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Anhydrous formic acid and acetic anhydride as solvent or additive in non-aqueous titrations

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The use and importance of formic acid and acetic anhydride (Ac_2O) is increasing in nonaqueous acid-base titrations, but their interaction with the solutes is poorly understood. This paper attempts to clarify the effect of the solvents; NMR and spectrophotometric investigations were done to reveal the interactions between some bases and the mentioned solvents. Anhydrous formic acid is a typical protogenic solvent but both the relative permittivity and acidity are higher than those of acetic acid (mostly used in assays of bases). These differences originate from the different chemical structures: liquid acetic acid contains basically cyclic dimers while formic acid forms linear associates. Ac_2O is obviously not an acidic but an aprotic (very slightly protophilic) solvent, which supposedly dissociates slightly into acetyl (CH_3CO^+) and acetate (AcO^-) ions. In fact, some bases react with Ac_2O forming an associate: the Ac^+ group is bound to the δ^- charged atom of the reactant while AcO^- is associated with the δ^+ group at appropriate distance.

1. Introduction

The background of the nonaqueous titrations has been previously reviewed (Buvári-Barcza and Barcza 2005). As mentioned, the use of some solvents and additives has increased because the general trend is to avoid the use of toxic reagents (and solvents). For example, in the quantitative analysis of halide salts of organic bases, glacial acetic acid/acetic anhydride or formic acid/acetic anhydride mixtures are used instead of the mercuric acetate method (Miller 1996). The Japanese Pharmacopoeia XIV uses this method e.g. in the assay of papaverine hydrochloride while the United States Pharmacopoea 26 still describes the mercuric acetate method.

In the present paper, the rather special properties of formic acid [HC(O)OH] and acetic anhydride [$CH_3C(O)OC(O)CH_3$]: Ac_2O] are discussed based on the data of spectrophotometric and NMR measurements. To reveal the interactions with the solutes, two model bases: 4-dimethylamino azobenzene and 4-dimethylamino pyridine were used.

2. Investigations and results

4-Dimethylamino-azobenzene (DMAAB, methyl yellow) is a well-known acid-base indicator; the tertiary amino group is not acetylated by Ac_2O. The molecule is a weak base ($pK_A = 3.226$) (Kilpatrick and Arenberg 1953), and protonation is coupled with significant spectral changes. Thus, we used this indicator for the comparison of the relative acidity of different systems. With our earlier experiences (Buvári et al. 1980), the experiments were planned and performed so that the probable disturbing effects of cis-trans isomerisation (more exactly the formation of cis isomer) of DMAAB could be eliminated.

The spectra of DMAAB solutions (made of uniformly 5×10^{-5} M concentrations with different solvents) are reported in Figs. 1–3. It is clear that acetic anhydride reacts with DMAAB as an aprotic solvent, whose properties can only be compared with those of acetone. The definite acidity of formic acid is also clear, while acetic acid takes on a medium position. The results with solvent mixtures are interesting and will be discussed in more detail later.

The main reason for the selection of 4-dimethylamino-pyridine (DMAP) was its well known interaction with Ac_2O, rather than the fact that it is a much stronger base ($pK_A = 9{,}70$) (Essery and Schofield 1961) than DMAAB.

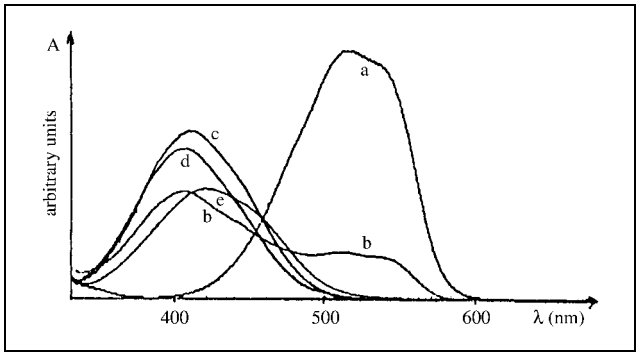


Fig. 1: UV-vis spectra of $5 \cdot 10^{-5}$ M DMAAB in formic acid (a), in glacial acetic acid (b), in Ac_2O (c), in acetone (d) and in dimethyl sulfoxide (e)

