Near-Infrared Spectroscopy of Amine Salts

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The purpose of this investigation was to study the applicability of near-infrared spectroscopy to pharmaceutical analysis. Of particular interest was a model series of aliphatic amine hydrochlorides, and as typical pharmaceutical examples, the sympathomimetic amine salts were studied. Both solid state and chloroform solution spectra were obtained and their qualitative and quantitative applications were evaluated.

THE SPECTRAL characteristics of amines, especially aromatic amines, have been well established in the near-infrared region (1). However, while amine salts have been studied in the infrared (2–4), little has been established in the near-infrared region probably because of a lack of suitable solvents and sampling techniques.

Since the medicinal use of amines, especially as their amine salts, is extensive, it was felt that an investigation into the application of the near-infrared for the direct analysis of pharmaceutical amine salts would be of interest. This is particularly true in the case of aliphatic amine salts where the absence of ultraviolet absorption makes alternate spectral methods even more desirable. Molar absorptivity values in the near-infrared region are usually low even compared to the infrared region. However, measurements in the near-infrared can offer the advantage of the high resolution of the quartz optics employed. Use of cells and techniques more analogous to ultraviolet techniques than to those of use in the infrared also may be a potential advantage.

Objectives of the present study were the development of sampling techniques together with an investigation of the qualitative aspects, sensitivity, and conformity to Beer's law of near-infrared measurements of amine salts.

EXPERIMENTAL

Instrumental Parameters.—Beckman DK 2A: sensitivity, 50; time constant, 0.2; recording speed, 18 mμ/min.; wavelength expansion, 50 mμ/cm. Zeiss PMQ II with a M4Q III monochromator: amplification 5/1/1 and slit widths less than 0.08 mm. Both instruments were calibrated for wavelength accuracy against 1,2,4-trichlorobenzene (5).

Reagents.—Commercially available amines and sympathomimetic amine salts of production grade were used without further purification. Except where indicated as being commercially available, amine salts were prepared by adding 50 ml. of a saturated solution of HCl in anhydrous ether to 10 ml. of amine dissolved in 10 ml. of anhydrous ether. The resulting product was filtered, washed with three portions of 50 ml. of anhydrous ether, air dried, and stored in a desiccator over silica gel.

The reagent grade chloroform used as a solvent in spectrophotometric measurements was passed through a column of alumina to remove traces of water and ethanol. This process was followed by noting the absence of the strong ethanol peak at 2.90 μ. Chloroform treated in this manner was stored in a brown bottle for use within 5 days.

Solid State Spectra.—In general, from 25 to 40 mg. of amine salts taken directly from a desiccator were reduced to a powder in an agate mortar and pestle as quickly as possible to avoid the adsorption of moisture. The powders were transferred to a KBr die (Limit Corp. KB-01) and a 13-mm. disk was formed at 20,000 lb. for 5 min. Spectra were obtained on a DK-2A spectrophotometer from 2.80 to 1.05 μ or to as low a wavelength as dispersion permitted. A base line was established on the lowest absorbance range possible at 2.65 μ and with a slit width below 0.3 mm. by manual attenuation of the reference shutter.

Solution and Liquid Spectra.—(*a*) Absorption spectra of from 0.1 to 3% solutions of amine salt in chloroform were obtained on a DK-2A spectrophotometer from 2.35 to 2.10 μ. Near-infrared 1-cm. matching pair cells were used with chloroform in the reference cell.

(*b*) Absorption spectra for the parent amines were obtained from 2.65 to 1.05 μ in a 0.25-mm. short-path cell against silica as the reference.

(*c*) Percentage-transmittance spectra were obtained from 2.15 to 1.70 μ for 1% chloroform solutions of amine salts and 0.1% chloroform solution of the parent amines. In both series, spectra were obtained in 1-cm. matching pair near-infrared cells with chloroform in the reference cell. The 90 to 100% range of the DK-2A instrument was used.

(*d*) Quantitative measurements were made with the Zeiss spectrophotometer on 200 to 500 mg./10-ml. solutions of amine salts in chloroform. The major peaks of the recorded spectra were reconfirmed in the 2.33 to 2.10 μ range and the absorbance of these peaks determined. The validity of Beer's law was examined by determining the absorbances for 1 in 2, 1 in 5, and 1 in 10 dilutions of these initial solutions. Micro quantitative measurements were also made in a similar manner but with the use of the Zeiss microcell equipment (507425) with 1-cm. cylindrical MR 5 microcells of 0.2-ml. volume.

