux (eq. 1). The results of Table 1 show that the groups displaced are benzyl, *t*-butyl, benzhydryl, trityl, and cinnamyl; and that the groups which are not displaced are methyl, ethyl, *n*-butyl, phenyl, α-naphthyl, *iso*-propyl, allyl, and propargyl. A pure S_N2 mechanism would require that methyl be most easily displaced, hence the results preclude any S_N2-like mechanism. A pure S_N1 mechanism would require that allyl and propargyl be displaced along with the others mentioned. The data, however, does not substantiate these predictions either. However, an ionization mechanism seems to be the most reasonable based on the evidence given here and on the para substitution results from the reaction of acetic anhydride with benzyldimethylamines (2).

Among the evidence which was used to choose a mechanistic pathway was the reaction of cinnamyldimethylamine. The cinnamyl group, as expected from the rule of vinylogy (3) reacts like the benzyl group, hence cinnamyldimethylamine undergoes displacement of the cinnamyl group on reaction with acetic anhydride. This reaction gave two products; 60% cinnamyl acetate, $CH_3COOCH_2CH{=}CHC_6H_5$, and 30% α-phenylallyl acetate, $CH_3COOCH(C_6H_5)$-$CH{=}CH_2$. This is a typical product spread for an allylic rearrangement in an S_N1 process (4).

The results of our experiments indicate the general mechanistic pathway shown in eq. 2 with its associated rate (eq. 3).[4]

Those amines which underwent displacement *via* C—N bond cleavage *all* have one group which can stabilize an incipient carbonium ion and *at least* one methyl group attached to nitrogen. This suggests that an ionization mechanism is taking place, but with steric requirements also present. An examination of the mechanism shown in eq. 2 and of its associated rate expression shown in eq. 3 indicates that CH_3COOR'' will not form at a reasonable rate if $K_{eq}(3)$ is very small, where $K_{eq}(3) = k_1/k_{-1}$. Also, if k_{-1}/k_2

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[3]Revision received July 16, 1971.

[4]The rate eq. 3 was obtained by the steady state treatment of the reaction mechanism shown in eq. 2.

TABLE 1. The acetylation of tertiary amines*

$$RR'R''N + (CH_3CO)_2O \rightarrow RR'NC(=O)CH_3 + CH_3C(=O){-}OR''$$

Amines which underwent the above reaction†	Amines which failed to undergo the above reaction‡
$(CH_3)_3CN(CH_3)_2$	$C_6H_5N(CH_3)_2$
$C_6H_5CH_2N(CH_3)_2$	$(C_6H_5)_2NCH_3$
$C_6H_5CH(CH_3)N(CH_3)_2$	$(C_6H_5)_3N$
$(C_6H_5CH_2)_2NCH_3$	α-$C_{10}H_7N(CH_3)_2$
$C_6H_5CH_2N(CH_3)CH_2CH_2OH$	$(CH_3CH_2CH_2CH_2)_3N$
$C_6H_5CH{=}CHCH_2N(CH_3)_2$§	$(CH_3)_2CHN(CH_3)_2$
$(C_6H_5)_2CHN(CH_3)_2$	$HC{\equiv}CCH_2N(CH_3)_2$
$(C_6H_5)_3CN(CH_3)_2$§	$CH_2{=}CHCH_2N(CH_3)_2$
	$C_6H_5CH_2N(CH_2CH_3)C_6H_5$
	$(C_6H_5CH_2)_3N$

*Except where indicated, all the amines were used as received from various chemical supply houses.
†The group displaced from each tertiary amine is indicated by being underlined.
‡In the case of unreacted amines, the starting amines were recovered quantitatively, and were not destroyed by other reactions.
§See Experimental section for preparation.

is much less than one, then the rate will be dependent only on k_1. If k_{-1}/k_2 is much greater than one, the reaction rate will be drastically diminished.

