higher during the first 4 hr than those attained following the oral dose, suggesting also that first-pass hepatic metabolism is important and that this phenomenon may be involved in the pharmacokinetics of cyclobenzaprine absorption in humans.

The presence of only a relatively small amount of unchanged drug in the urine (0.2–1.5% of the administered doses) would suggest that the drug was virtually completely metabolized in humans. The extent of metabolism may not be quite this complete since, after administration of ^{14}C-labeled drug[12], only 6.3% of a 10-mg po dose and 7.1% of a 10-mg iv dose were excreted in the 24-hr urine.

No peaks attributable to metabolites of cyclobenzaprine in plasma were observed during assay of the human samples. Norcyclobenzaprine was presumably present in the plasma, since it was found in the urine, but the detection limit for the desmethyl derivative was much higher than for cyclobenzaprine because of less favorable GLC and extraction properties[12]. In contrast, nortriptyline is readily detected in plasma after administration of amitriptyline, a drug having a structure very similar to that of cyclobenzaprine (3, 5, 6).

GLC analysis of the urine samples revealed the presence of an additional peak at 3.2 min, the same retention time as that of N-desmethylcyclobenzaprine (Fig. 2). Treatment of the final ethyl acetate extract with trifluoroacetic anhydride before GLC analysis caused the disappearance of the 3.2-min peak and the appearance of a new peak at 5.0 min, the same retention time as that of the trifluoroacetyl derivative of authentic N-desmethylcyclobenzaprine. The possibility that the metabolite was didesmethylcyclobenzaprine was ruled out by the fact that, although the retention time of the free amine was similar to that of the metabolite, the retention time of its trifluoroacetyl derivative was 4.0 min.

The desmethyl metabolite was most predominant in the 8–24-hr urine samples and appeared to be present in equal or higher concentrations compared to unchanged cyclobenzaprine. Evidently, the N-desmethyl metabolite was present in plasma in concentrations too low to be detected, but urinary levels were sufficiently high for identification.

The present GLC method is suitable for the quantitative assay of cyclobenzaprine in human plasma and urine samples after administration of a single 40-mg dose. Greater sensitivity may be necessary when a smaller dose is administered and can be achieved by using a larger plasma sample for assay.

REFERENCES

(1) P. Molina-Negro and R. A. Illingworth, *Union Med. Can.*, **100**, 1947(1971).
(2) N. N. Share and C. S. McFarlane, *Neuropharmacology*, **14**, 9(1975).
(3) H. B. Hucker and S. C. Stauffer, *J. Pharm. Sci.*, **63**, 296(1974).
(4) D. B. Faber, *J. Chromatogr.*, **74**, 85(1972).
(5) H. B. Hucker, S. C. Stauffer, F. G. Clayton, B. R. S. Nakra, and R. Gaind, *J. Clin. Pharmacol.*, **15**, 168(1975).
(6) R. A. Braithwaite and B. Widdop, *Clin. Chim. Acta*, **35**, 461(1971).

[12] Unpublished work.

Kinetics of Acid Neutralization by Aluminum Hydroxide Gel

STEVEN L. NAIL [*], JOE L. WHITE [‡], and STANLEY L. HEM [*x]

Abstract [□] The rate of acid neutralization by an aluminum hydroxide gel prepared by the reaction of aluminum chloride solution and strong ammonia solution was studied. The decrease in acid-consuming capacity during aging as measured by the USP test is due to a decrease in the rate of reaction rather than to a decrease in equilibrium reactivity. The reactivity profile has three phases, which are shown to be related to the structure of the gel. The rate of loss of reactivity is directly related to the extent of washing.

Keyphrases [□] Aluminum hydroxide gel—kinetics of acid neutralization, effect of aging, reactivity related to gel structure [□] Acid neutralization—by aluminum hydroxide gel, effect of aging, reactivity related to gel structure [□] Gels—aluminum hydroxide, kinetics of acid neutralization, reactivity related to gel structure [□] Antacids—aluminum hydroxide gel, kinetics of acid neutralization, effect of aging

Aluminum hydroxide gel is known to lose acid reactivity on aging (1–3). The purposes of this investigation were: (*a*) to study this neutralization reaction for an aluminum hydroxide gel prepared by the reaction of aluminum chloride solution with strong ammonia solution; and (*b*) to determine whether the decrease in acid reactivity, as determined by a modification of the USP acid-consuming capacity test (4), was attributable to a decreased rate of reaction or to a decrease in equilibrium reactivity.