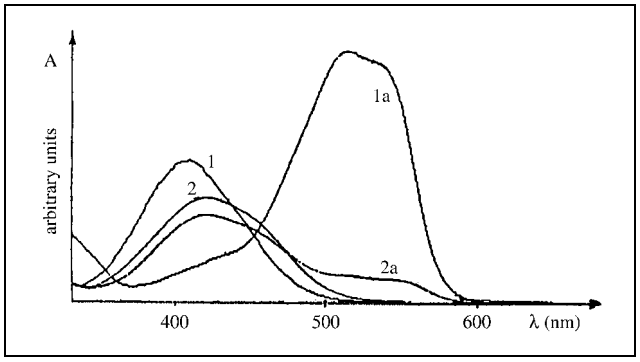


Fig. 2: The effect of the solvent basicity on the spectra of DMAAB ($5 \cdot 10^{-5}$ M): in acetone (1), in acetone containing 10^{-1} M H_2SO_4 (1a), in dimethyl sulfoxide (2), in dimethyl sulfoxide containing 10^{-1} M H_2SO_4 (2a)

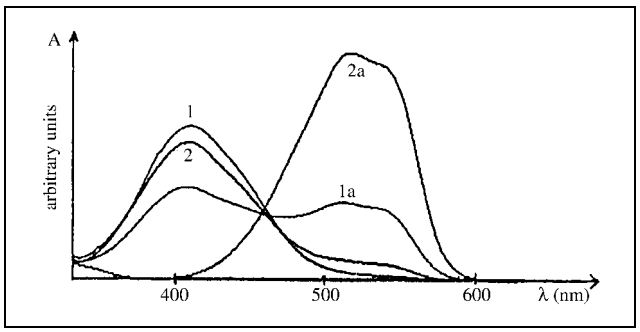


Fig. 3: UV-vis spectra of $5 \cdot 10^{-5}$ M DMAAB in acetic anhydride and glacial acetic acid (1–1a) as well as in acetic anhydride and anhydrous formic acid (2–2a). In Ac_2O : AcOH mixtures of 9 : 1 (1), and 1 : 1 (1a) molar ratios; in Ac_2O : HCOOH mixtures of 9 : 1 (2), and 1 : 1 (2a) molar ratios

The special interaction becomes apparent with the high catalytic activity of DMAP in acetylation reactions, and the presence of *N*-acetyl-4-dimethylamino-pyridinium (acetate) can also be detected in the systems (Höfle et al. 1978).

The UV-spectra of 10^{-4} M DMAP solutions in different solvents are shown in Figs. 4–6. These spectra show that the product, formed during the dissolution of DMAP in acetic anhydride, is not identical with the protonated DMAP.

Similar conclusions can be drawn from the results of ^{1}H NMR investigations, which are presented in Figs. 7–10. The peaks of the methyl protons of the solvent molecule can be observed in Ac_2O at $\delta = 0.26$ ppm, in AcOH at -0.02 ppm in the ^{1}H spectra (Fig. 7); while in the mixture, two separated, sharp peaks appear slightly shifted: at

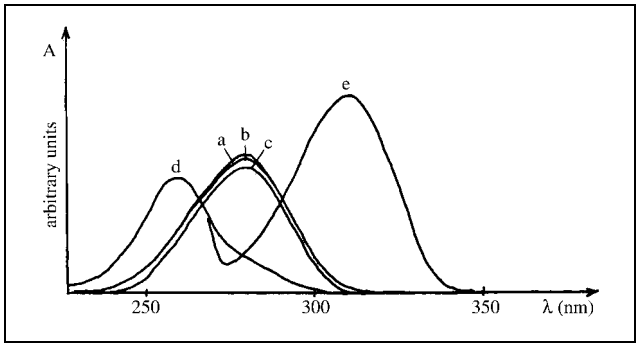


Fig. 4: UV spectra of 10^{-4} M DMAP: in glacial acetic acid (a), in water (b), in 0,1 M aqueous HCl (c), in 0,1 M aqueous NaOH (d) and in acetic anhydride (e)

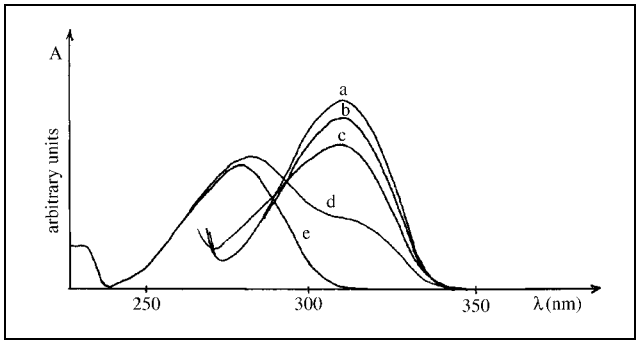


Fig. 5: UV spectra of 10^{-4} M DMAP in acetic anhydride and/or glacial acetic acid: in acetic anhydride (a); in Ac_2O : AcOH mixtures of 9 : 1 (b), 1 : 1 (c) and 1 : 9 (d) molar ratios; and in AcOH (e)