We postulate three fundamental reasons why reaction occurred or did not occur:

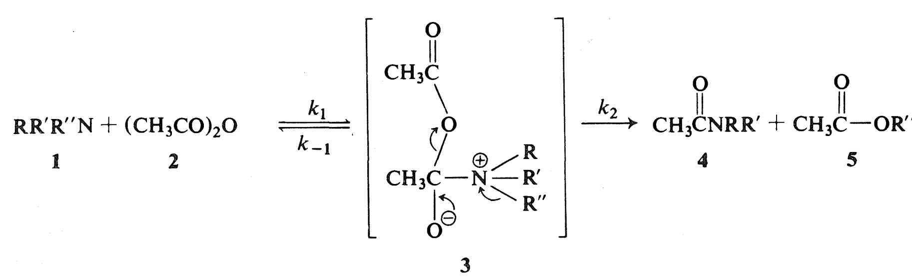
A. For amines with phenyl substituents, electronic considerations make k_1 rather small due to electron-withdrawal by the aromatic ring. Hence **3** is never reached.

B. For *very* sterically hindered amines, K_{eq}(**3**) is very small due to a decrease in k_1. Thus, the rate will decrease as a function of k_1.

C. For the R″ group to be displaced by C—N cleavage *via* ionization, R″ must be a good carbonium ion, *and* **3** must be bulky enough to require a collapse to product in order to lower its energy. Both of these considerations necessitate a large k_2, which makes the denominator of the rate equation unity. Thus, the rate is only a function of k_1, which is large enough for all the amines studied except the anilines and perhaps the very sterically crowded amines.

There are thus two structural requirements, electronic and steric; and it is the subtle interplay of these factors which determines whether or not C—N bond cleavage will occur. Intermediate **3** must be sterically crowded enough to undergo S_N1 displacement to products due to the release of energy associated with steric strain, but not so

[2]



[3]

$$\frac{d(CH_3COOR'')}{dt} = \frac{k_1[RR'R''N][(CH_3CO)_2O]}{1 + k_{-1}/k_2}$$

TABLE 2. Structural requirements of *t*-amines in acetylation reaction*

Amines which fulfill *both* the electronic requirements and the steric requirements of the reaction		Amines which do not satisfy both the electronic requirements *and* the steric requirements of the reaction	
$(CH_3)_3CN(CH_3)_2$	(*C*)	$C_6H_5N(CH_3)_2$	(*A*)
$C_6H_5CH_2N(CH_3)_2$	(*C*)	$(C_6H_5)_2NCH_3$	(*A*)
$C_6H_5CHN(CH_3)_2$ (CH$_3$)	(*C*)	$(C_6H_5)_3N$	(*A*)
		α-$C_{10}H_7N(CH_3)_2$	(*A*)
$(C_6H_5CH_2)_2NCH_3$	(*C*)	$(CH_3CH_2CH_2CH_2)_3N$	(*B*) and (*C*)
$C_6H_5CH_2NCH_2CH_2OH$ (CH$_3$)	(*C*)	$(CH_3)_2CHN(CH_3)_2$	(*C*)
		$HC{\equiv}CCH_2N(CH_3)_2$	(*C*)
$C_6H_5CH{=}CHCH_2N(CH_3)_2$	(*C*)	$CH_2{=}CHCH_2N(CH_3)_2$	(*C*)
$(C_6H_5)_2CHN(CH_3)_2$	(*C*)	$(C_6H_5CH_2)_3N$	(*B*)
$(C_6H_5)_3CN(CH_3)_2$	(*C*)	$C_6H_5CH_2NC_6H_5$ (CH$_2$CH$_3$)	(*A*)

*The *A*, *B*, or *C* after each amine refer to the reasons set forth in the discussion. These reasons can be applied to justify the above amines as concerns their reactivities.

sterically crowded so as to prevent its formation at all; for the prevention of its formation would preclude any question of how **3** would go to product. The electronic considerations are that no groups can be present on the amine which make k_1 very small; phenyl qualifies as such a group. Also, in order for the displacement from **3** to products to occur, there must be present a potentially stable carbonium ion, one which can undergo S_N1 displacement.