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TABLE I.—SOLID STATE SPECTRA OF MODEL AMINE HYDROCHLORIDES

Compd.	Absorption Bands, mμ
Ammonium chloride[a]	2633, 2342, 2195, 2075, 1950,[b] 1672, 1503
Primary amine salts	
Butylamine	2464,[b] 2426, 2411, 2335, 2307, 2252, 2170, 1719
tert-Butylamine[a]	2560,[b] 2514, 2451, 2384, 2339, 2306, 2269, 2223, 2192, 1691
Cyclohexylamine	2738, 2680, 2342, 2618, 2568, 2528, 2493, 2478, 2426, 2377, 2339, 2300, 2254, 2200, 1746,[b] 1706
Ethylamine[a]	2593, 2522, 2387, 2372, 2304, 2256, 2207, 2162, 1675, 1651
Isobutylamine	2603, 2556, 2401, 2334, 2307, 2265, 2217, 2170, 1687
Isopropylamine	2547, 2383, 2348, 2306, 2263, 2194, 1689
Methylamine[a,c]	2523, 2488, 2333, 2250, 2238, 2134, 1677
Propylamine	2550, 2496, 2458, 2405, 2329, 2292, 2262, 2138, 1726, 1689
Secondary amine salts	
Dibutylamine	2514, 2415, 2399, 2336, 2297, 2272, 2194,[b] 1759, 1719
Diethylamine	2638, 2603, 2558, 2515, 2462, 2411, 2380, 2353, 2297, 2257, 2197, 1726, 1681
Diisobutylamine	2620, 2556, 2508, 2450, 2409, 2312, 2269, 2200,[b] 1701
Dipropylamine	2711, 2596, 2344, 2453, 2422, 2399, 2337, 2304, 2274, 2307,[b] 1741, 1699
Piperidine	2703, 2668, 2646, 2603, 2568, 2556, 2498, 2478, 2435, 2415, 2347, 2332, 2304, 2285, 2266, 2200, 1747, 1721
Tertiary amine salts	
Tributylamine	2653,[b] 2563, 2513, 2450, 2407, 2252,[b] 2335, 2306, 2294, 2272, 1703
Triethylamine[d]	2663, 2633, 2581, 2474, 2453, 2399, 2346, 2307, 2295, 2260, 1759, 1693, 1681
Trimethylamine[c]	2492, 2448, 2346, 2257, 2096, 2014, 1804, 1671

[a] Solubility too limited to obtain spectra in chloroform in the 2.32 to 1.70-μ regions. [b] Partially resolved peak as a shoulder on a more intense peak. [c] Spectra influenced by the hygroscopic character of the salt. [d] There were no significant differences between the hydrochloride and hydrobromide salts.

RESULTS AND DISCUSSION

As is true in the infrared, carbon tetrachloride and carbon disulfide are also generally the most useful solvents in the near-infrared. However, neither solvent was of value in the present investigation either because of the interaction of the parent amines with these solvents (6, 7) or because of the lack of solubility of amine salts in the solvents.

Within their well-recognized limitations (3) solid state spectra appeared to be a promising approach to the authors' primary objective of the direct measurement of amine salts. Disks were prepared in the ratio of from 5 to 20 mg. of amine salt to 200 to 400 mg. of KCl. However, dispersion was great at either the high concentration or thick disks required for usable absorption. It was noted, however, that model amine salts could be pressed directly into satisfactory disks without addition of the halide salts. The spectra so obtained are summarized in Table I and a set of typical examples are shown in Fig. 1. It was also possible to form transparent disks directly with some sympathomimetic amine salts as summarized in Table II. In general, disks were formed under 10 tons force, although a few amine salts produced disks at even lower force. However, for the majority of compounds, it is reasonable to assume that a 20-ton system with a properly designed die for the efficient application of vacuum (8) would result in disks with less dispersion. In the present study, dispersion was partly compensated by the use of a KBr disk with high dispersion or by manual attenuation of the reference shutter. In either case, a slit width no greater than 0.3 mm. at 2.65 μ with a sensitivity of 50 was used. Under these parameters, there was no distortion of a test spectrum of didymium. Disks where held in the spectrophotometer in a pellet holder similar to the Beckman holder but with a threaded connection at the sample position to permit access to variable thickness disks. The crystalline form of the amine salt is important for disk formation. For example, 2-phenylethylamine hydrochloride in the form of platelets could not be compressed but in a microcrystalline form was compressible.