EXPERIMENTAL

Materials—All chemicals used were either reagent or analytical grade.

Aluminum Hydroxide Gel Preparation—A 4-liter batch of gel was prepared by the addition of 13% (v/v) strong ammonia solution to a solution of 287.2 g of aluminum chloride hexahydrate in 3340 ml of distilled water. Strong ammonia solution was added with agitation at a rate of approximately 120 ml/min to a final pH of 7.0. After precipitation, the gel was divided into four equal portions. The first portion (I) was washed with 1 liter of distilled water by draining through a canvas bag, and a second portion (II) was washed with 5 liters of distilled water. The gels were diluted to 1 liter with distilled water, stored in tightly closed glass containers, and aged at 25°.

Analytical Procedures—The equivalent aluminum oxide content was determined by the ethylenediaminetetraacetic acid titration (4). The gels contained between 1.40 and 1.50% equivalent of aluminum oxide.

The total chloride content was determined by the Volhard titration (5) after 3 g of gel was dissolved in 15 ml of 6 N nitric acid.

The rate of reaction of the gel with acid was studied by preparing a series of 5-g samples of gel in 125-ml glass-stoppered flasks and adding 50 ml of 0.1 N HCl. Samples were then placed in a water bath[1]

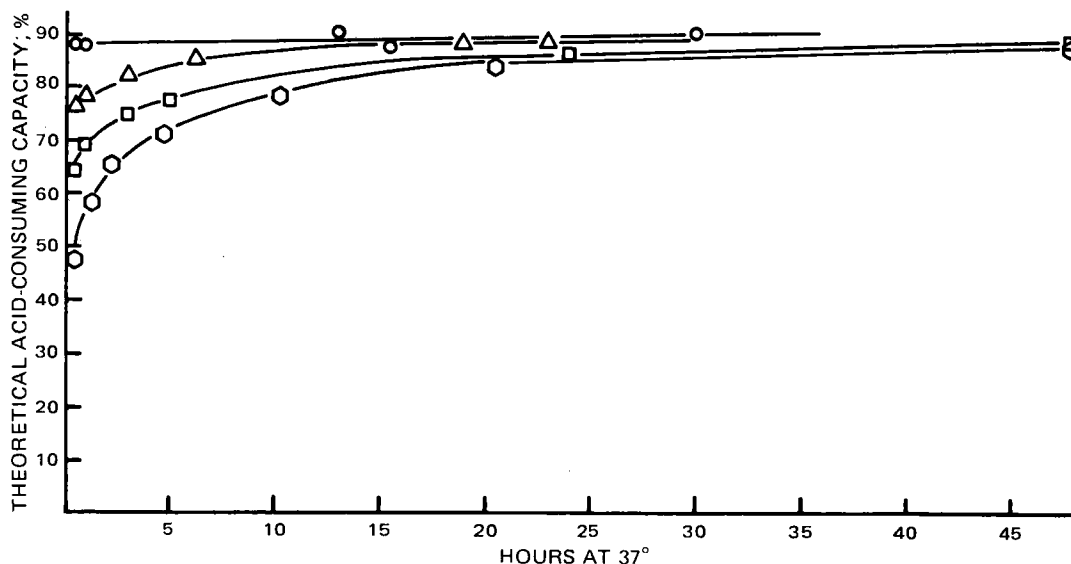[1] Thermo-Shake incubator shaker, Forma Scientific, Pittsburgh, Pa.

Figure 1—*Change in rate of reaction of Gel I with acid during aging. Key:* O, *1 day;* △, *30 days;* □, *50 days; and* O, *163 days.*

at 37° with agitation. Samples were removed from the bath after periods ranging from 0.5 hr to 1 week, and the amount of acid neutralized was determined by back-titrating the sample to pH 3.5 with standard 0.1 N NaOH. The acid reactivity of each gel was expressed as the percent of the theoretical acid-consuming capacity (TACC):

$$TACC = \frac{W \times A \times 60}{10.2} \qquad (Eq.\ 1)$$

where W = weight of gel sample in grams, and A = assay of gel as percent aluminum oxide.

This procedure was repeated for each gel at various times during aging.