Table 2 shows whether each amine can fulfill *both* the electronic *and* the steric requirements of the reaction, as detailed above. Satisfying one of the requirements is not enough for a successful reaction. The amine *must* satisfy *both* requirements in order to go to products. Those amines which satisfy both requirements were, in fact, the only ones which experimentally were found to undergo C—N cleavage (see Table 1).

The lone inconsistent result is that of allyldimethylamine. The steric requirements of cinnamyldimethylamine, in the preferred *trans* isomer, are quite the same as those of the allyldimethylamine since the vinyl group removes the phenyl ring from the reaction site. Thus, the allyl group should be displaced as is the cinnamyl group. The fact that the allyldimethylamine is inert with acetic anhydride is thus explained only on the grounds that the electronic factors for the formation of a good carbonium ion are not sufficient for the allyl group.

Besides acetic anhydride, the displacement of the benzyl group from benzyldimethylamine was successfully accomplished using trifluoroacetic anhydride. This result supports the proposed mechanism since k_1 will be larger due to the electron-withdrawing effect of the three fluorine atoms, while the steric requirements are approximately the same as the parent acetic anhydride.

Experimental

All melting points were obtained on a Fisher-Johns hot plate and are uncorrected. All boiling points were obtained using standard vacuum distillation techniques and are uncorrected. All n.m.r. spectra were taken on a Varian A-60A instrument as 50% CCl_4 solutions, using 1% TMS as internal standard, except in those cases where solubility considerations required $CDCl_3$ as solvent. All i.r. spectra were taken as neat smears (for liquids) or as KBr pellets (for solids), and were performed on a Beckman IR-5A spectrophotometer. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Illinois.

Acetylation of Tertiary Amines

Since all the reactions of the tertiary amines with acetic anhydride were nearly the same, a general procedure will be used to illustrate how each amine was reacted with the acetic anhydride.

The Reaction of Acetic Anhydride with Tertiary Amine

Tertiary amine (0.1 mol) was added dropwise to a well-stirred mixture of acetic anhydride (140 ml) and anhydrous sodium acetate (1 g). The temperature of the reaction mixture remained the same during the addition. The mixture was heated at reflux for 24 h and then rotary evaporated at 80° and 30 mm for 1 h, leaving a thick sludge. Water (100 ml) was added to the sludge and the aqueous mixture was extracted with 100 ml of ether (25 ml per extraction), and the combined ether layer was dried ($MgSO_4$), filtered, and concentrated on the rotary evaporator at reduced pressure, leaving a crude

product. The product was purified by usual techniques of distillation (for liquids) and crystallization (for solids). The i.r. and n.m.r. spectra were taken of the product and compared with the spectra of the starting material. The cases of benzyl acetate and *t*-butyl acetate were verified by comparison with authentic samples of these compounds.

Preparation of Trityldimethylamine

Dimethylamine was bubbled slowly into a 500 ml flask of benzene (100 ml) at 10° with stirring until 15 g (0.33 mol) was added. Then triphenylmethyl chloride (27.9 g, 0.1 mol) in benzene (75 ml) was added dropwise over a 20 min period to the cold (+10°) solution. The mixture was then stirred at 25° for 6 days in a well-stoppered flask. Hydrochloric acid (200 ml, 3 *N*) was added and the aqueous layer was made basic with 40% KOH. A voluminous solid precipitated out of solution. The white solid was removed from the mixture by filtration and then was extracted with ether (200 ml) four times. The combined ether layer was dried (KOH pellets), filtered, and concentrated at reduced pressure, leaving a crystalline white solid (24 g, 83%), m.p. 94.5–97.0°; mixed m.p. with trityl chloride gave a m.p. range of 80–120°; n.m.r. (CCl_4), τ 2.4–3.0 (multiplet, phenyl protons, 15H): 7.96 (singlet, methyl protons, 6H).