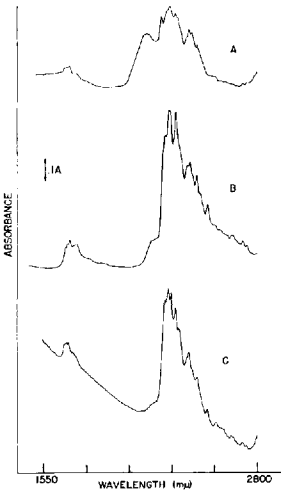

Fig. 1.—Solid state spectra. Key: A, butylamine hydrochloride; B, dibutylamine hydrochloride; C, tributylamine hydrochloride.

As can be noted in Fig. 1, the solid state spectra revealed a series of moderately strong absorbance peaks in the region from 2.55 to 2.15 μ which hold promise for quantitative measurements. Of the solvents and combination of solvents tested showing at least partial transparency (1) in the region of

TABLE II.—SOLID STATE SPECTRA OF SYMPATHOMIMETIC SALTS

Compd.	Absorption Bands, mμ
Aliphatic amine salts	
Cyclopentamine hydrochloride[a]	2571,[b] 2473, 2418, 2375, 2336, 2291, 2255, 1749, 1713
Isometheptane mucate	2656, 2526, 2496, 2451, 2394, 2326, 2294, 2267, 2248, 2150, 1716
Methylhexaneamine hydrochloride[a]	2444, 2407,[b] 2380, 2347, 2307, 2156, 1768, 1719, 1696
Tuaminoheptane sulfate	2439, 2379,[b] 2375, 2345, 2304, 2157, 1766, 1724
Imidazole salt	
Tetrahydrozoline hydrochloride	2643, 2600,[b] 2502, 2464, 2427, 2371, 2332, 2312, 2284, 2267, 2179, 2147, 1683
Phenylethylamine salts	
Amphetamine sulfate	2743, 2469, 2349, 2296, 2258, 2160, 1676
Ephedrine sulfate	2762, 2471, 2439, 2371, 2342, 2286, 2242, 2222, 2184, 2157, 2140, 1676
Mephentermine sulfate	2468, 2404, 2355, 2287, 2251, 2160, 1950, 1676
Metaraminol bitartrate	2651, 2267, 2445, 2296, 2253, 2144, 1663
Methoxyphenamine hydrochloride	2750, 2575,[b] 2474, 2434, 2385, 2338, 2290, 2258, 2162, 1681
Phenmetrazine hydrochloride[a]	2696, 2618, 2570, 2548,[b] 2525, 2484, 2458, 2420, 2369, 2354, 2317, 2302, 2259, 2150, 2137, 1691,[b] 1676
Phenylethylamine hydrochloride	2736, 2540,[b] 2473, 2350, 2280,[b] 2255, 2186, 2162, 1673
Phenylpropanolamine hydrochloride	2692, 2463, 2382, 2302, 2257, 2197, 1676
Phenylpropylmethylamine hydrochloride[a]	2778, 2618, 2464, 2418, 2375, 2323,[b] 2286, 2256, 2182,[b] 2162, 2148,[b] 1686

[a] Solubility was sufficient to obtain spectra in chloroform from 2.32 to 1.70 μ. In addition to the compounds listed in the table, the following sympathomimetic hydrochlorides had sufficient solubility to obtain spectra in chloroform: diethylpropion, methamphetamine, β-phenylpropylamine, and propylhexedrine. [b] Partially resolved peak as a shoulder on a more intense peak.

TABLE III.—MOLAR ABSORPTIVITIES OF AMINE SALTS

Compd.	$\lambda_{max.}$ (ε)
Primary amine salts	
1-Adamantanamine HCl	2298 mμ (2.95); 2223 mμ (1.06)
Isopropylamine HCl	2298 mμ (2.58); 2258 mμ (2.40); 2183 mμ (1.22)
Secondary amine salts	
Diethylamine HCl	2298 mμ (3.02); 2258 mμ (4.24)
Phenmetrazine HCl	2283 mμ (2.52); 2258 mμ (2.69)
Phenylpropylmethylamine HCl	2298 mμ (2.31); 2258 mμ (3.46); 2173 mμ (1.32)