RESULTS AND DISCUSSION

The rate of reaction of each gel with acid is shown in Figs. 1 and 2. The *general features of the* reaction rate curve for Gels I and II are similar. Equilibrium reactivity is reached within 0.5 hr for the gel aged 1 day. After further aging, three types of kinetic behavior become apparent. A portion of each gel reacts almost immediately, and the amount of this fast reacting portion decreases with age. The gel then reacts at a slower rate until the equilibrium reactivity is reached, the rate during this period becoming slower as the gel ages (curved portions of Figs. 1 and 2). However, the gels appear to reach the same end-point reactivity if sufficient time is allowed for the reaction to proceed. The slope is nearly zero in all cases after about 20 hr, indicating a final period represented by a slow zero-order reaction.

For the intermediate rate portion of the reaction curve, the essentially straight portion of the curve is extrapolated to time zero, and the difference between the percent of the theoretical acid-consuming capacity from the extrapolated zero-order line ($TACC_\infty$) and the percent of the theoretical acid-consuming capacity at time t ($TACC_t$) is calculated. When the negative log of this value is plotted against time, a straight line results, indicating that the reaction follows apparent first-order kinetics during this period.

If similar plots are made for each aging time studied, a series of straight lines is obtained (Figs. 3 and 4). The slopes of these lines decrease with increasing age, indicating a slower reaction rate. The y-intercept of these plots provides an accurate determination of the amount of immediately reacting material present at each aging period. Plotting the log of the amount of immediately reacting material determined in this manner against aging time also gives a straight line, indicating a first-order decrease in this quantity (Fig. 5). The rate of decrease in the fast reacting portion follows the order II > I.

Smith (6) also observed three types of kinetic behavior in the reaction of dilute hydroxyaluminum systems with 8-hydroxy-7-iodo-5-quinolinesulfonic acid (III). The slow zero-order portion was attributed to reaction of microcrystalline material with III. It seems reasonable that the slow portions of Figs. 1 and 2 would result from acid attack on the surface of highly ordered material.

The first-order portion of the reaction curve is believed to result from acid attack on material that is less ordered; *i.e.*, protons can penetrate the gel structure more readily than in the zero-order portion.
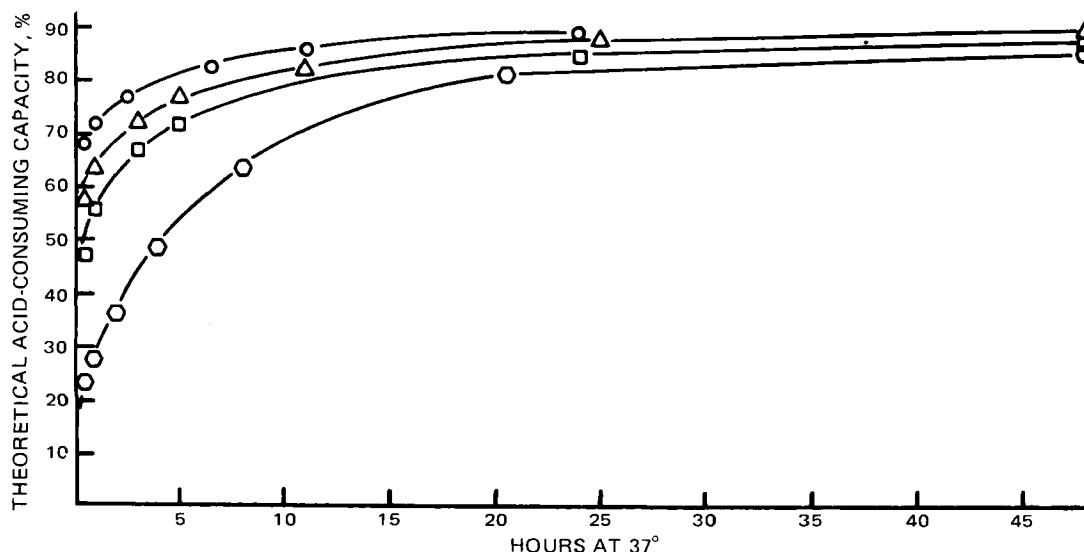