Anal. Calcd. for $C_{21}H_{21}N$: C, 87.81; H, 7.32; N, 4.88. Found: C, 87.74; H. 7.51; N, 5.00.

Preparation of Cinnamyldimethylamine

Dimethylamine was bubbled into a flask of cold (10°) benzene (75 ml) until 8.75 g (0.20 mol) was added. Cinnamyl chloride (8.60 g, 0.05 mol) was added dropwise over 20 min and the mixture was stirred at 25° for 4 days in a well-stoppered flask. Hydrochloric acid (200 ml, 3 *N*) was added and the aqueous layer was made basic with 40% KOH. A white solid precipitated from solution. The mixture was extracted with ether (200 ml, 50 ml per extraction), and the combined ether layer was dried (K_2CO_3), filtered, and concentrated at reduced pressure, leaving a viscous yellow liquid (8.0 g, 83%), b.p. 61–63°/0.25 mm (2); n.m.r. (CCl_4), τ 2.7 (singlet, phenyl protons, 5H); 3.5 (multiplet, vinyl protons, 2H); 7.03 (doublet, methylene protons, 2H); 7.80 (singlet, methyl protons, 6H); i.r. (neat), ν (cm^{-1}) 1370 (methyl stretch).

The Acetylation of Cinnamyldimethylamine to Cinnamyl Acetate and α-Phenylallyl Acetate (2)

Cinnamyldimethylamine (4.03 g, 0.025 mol), acetic anhydride (75 ml), and sodium acetate (0.5 g) were stirred together at reflux for 48 h. The mixture was then rotary evaporated at 80° and 5 mm for 3 h to remove the acetic anhydride. The residue was then treated with water (100 ml) and then extracted with ether (250 ml, 50 ml per extraction). The combined ether layer was dried ($MgSO_4$), filtered, and concentrated at reduced pressure, leaving 4.1 g of red liquid. The red liquid was distilled under vacuum through a 4-in. Vigreux column. Two products were distilled; first was 1.0 g of a clear white liquid, α-phenylallyl acetate (b.p. 61–65°/0.025 mm); n.m.r. (CCl_4), τ 2.71 (singlet, phenyl protons, 4.9H); 3.70 (doublet, vinyl proton alpha to phenyl, 1H); 4.00 (multiplet, vinyl proton, 1H); 4.90 (multiplet, terminal methylene, 2H); 8.06 (singlet, methyl protons, 3H); second product was a 2.0 g fraction of clear white liquid, cinnamyl acetate (b.p. 81–84°/0.025 mm); n.m.r. (CCl_4), τ 2.70 (singlet, phenyl protons, 5H); 3.40 (doublet, vinyl proton alpha to phenyl, 1H); 3.5–4.0 (multiplet, vinyl proton beta to phenyl, 1H); 5.33 (doublet, methylene protons, 2H); 8.02 (singlet, methyl protons, 3H).

The cinnamyl acetate (0.58 g) was then placed in a mixture of acetic anhydride (13 ml), acetic acid (0.5 g), and sodium acetate (0.05 g). The mixture was heated at reflux for 24 h, then worked-up as above leaving a single pure compound which had an i.r. and n.m.r. identical with cinnamyl acetate.

Product Data

The yields of the successful reactions were as follows: dimethyl-*t*-butylamine gave 50% *t*-butyl acetate; dimethylbenzylamine gave 40% benzyl acetate; *N,N*-α-trimethylbenzylamine gave 55% α-methylphenethyl acetate; dibenzylmethylamine gave 10% benzyl acetate; *N*-benzyl-*N*-methylethanolamine gave 30% benzyl acetate; dimethylcinnamylamine gave 70% of a 2:1 mixture of cinnamyl acetate and α-phenylallyl acetate; benzhydryldimethylamine gave 25% benzhydryl acetate; trityldimethylamine gave a small yield (< 10%) of trityl acetate.

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