TABLE IV.—SPECTRA OF AMINE HYDROCHLORIDES AND THEIR PARENT AMINES IN CHLOROFORM FROM 2.15 to 1.70 μ

Compd.	Bands, mμ: Amine Hydrochloride	Parent Amine
Primary		
Butylamine	1988, 1902, 1878, 1744	2134, 2112, 2018, 1892, 1814,[a] 1724
tert-Butylamine[b]	1895	2136, 2068, 2026, 1888
Cyclohexylamine	2074,[a] 1986,[a] 1906,[a] 1810, 1786, 1750, 1721	2157, 2126, 2102, 2025, 1892, 1812,[a] 1756, 1728
Isobutylamine	1989,[a] 1898, 1759, 1724, 1707	2107, 2019, 1892, 1826,[a] 1771, 1721
Isopropylamine	1999,[a] 1911,[a] 1875, 1810, 1776, 1724	2187, 2110, 2063, 2023, 1885, 1823, 1767, 1732
Propylamine	1905, 1884, 1796, 1713	2114, 2019, 1887, 1812,[a] 1726
Secondary		
Dibutylamine	2061, 1897, 1765,[a] 1721	2092, 2021,[a] 1893, 1810,[a] 1752, 1725
Diethylamine	2058, 1897, 1810[a]	2097, 2019,[a] 1892, 1820
Dipropylamine	2061, 1976,[a] 1897	2092, 2024, 1892, 1812,[a] 1753, 1723
Diisobutylamine	2063, 1897, 1810,[a] 1761,[a] 1733,[a] 1716	2092, 1892, 1810,[a] 1771,[a] 1740, 1725
Diisopropylamine	2058, 1969, 1896, 1830, 1793, 1752, 1721	2102, 1892, 1815, 1760, 1717
Tertiary		
Tributylamine	2062, 1900, 1756,[a] 1748,[a] 1702	1888, 1800,[a] 1751,[a] 1723
Triethylamine	2058, 2028,[a] 1897, 1878, 1832, 1761, 1711	2045, 2023, 1887, 1713[a]

[a] Partially resolved peak as a shoulder on a more intense peak. [b] A saturated solution of *tert*-butylamine hydrochloride is less concentrated than the normal 1% solutions.

Fig. 2.—Percentage transmittance spectra from 2.15 to 1.70 μ. A, butylamine hydrochloride; B, dibutylamine hydrochloride; C, tributylamine hydrochloride; D, butylamine; E, dibutylamine; F, tributylamine.

interest, chloroform was found to be the most useful. That is, the hydrochloride salts of amines divorced of other polar groups exhibit sufficient solubility to permit the quantitative measurement of these salts in the chloroform transparent portion (2.32 to 2.10) of the region of interest. Indication is given in Tables I and II of the compounds which could be measured in this manner.

Quantitative dilutions of the initial 1 to 3.5% chloroform solutions used to obtain these recorded spectra indicated conformity to Beer's law. Typical compounds were further examined in this regard on a Zeiss single beam instrument and conformity to Beer's law was established. The compounds tested, together with molar absorptivity of major peaks in the 2.32 to 2.10 μ region, are listed in Table III. Thus, 1% concentrations yield absorbance values in the order of 0.1 to 0.3. The use of microcells permits from 0.4 to 0.6 mmole of compound to be measured. For example, 2 mg. of adamantanamine hydrochloride can be determined in a 1-cm. microcell if total volume of solution is limited to the 0.2-ml. volume of the cell.

Spectra of solid state amine salts, especially in the 2.70 to 2.10 μ region, are complex enough and sensitive to small changes in structure to be useful for the "fingerprint" comparison and identification of these compounds. A comparison of the spectra of closely related compounds such as *n*-propylamine hydrochloride to that of isopropylamine hydrochloride (Table I) illustrates this point. The effectiveness of a comparison of this type is also illustrated with the butylamine salt series in Fig. 1. These spectra are a useful adjunct to infrared spectra in this regard.

Although the 2.70 to 2.20 μ region was the most complex and contained the most intensive absorbance bands, it was not readily possible to assign bands due to amine salts. The suspected presence of bands in this region based upon protonated nitrogen is supported by the solid state spectra of ammonium chloride (Table I). However, overtone and combination bands due to CH stretching are also exhibited in this region (1) and tend to obscure the amine salt bands.

Just below 2.20 μ and extending to 2.12 μ, there was observed for every primary amine salt studied, a broad band of medium intensity. A band in this region does not correspond to a calculated overtone for primary amine salt absorption in the infrared (2, 3). However, this band was consistently present in primary amine salts and except for the *N*-methylamines and cyclic amines studied was absent in the secondary and tertiary amine salts. The butylamine salts in Fig. 1 are a typical illustration of this difference in the 2.20 to 2.12 μ region.

The primary amine band consistently exhibits a shift of from 10 to 50 mμ to higher wavelengths when a spectrum in chloroform is compared to the corresponding spectrum of the solid state. The band at 2.25 to 2.27 μ is not shifted in this manner while the band at 2.32–2.27 μ is usually constant but with some compounds exhibits a 15 to 20 mμ hypsochromic shift in chloroform.