Figure 2—*Change in rate of reaction of Gel II with acid during aging. Key:* O, *30 days;* △, *50 days;* □, *72 days; and* O, *157 days.*
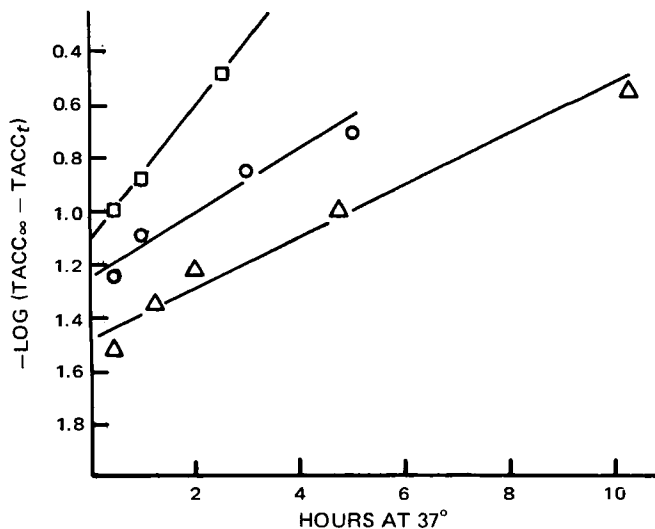
Figure 3—*Change in rate of first-order portion of Gel I during aging.*
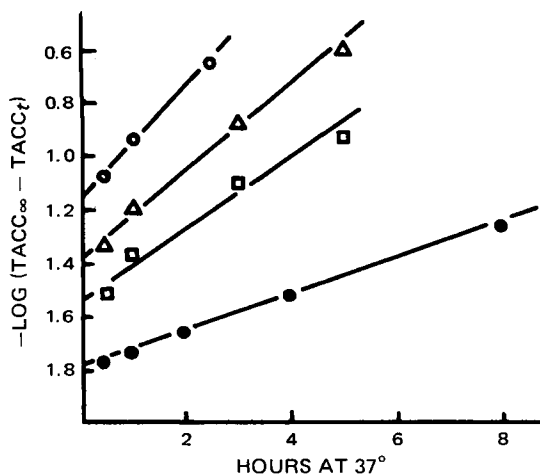*Key: □, 30 days; ○, 50 days; and △, 163 days.*

Figure 4—*Change in rate of first-order portion of Gel II during aging. Key: ○, 30 days; △, 50 days; □, 72 days; and ●, 157 days.*
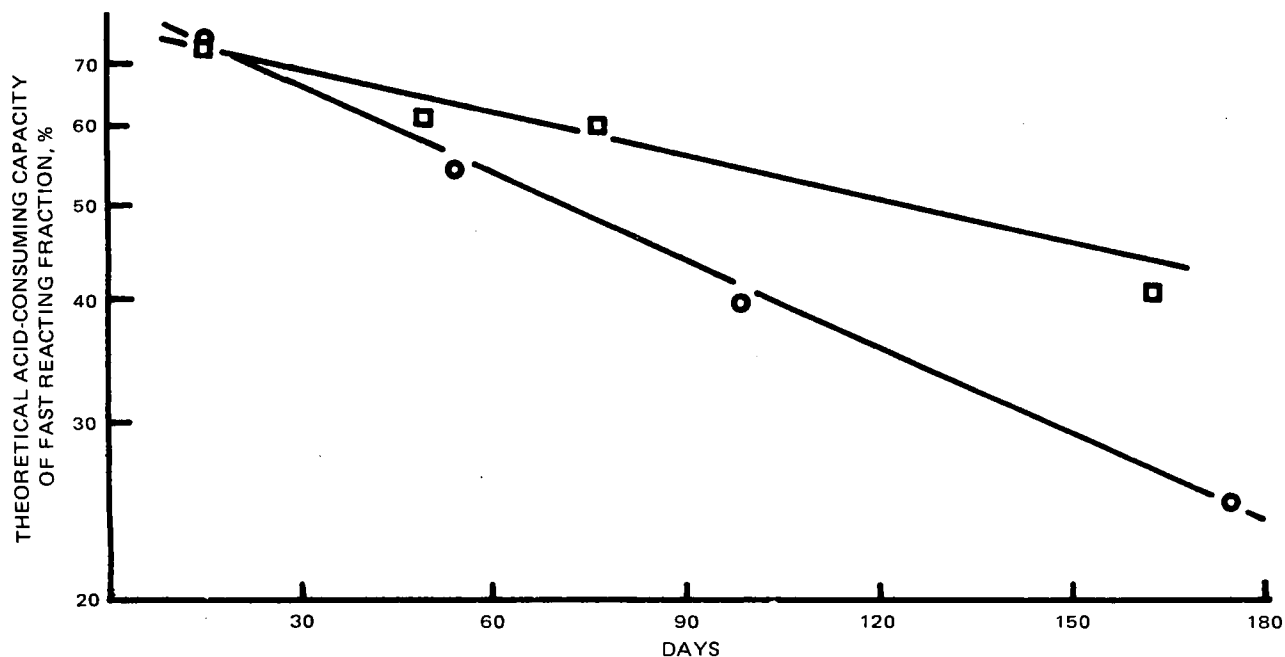
The initial fast reacting portion of Figs. 1 and 2 probably results from acid attack on easily accessible hydroxyl groups. Hydroxyl groups on the edge of the hydroxyaluminum particles would be readily accessible, and neutralization of these hydroxyl groups might explain the initial fast reaction rate. Particle growth by formation of double hydroxide bridges between the edges of adjacent particles (6) would decrease the relative number of edge hydroxyls, thus explaining the observed decrease in the fast reacting portion of the gel during aging.