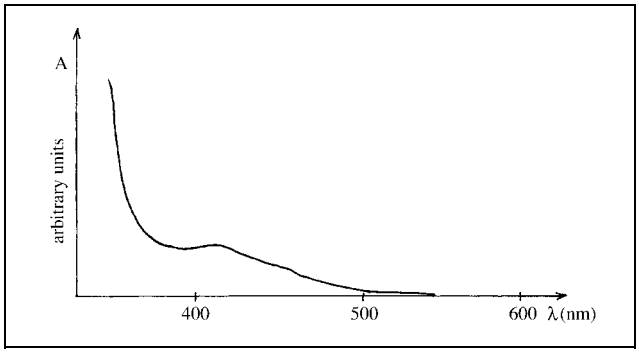


Fig. 6: Spectrum of 10^{-1} M DMAP in Ac_2O over $\lambda = 350$ nm

$\delta = 0.14$ and 0.00 ppm. These peaks are shifted by -0.15 and -0.21 ppm in solutions containing DMAP (Fig. 8), respectively. Two new peaks (-0.42 and $+0.47$ ppm) appear in solutions of Ac_2O, corresponding to the CH_3 groups of the (bound) acetate and acetyl ions, respectively. It is noteworthy in the latter case that the spectrum recorded in the solvent mixture is not a simple superposition of those obtained in the pure solvents; namely less peaks are observed: the coalescence of the signs of dimeric acetic acid and acetate ion is the most probable because of their dynamic interaction:

$$(AcOH)_2 + AcO^- \Leftrightarrow (AcOH \cdots {}^-OAc) + AcOH \quad (1)$$

The peaks of pyridine skeleton and $N(CH_3)$ group found in the ^{1}H NMR spectra (Fig. 8) show similar shifts and multiplicities.

The characteristic ^{13}C peaks of dimethylamino groups of the dissolved DMAP (Figs. 7 and 9) are found at around 43 ppm, while the further ^{13}C peaks of DMAP are assigned as follow: C-4 at 160–161; C-3 at 139–142 and C-3 at ~110 ppm. The peak at 170.5 ppm must be attached to the CO group of the acetylated species.

The spectrum is significantly simplified in presence of sulfuric acid (Fig. 10) because of the more rapid exchanges, causing the peaks to become broadened considerably. The peak at 179 ppm is assigned to acetyl sulfuric acid [$CH_3C(O)OS(O)_2OH$: Russel and Cameron (1938)].

The assignments of the peaks in ^{1}H coupled ^{13}C spectra are as follows: the focus of the quartet of the solvent methyl groups is in Ac_2O 21.51 ppm and in AcOH 19.73 ppm; the signs of the carbonyls can be observed at 167.20 and 177.75 ppm, respectively. The spectrum of the solvent mixture contains essentially the sum of these peaks, which are shifted to some degree (like the ^{1}H spectra). The doublings of the solvent peaks in the spectrum of the DMAP solutions