To study the weak bands below 2.12 μ, per cent transmission spectra of chloroform solutions recorded on the 90 to 100% expansion scale of the DK 2-A instrument were found to be the most helpful. Chloroform in a 1-cm. cell is transparent below 2.32 μ with the exception of two brief ranges (1.86 to 1.85 μ and 1.70 to 1.67 μ) and, therefore, offered a satisfactory medium for the comparison of amine salts and their parent amines. Concentrations were chosen such that the spectral region from 2.15 to 1.70 μ could be expanded full scale on the 90 to 100% range. For the amine salts, 1% solutions were satisfactory while the parent primary amines were run as 0.05% solutions and the remaining free bases as 0.1% solutions. The results are summarized in Table IV and typical examples are shown in Fig. 2.

All spectra of both amine salts and their parent amines have a band between 1.90 and 1.87 μ. This band exhibits a bathochromic shift of 3 to 10 mμ in the salts as compared to their parent amine and is the major similarity between a given amine salt and its parent amine in this region.

There is no other significant absorption from 2.15 to 1.70 μ for primary amine salts which is in direct contrast to the very strong combination band noted in the present investigation and previously reported for the free base primary amines (1). The absence of bands by this technique in this region for primary amine salts and the presence of a band at 2.05 μ for both secondary and tertiary amine salts offer a second method of distinguishing primary amine salts. Again, the 2.05 μ band does not correspond to an overtone for reported (2, 3) NH stretching bands in the infrared.

SUMMARY

The spectra of both model amine hydrochlorides and pharmaceutical amine salts have been observed in the near-infrared. Solid state spectra and solutions of hydrochlorides in chloroform have been shown to be useful sampling techniques and have

applications for qualitative work. Bands in the 2.15 to 2.32 μ region have been shown to be useful for the quantitative measurement of amine hydrochloride salts. Primary amine salts were distinguished from secondary and tertiary amine salts on the basis of the presence of a 2.18 μ band and the absence of a band at 2.05 μ.

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Applications of the Montmorillonites in Tablet Making

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The montmorillonites were studied for their use as disintegrants, binders, and lubricants for the manufacture of compressed tablets. It was found that the clays, although traditionally believed to be inert materials, agglomerated with several macromolecules commonly used as tablet binders. When added dry to prepared granulations, magnesium aluminum silicate F was an excellent disintegrant which produced tablets disintegrating twice as fast as those containing an equal amount of cornstarch. Furthermore, the clays contained a lower moisture content and were more compressible than starch. However, the other grades of montmorillonite studied were less effective as disintegrating agents than starch, and wet granulation of the clays with the diluents substantially decreased the effectiveness of these materials as disintegrants.

MONTMORILLONITE is the name given to a clay mineral first found near Montmorillon, France. Essentially, it has the composition $Al_2O_3 \cdot 4SiO_4 \cdot H_2O \cdot xH_2O$. Many minerals of similar properties, but distinctly different chemical compositions, have since been found (1). The clay minerals frequently exhibit properties which are highly desirable for any products used as disintegrants, binders, and fillers, or viscosity imparting agents. They have a high swelling volume in water, form gels at low concentrations, are chemically inert and stable to a wide range of temperatures, and are smooth, white to off-white fine powders. This study was undertaken to investigate the extent of application and limitations of the montmorillonite type of clays in tablet making, based on and in view of selected physical properties of the clays which were previously determined (2).

Bentonite and magnesium aluminum silicate[1] have been studied by several workers as tablet disintegrating agents. Granberg and Benton (3) reported that bentonite was an effective filler and disintegrating agent in thyroid tablets. Gross and Becker (4), on the other hand, found that neither bentonite nor magnesium aluminum silicate, in concentrations up to 17%, produced any disintegrating effect in tablets. However, Firouzabadian and Huyck (5) and Ward and Trachtenberg (6), who conducted comparative studies on the effectiveness of tablet disintegrants, found that magnesium aluminum silicates were among the best disintegrants studied. Nair and Bhatia (7) in another comparative study reported that sulfathiazole tablets containing magnesium aluminum silicate as the disintegrant appeared to have the most rapid distintegration time when most of the clay product was added after granulation and only a small portion before granulation. A suspension of 20% montmorillonite clay has been used as a granulating agent with reported disintegration activity (8).

EXPERIMENTAL AND RESULTS

The three commercial montmorillonites studied in this work will be referred to as clay I, II ,and III,[2] respectively. The composition and properties of these

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[1] Marketed as Veegum by the R. T. Vanderbilt Co., New York, N. Y.

[2] Marketed as Veegum, Veegum F, and Veegum WG by the R. T. Vanderbilt Co., New York, N. Y.