J. Pharm. Pharmacol. 1998, 50 (Supplement): 123

Analysis of amines of pharmaceutical interest using tetrabromophenolphthalein ethyl ester dye and benzethonium chloride

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. Primary, secondary and tertiary alkylamines R_3-N (R_3 are three radicals on depending of 1^y, 2^y and 3^y amine) have been determined using its addition reaction with tetrabromophenolphthalein ethyl ester dye (HTBPE) which generates a colored hydrogen bonded complex (HBC) in a nonpolar solvent (Sakai, 1997). The reaction could be written as:

HTBPE + R_3-N $\leftrightarrow$ R_3-N··H··TBPE -1-

Yellow colorless violet

where R_3-N··H··TBPE is the HBC. Although this reaction is unspecific the selective determination of 3^y (or 2^y) alkylamines in the presence of 1^y amines can also be carried out due to both, the lower complex formation constants, K_1, for 1^y amines and the stronger decrease of K_1 for 1^y amines with an increase in temperature. However, at high temperature ($\approx$60°C as described in literature) the K_1 values for tertiary and secondary amines are too low for providing a good analytical reaction, since reaction 1, even for 3^y and 2^y amines, is not a very strong reaction, being moreover strongly exothermic. Therefore, in this communication we propose the addition of benzethonium chloride, BZCl, to the mixture dye-amine whose reaction could be expressed as:

R_3-N··H··TBPE + BZCl $\leftrightarrow$ $TBPE^-BZ^+$ + Cl^-R–NH^+ -2-

Violet colorless blue colorless

Being $TBPE^-BZ^+$ the dye-benzethonium ion pair and K_2 the formation constant for this new reaction. Although the reaction of BZCl has been previously described using other dyes (Gainza,1997) its analytical interest is now described for the first time using a dye of very different structure, HTBPE. Apparently, this reaction breaks the hydrogen bridge generating an ion associate as evidenced for the hyperchromic and bathochromic shift in the visible absorption spectra.

In the table appear the calculated values of K_1 and $K=K_1K_2$. at 20°C using an iterative calculus program from visible spectrophotometric measurements of solutions containing HTBPE-amine binary and HTBPE-amine-benzethonium ternary mixtures. The proposed analysis method conditions (Benzethonium Method) are: [HTBPE]= [BZCl] = $2.5\cdot10^{-4}$M=constant and [amine] from 0.2 to $2\cdot10^{-5}$M;a blank without amine was also prepared. In this conditions the apparent molar absorptivities, ϵ ($L\cdot mol^{-1}cm^{-1}$), at 606 nm in chloroform at 20 and 60°C also appear in the table. The ϵ values indicate that, 2^y (di*n*butylamine) and 3^y amines of pharmaceutical interest (atropine, quinine, etc) or, tertiary alkylamines (tri*n*butylamine, etc) are determined with good sensibility and accurate at 20 and 60°C. Primary amines can also determined at 20°C but not at 60°C.

Amine	K_1(20°C)	K(20°C)	ϵ(20°C)	ϵ(60°C)
Atropine	27916	27820	68798	53822
Quinine	56707	76009	73795	58581
Tri*n*butylamine	81144	29998	71299	57289
Di*n*butylamine	12692	44258	51980	37589
*n*butylamine	1320	--	10857	6258

Therefore at 60°C, 2^y and 3^y amines can be determined with negligible interference from 1^y amines if its concentration is less than $5\cdot10^{-6}$M. The standard deviation was 3% for five determinations of 3^y (or 2^y amine). Moreover, a mixture of a 1^y and 3^y (or 2^y) amines can be determined simultaneously without previous separation using the Benzethonium Method at 8°C since a so low temperature, the reaction 2 is completed and all the present amine (1^y, 2^y and 3^y amine) is transformed to $TBPE^-BZ^+$ whichshows a ϵ=81000 $L\cdot mol^{-1}cm^{-1}$ at 606nm. So, absorbance gives the total concentration of 3^y (and/or2^y) and 1^y amine then to a high temperature only the 3^y amine is determined (the standard deviation was 3%). The use of BZCl presents the additional advantage of that $TBPE^-BZ^+$ is a more stable associate which shows bathochromism and hyperchromism against R_3-N··H··TBPE since the absorption maximum peak of the R_3-N··H··TBPE associate appears before 580nm for any amine and it is displaced forward 606nm being the molar absorptivity of $TBPE^-BZ^+$ ion pair twice higher than that of the R_3-N··H··TBPE associate. All these results suggest that the whole reaction (the sum of reactions 1 and 2) is a better and more effective analytical reaction than reaction 1 which is the only described in literature (Sakai, 1997).

Sakai T. Watanabe, S. and Yamamoto, S. (1997). Anal. Chem. 69:1266-1270

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