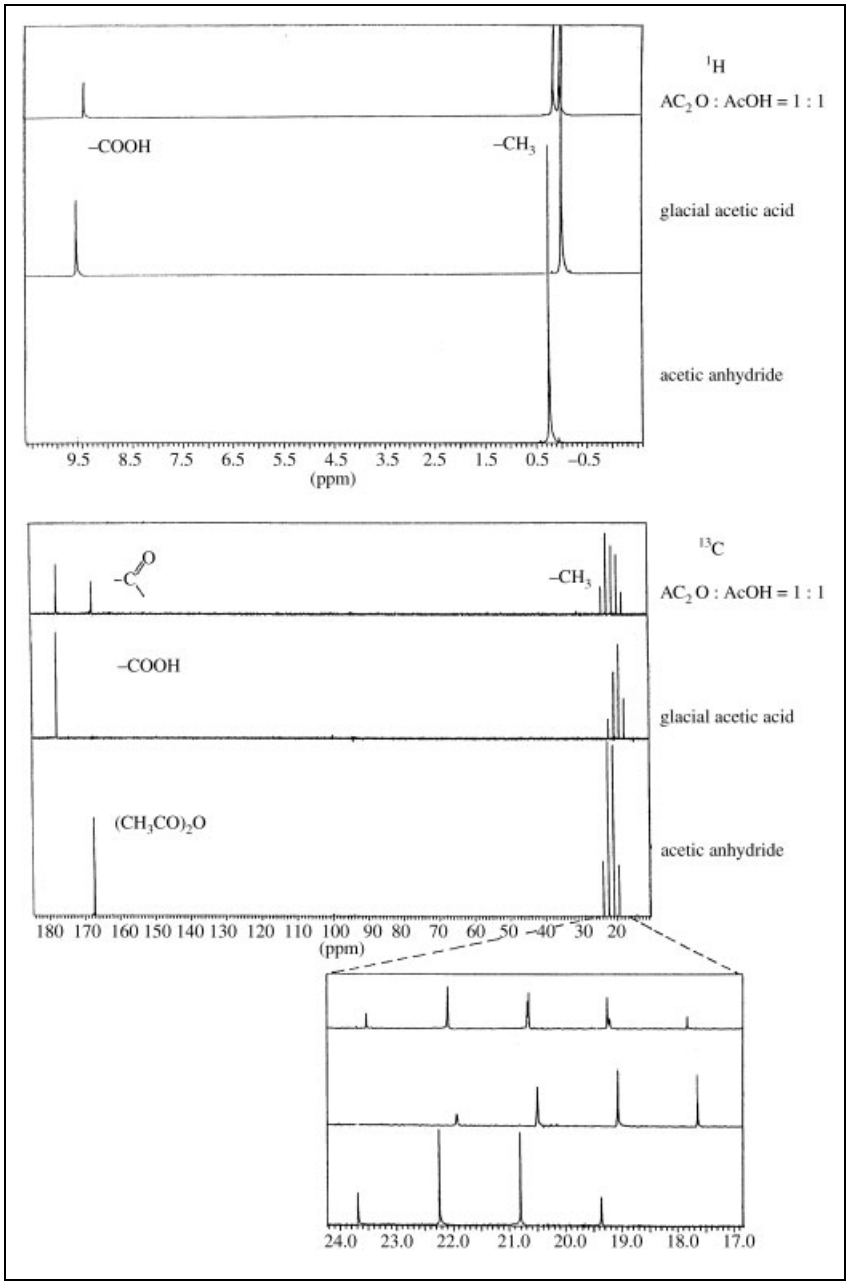


Fig. 7:
^{1}H and ^{13}C NMR spectra of glacial acetic acid and acetic anhydride as well as their 1 : 1 mixture

in Ac_2O is very remarkable, but again only two peak groups can be observed in $Ac_2O-AcOH$ mixture (like in the ^{1}H spectra).

3. Discussion

The results measured with formic acid fit extremely well in the expectations outlined earlier (Buvári-Barcza and Barcza 2005); its behaviour is defined by the stabilization of non-cyclic, linear associates in the liquid state. It seems that the implications of the dissociation constant of dimeric formic acid, measured in aqueous solution (Barcza and Mihályi 1977), can be extrapolated for anhydrous formic acid, too. Its highest acidity in the series of Ac_2O – glacial acetic acid – HCOOH is exactly proved by the behaviour of DMAAB (Fig. 1).

It is a well known fact that concentrated formic acid must (and can) be stabilized with ~5% H_2O and this high water content (acting as a base) can interfere with the titrations in glacial acetic acid – HCOOH mixtures.

Formic acid is generally used in mixtures with acetic anhydride in order to eliminate the disturbing effect of water. But the interaction of the components can slowly lead to the formation of a mixed anhydride: HC(O)OAc, which is not a stable compound but decomposed slowly under the formation of CO and AcOH (Zielinski et al. 1998). The decomposition is accelerated and bubbling can be observed in the experiments when a catalyst (like an acid or DMAP) is present. The consequence of the considerable and rapid decomposition is that perchloric acid standard solution in formic acid can not be prepared.