The direct relationship between the degree of washing and the decreased rate of acid neutralization is consistent with the inhibition of secondary polymerization by the chloride ion (7). Chloride ions can occupy edge positions on the hydroxyaluminum polymers and thereby block further polymerization at these sites. Gel I, which was washed with 1 liter of distilled water, contains 0.80 mEq of chloride/mmole of aluminum and changes more slowly than Gel II, which was washed with 5 liters of distilled water and contains 0.35 mEq of chloride/mmole of aluminum. Inhibition of this reaction retards particle growth and the subsequent development of crystalline forms of aluminum hydroxide.

Calculation of the theoretical acid-consuming capacity of a gel is based on the reaction of 6 equivalents of hydrochloric acid with 1 mole of aluminum oxide or of 3 equivalents of acid with 1 mole of aluminum hydroxide. In other words, calculation of the theoretical acid-consuming capacity is based on a bound hydroxide to aluminum ratio of 3. Previous investigations (7, 8) showed that this is not always the case. The gels studied, resulting from the reaction of aluminum chloride solution with strong ammonia solution to a final pH of 7.0, were shown to have an average ratio of bound hydroxide to aluminum of 2.55 (7). This ratio increases with age due to secondary polymerization of the hydroxyaluminum particles (7). This explains why the equilibrium reactivity of these gels is less than 100% of theoretical capacity. Complete reaction of a gel with a bound hydroxide to aluminum ratio of 2.55 would consume 85% of the theoretical amount. The gels in this study initially consumed about 90% of the theoretical capacity at equilibrium, somewhat higher than the value predicted by the hydroxide to aluminum ratio but in reasonable agreement with theory.

SUMMARY

Aluminum hydroxide gel prepared from aluminum chloride and ammonium hydroxide at a final pH of 7.0 has an acid reactivity profile with three phases: (a) an initial fast reacting portion whose contribution decreases as the gel ages; (b) a portion that reacts with acid according to apparent first-order kinetics at a rate that decreases with age; and (c) a slow, zero-order reacting portion believed to be highly ordered material.

The decrease in USP acid-consuming capacity is due to a decreased

Figure 5—*Change in fast reacting portion of gels during aging. Key: □, Gel I; and ○, Gel II.*

rate of reactivity rather than to a change in equilibrium reactivity. The USP acid-consuming capacity test is based on the amount of acid neutralized by the gel in 1 hr. Thus, the acid reactivity measured by the USP test decreased during aging, although the equilibrium reactivity of the gels was unchanged.

REFERENCES

(1) S. L. Hem, E. J. Russo, S. M. Bahal, and R. S. Levi, J. Pharm. Sci., 59, 317(1970).

(2) S. L. Nail, J. L. White, and S. L. Hem, ibid., 64, 1166(1975).

(3) Ibid., 65, 231(1976).

(4) "The United States Pharmacopeia," 18th rev., Mack Publishing Co., Easton, Pa., 1970, p. 26.