Acetyl perchlorate can be formed in the reaction of perchloric acid and Ac_2O or of silver perchlorate and acetyl bromide (Jander and Surawski 1961). In acid-base interactions acetyl perchlorate reacts in Ac_2O like a strong acid, but its solution is unstable, indicated by the continuous discolouration. This colour suggests that the tetrahedral symmetry of perchlorate in $AcClO_4$ is distorted and chlorine oxides are formed (Greenwood and Earnshaw 1990). Because of the decomposition, perchloric acid solutions

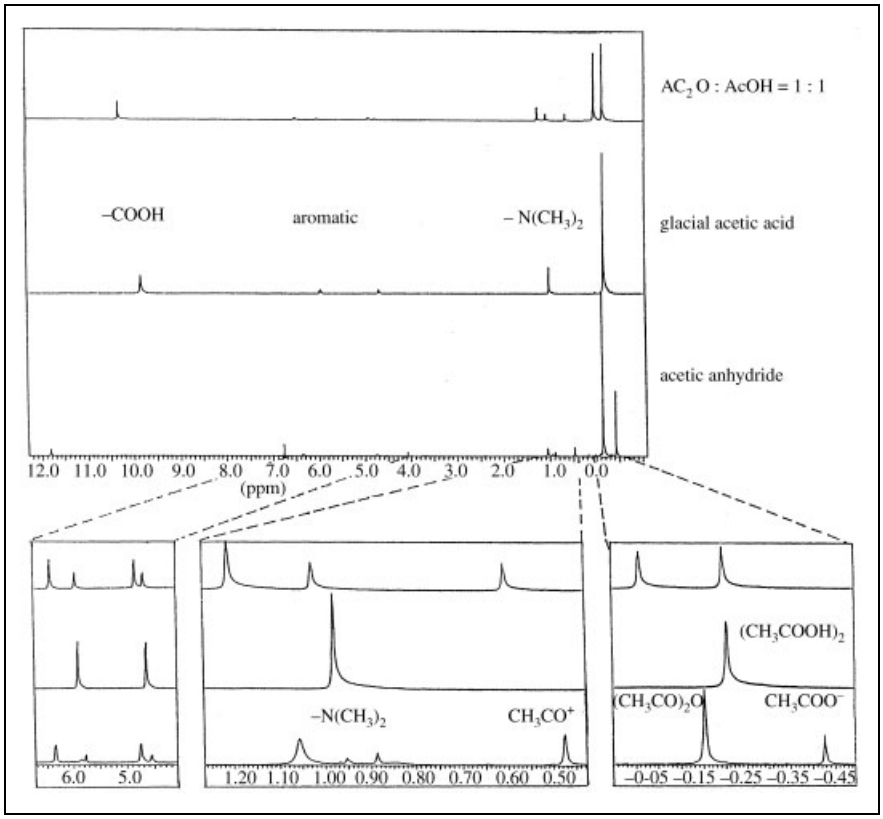


Fig. 8:
^{1}H NMR spectra of DMAP solutions

must be prepared with glacial acetic acid for the acid-base titrations in Ac_2O, too (Russel and Cameron 1938).

It can be concluded that acetyl cation can exist only when it is stabilized by some further interaction. The DMAAB is unable to interact with Ac_2O this way, as shown by the colour of its basic (unprotonated) form (Figs. 1–2).

The spectra of protonated and unprotonated DMAP can be well distinguished as shown in Fig. 4 (a–d), and the maximum is shifted to longer wavelengths due to protonation ($\lambda_{max} = 260$ nm $\rightarrow$ $\lambda_{max} = 280$ nm). Comparing the spectrum 4 (e) with the spectra 4 (a–d), however, it must be realized that in Ac_2O the base takes part in another interaction, resulting in a red shift highly exceeding the effect of the protonation ($\lambda_{max} = 311$ nm).

The more concentrated solutions of DMAP in Ac_2O are of remarkably bright colour. The characteristic absorption at $\lambda = 413$ nm (Fig. 6) can be assigned to the quinoidal character of the associate, though with a relatively low molar absorptivity ($\log \varepsilon = 2.942$, compared to $\log \varepsilon = 4.477$ at 311 nm.)

The totally different behaviours of DMAP and DMAAB support the assumption that the equilibrium concentration of (free) acetyl cations is practically zero in acetic anhydride and consequently there is no reaction with DMAAB.

The next question is whether the product, *N*-acetyl-4-dimethylamino-pyridinium-acetate does dissociate in Ac_2O of relatively low dielectric constant at all. In contrast to the experiences with DMAAB, the results suggest that (like the solutions in glacial acetic acid where practically only H-bridged ion pairs are formed in acid-base reactions) the interaction of DMAP and Ac_2O results in an undissociated complex. In this species, the δ^+ charged C atom of one of the Ac_2O carbonyl groups is presumed to connect to the N of the pyridine skeleton, causing a quinoidal rearrangement, shifting the δ^+ charge to the dimethylamino nitrogen, which is able then to interact with the second AcO group (preformed acetate) of the Ac_2O. Acetyl cation can be stabilized in this supramolecule in equilibrium, and DMAP can catalyse the acetylation reactions of acetic anhydride.

The results of ^{1}H and ^{13}C NMR studies of DMAP solutions in Ac_2O support these findings, first of all in comparison with the spectra measured in glacial acetic acid (Figs. 7–10). The shifts of dimethylamino ^{1}H peaks depend on whether DMAP is in protonated form or in Ac_2O complex (Fig. 8). The difference between the two forms can be observed in the ^{13}C spectrum as well, but the variations of solvent carbonyl and methyl signals seem more informative (Fig. 9).

Conclusion 1: Anhydrous formic acid is a typical protogenic solvent of much higher acidity than glacial acetic acid. This difference is the result of the different structures in the liquid phase: acetic acid forms mainly cyclic dimers while formic acid contains linear associates.

Conclusion 2: Ac_2O is not an acidic solvent, its effect in analytical chemistry is based on unique reactions and interactions.

In spite of the slow reaction between acetic anhydride and HCOOH in the mixture:

$$HC(O)OH + Ac_2O \rightarrow HC(O)OAc + AcOH \qquad (2)$$

and the slow decomposition of the mixed anhydride:

$$HC(O)OAc \rightarrow CO + AcOH \qquad (3)$$

formic acid and Ac_2O can exist in the presence of each other for a while and H-bonds are certainly formed among them. The associate is supposedly similar to that depicted earlier (Buvári-Barcza and Barcza 2005: with HOOCH instead of the H^+).

The effect of H-bonded interaction between Ac_2O and HCOOH is supported by experimental facts; i.e., the protonation of DMAAB is practically identical in pure formic