(5) I. M. Kolthoff, E. B. Sandell, E. J. Meehan, and S. Bruckenstein, "Quantitative Analysis," 4th ed., Macmillan, London, England, 1969, p. 799.

(6) R. W. Smith, Adv. Chem., 106, 250(1971).

(7) S. L. Nail, J. L. White, and S. L. Hem, J. Pharm. Sci., 65, 1192(1976).

(8) Ibid., 65, 1188(1976).

IR Spectroscopic Characterization of 2-Thiohydantoins and 2-Thiobarbiturates

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Abstract □ A characterization of 2-thiohydantoins and 2-thiobarbiturates by IR spectra is proposed, using three characteristic group frequencies: the "thioureide band" around 1500 cm^{-1} and the antisymmetric-symmetric stretching modes of NCS bonds around 1400 and 1200 cm^{-1}. The general characteristic absorption areas are found by comparison with N-phenylthioureas and thioanilides.

Keyphrases □ Thiohydantoins—characterization by IR spectroscopy □ Thiobarbiturates—characterization by IR spectroscopy □ IR spectroscopy—characterization of thiohydantoins and thiobarbiturates

Whereas the origin and localization of the characteristic group frequencies of the carbonyl in hydantoins (1) and barbiturates (2) have been thoroughly studied, the question is still open for the corresponding thio compounds because of difficulties in assignments. Strong coupling occurs between the C–S and C–N vibrations, resulting in numerous bands in the 1550–1200-cm^{-1} region, each of which contains a significant contribution from the C=S stretching mode (3).

The identification in the literature is often based on the "thioureide band," as defined previously (4, 5), in spite of the absence of a C=S contribution to this mode[1].

A new characterization of the thiohydantoins and thiobarbiturates series by IR spectra, involving the antisymmetric and symmetric stretching modes of NCS bonds, is now reported.
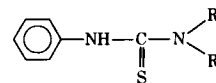
EXPERIMENTAL

IR spectra were recorded[2] using the potassium bromide pellets technique (1 mg/200 mg) after the compounds were dried overnight under vacuum (0.2 mm Hg at 60°). The structures of utilized compounds were confirmed by comparison with literature data or by mass

Table I—Characteristic Bands (Centimeters⁻¹) of N-Phenylthioureas

Compound		$\nu_{thioureide}$	ν_{as} NCS/ ν_s NCS^a
I	R$_1$ = H, R$_2$ = H	1530	1450/1232
II	R$_1$ = H, R$_2$ = C$_6$H$_5$	1555	1452/1245
III	R$_1$ = C$_6$H$_5$, R$_2$ = C$_6$H$_4$—OCH$_3$	1550	1450/1240
IV	R$_1$ = R$_2$ = cyclo-(CH$_2$)$_5$	1540	1440/1230
V	R$_1$ = H, R$_2$ = C$_6$H$_5$—CH$_2$—CH—CH$_3$	1538	1450/1245
VI	R$_1$ = CH$_3$, R$_2$ = C$_6$H$_5$—CH(OH)-—CH—CH$_3$	1538	1450/1260
VII	R$_1$ = H, R$_2$ = cyclo C$_6$H$_{11}$—CH—COOH	1515	1410/1230

^{a} ν_{as} NCS and ν_s NCS designate the antisymmetric and symmetric stretching modes of the NCS function.

spectrometry[3] (ionization potential of 70 ev).

N-Phenylthioureas (I–VII) were obtained by interaction of phenyl isothiocyanate and amines in ether and subsequent recrystallization in methanol (6). The properties of I–IV (6) and VII (7) were in agreement with the literature.

Compound V had a melting point of 104–107°; m/e 270 (M⁺), 236 (—H$_2$S), 145 [C$_6$H$_5$CH$_2$CH(CH$_3$)NC], 135 (C$_6$H$_5$NCS), 91 (C$_6$H$_5$CH$_2$), and 77 (C$_6$H$_5$). Compound VI had a melting point of 114–117°; m/e 282 (—H$_2$O), 264 (—H$_2$S), 207 (C$_6$H$_5$NH$_2$), 145

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[1] The "thioureide band" is due to a νC–N mode; coupling between νC–N and δ NH may occur in suitable cases. This band is designated as the B band in the classification of Jensen and Nielsen (5).

[2] Perkin-Elmer model 621.

[3] LKB 900 S.