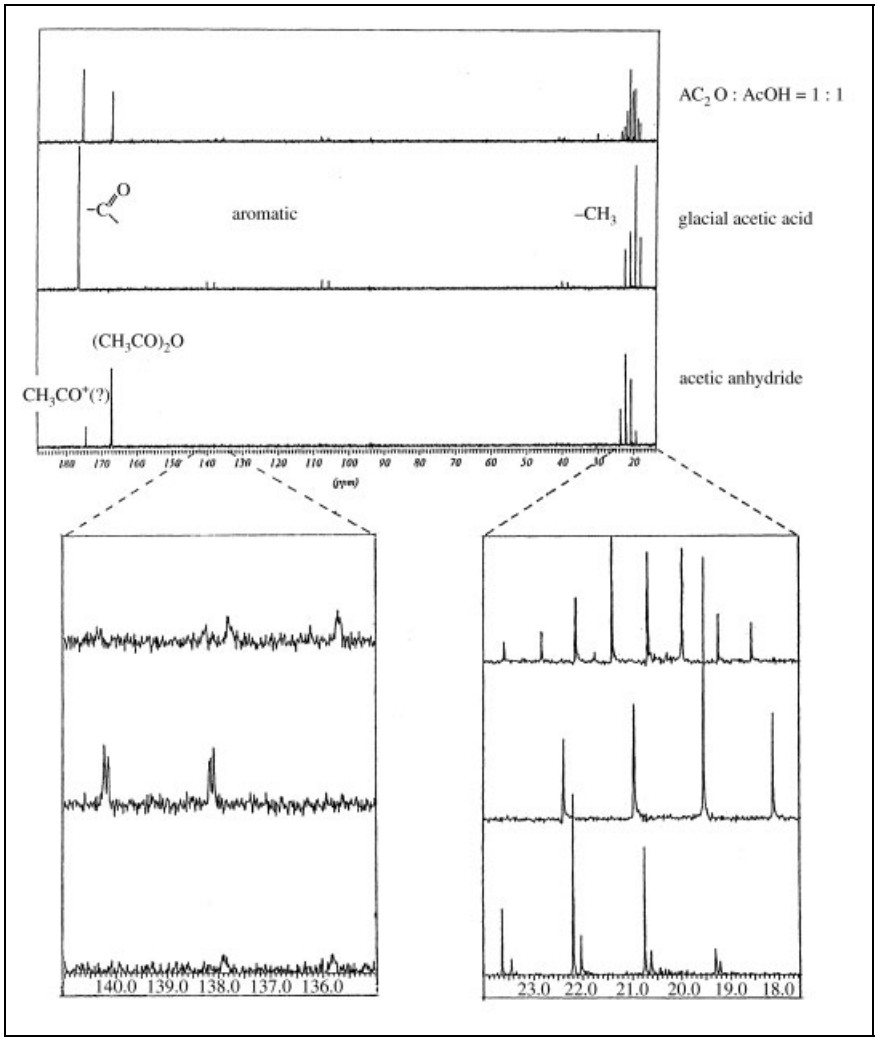


Fig. 9:
^{13}C NMR spectra of DMAP solutions

acid (Fig. 1, a) and in 1 : 1 HCOOH−Ac_2O mixture (Fig. 3, 2a), while DMAAB is hardly protonated in the 1 : 9 mixture (Fig. 3, 2). It is obvious that the formic acid reacts in the latter case firstly with Ac_2O, which is present in large excess (that is the interaction with acetic anhydride hinders the oligomerization of formic acid and the acidities of monomeric formic or acetic acid are closer to each other than those of the dimeric forms (Barcza and Mihályi 1977).

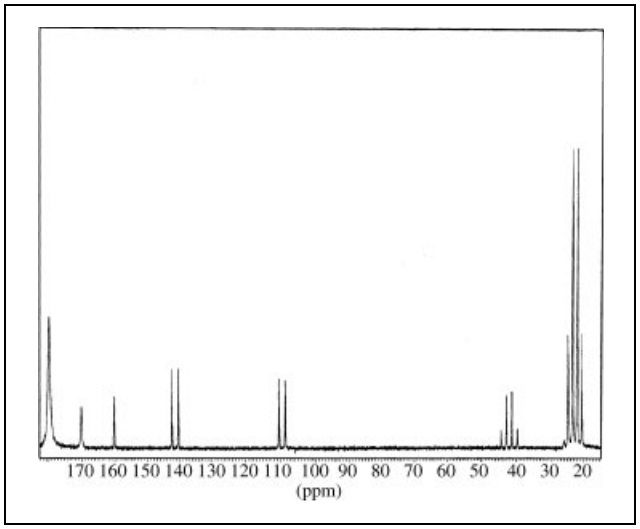


Fig. 10: ^{13}C NMR spectrum of DMAP in 1 : 1 Ac_2O : AcOH mixture containing 20% H_2SO_4

Although the central role of formyl cation (HCO^+) can be assumed in the kinetics of the decomposition (Zielinski et al. 1998), nothing is known about its special properties in acid-base reactions, in contrast to an Ac^+ cation.

The stabilization of the potential anion (the formate or acetate, respectively) by H-bonds seems more important, e.g.:

$$HC(O)O^- + HO(O)CH \Leftrightarrow HC(O)O^- \cdots HOC(O)H \quad (4)$$

In aqueous solution, the equilibrium constant for this reaction is $4.17 \times 10^{-1}\,M^{-1}$ (at 25 °C and in 1,000 M $NaClO_4$) (Barcza and Mihályi 1977). Though this value is rather low, extrapolating it for anhydrous formic acid, where HCOOH is in high excess, the probability of the association is considerable. In analytical chemistry this means that the accuracy of the titrations is increasing, i.e. weaker bases can be determined.

[It should be mentioned that the formation constant of acetic acid-acetate associate (corresponding to Eq. 4) is 6.17×10^{-1}, while that of propionic acid-propionate interaction is 1.05×10^{0} (Barcza and Mihályi 1977). Since the formation constant of hydrogen-bis(propionate) is the highest in aqueous media, extrapolating this fact for anhydrous propionic acid, some advantage of its use in non-aqueous titrations can be explained.]

The possibility of the titrations of halides and HX salts of organic bases both in Ac_2O-formic acid and Ac_2O-glacial

acetic acid mixtures depends undoubtedly on the formation of undissociated acetyl halides. However, not all HX salts can be analysed in this way (Kilpatrick and Arenberg 1953; Miller 1996).

The following idea is proposed: the reaction

$$X^- + Ac_2O = AcX + AcO^- \quad (5)$$

does not proceed directly as indicated, but the first step is:

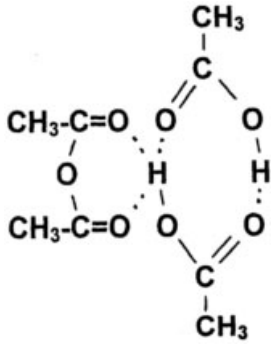
$$\equiv N{-}H^+ \cdots X^- + AcOH_2^+ \cdots Ac^- \Leftrightarrow \equiv N{-}H^+ \ldots Ac^- + AcOH_2^+ \cdots X^- \quad (6)$$

then (as discussed):

$$AcOH_2^+ \cdots X^- + Ac_2O \Leftrightarrow AcX + 2\ AcOH \quad (7)$$

This idea implies that the acidity of the solvent mixture exceeds that of the hydrogen halides; HX ($AcOH_2^+ \cdots X^-$) is formed in the first step next to the protonated base acetate, and the transformation of HX to AcX is required only for the completeness of the titration. (More probable is that these two parallel equilibria are mutually reinforced.)

The acidity of the solvent mixture is increased due to the shift of equilibria by the formation of hydrogen-bis(acetate) ($AcOH \cdots {}^-OAc$) in acetic anhydride-glacial acetic acid mixtures as well, but the H-bonded interaction between acetic anhydride and acetic acid is of similar importance. Although monomeric acetic acid can also be present in glacial acetic acid and the formation of a H-bonded associate ($Ac_2O \cdots HOAc$) can be assumed in the mixture, the stable dimeric structure of liquid acetic acid have to be considered as well. The acetic anhydride and dimeric acetic acid can interact by trifurcated H-bond, producing a supramolecule (**1**) of superacid character. It follows that the remained monofurcated H-bond is weakened due to



the high electron withdrawing effect in the region of the trifurcated H-bond, and the loosened proton is ready for further interactions, e.g. with the proton acceptor base to be titrated.

While DMAAB reacts in an identical manner in both 1 : 9 $AcOH : Ac_2O$ mixture and pure Ac_2O [in good agreement with the statement of the literature (Wimer 1958), that Ac_2O mixtures with less than 20% AcOH content can be regarded as acetic anhydride], it experiences much higher acidity in the 1 : 1 mixture than in glacial acetic acid (Fig. 3, 1a and Fig. 1, b), giving experimental proof for the existence of the associate of peculiar acidity between acetic anhydride and dimeric acetic acid.

Conclusion 3: In spite of the fact that the NMR spectra do not show any significant interaction between Ac_2O and AcOH, the behaviour of DMAAB proves that the $Ac_2O-AcOH$ mixture is more acidic than pure glacial acetic acid (Fig. 3). The reason can be the formation of a superacid containing one Ac_2O and a dimeric acetic acid species held together by trifurcated H-bonding.

4. Experimental

Glacial acetic acid ($\geq$99.7%, acetic anhydride content $\leq$ 0.01%, $\varrho = 1.05$) and acetone ($\geq$99.5%, water content $\leq$ 0.5%, $\varrho = 0.79$) were from Sigma-Aldrich products, while formic acid ($\sim$96%, acetic acid content $\leq$ 0.4%, $\varrho = 1.22$), acetic anhydride ($\sim$99%, $\varrho = 1.08$) and dimethyl sulfoxide ($\geq$99.9%, water content $\leq$ 0.1%, $\varrho = 1.10$) were purchased from Reanal Ltd. Solvents were used without further purifications (to avoid any possible secondary contamination). 4-Dimethylamino azobenzene was also a product of Reanal Ltd., while 4-dimethylamino pyridine was purchased from Sigma-Aldrich Ltd. These and other reagents were of analytical purity.

Absorption spectra were recorded on a Perkin-Elmer Lambda 15 spectrophotometer at 25 $\pm$ 1 °C, using 1.00, 5.00 and 10.00 mm quartz cells.

^1H NMR spectra were recorded at 360 MHz, ^{13}C NMR spectra at 80 MHz with a Bruker AMX360 spectrometer using a 5 mm QNP probehead in the unlocked mode. Characteristic parameters (flip angle, pulse repetition time, spectral window, number of scans) were chosen so as to obtain high quality spectra and quantitative integration wherever possible. The chemical shifts are reported in ppm for ^1H and ^{13}C spectra toward higher frequencies with respect to TMS as an external standard (0.00 ppm in both cases).

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