Mechanistic Applications of High Performance Liquid Chromatography. Rate–Product Correlations for Competing Solvolysis and Aminolysis of Benzoyl Chloride

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Rates and products for methanolysis of benzoyl chloride in the presence of *m*-nitroaniline (10^{-4}—10^{-1} M) are reported. There is a good correlation between the rate enhancement caused by the added amine and the formation of amide product. The aminolysis reaction is first order in added amine, and similar results are observed for *o*- and *p*-nitroanilines. The results demonstrate that the reactions of nitroanilines involve these amines as nucleophiles, not as base catalysts. The presence or absence of rate–product correlations is an established probe of reaction mechanism, which can be implemented conveniently and with good accuracy by reversed-phase high performance liquid chromatography. Many of the measurements of product compositions reported in this paper were made on the same very dilute solutions used to obtain the kinetic data conductimetrically. Such low concentrations of neutral nucleophiles minimised the medium effect on reactivity. Selectivity data for reactions of benzoyl chloride with *o*-nitroaniline and (i) methanol or (ii) water in aqueous acetone are also reported. It is shown that the selectivity [see equation (5)] is independent of the concentration of nitroaniline.

Reversed-phase high performance liquid chromatography (h.p.l.c.) is currently applied routinely for both qualitative and quantitative organic analysis.[1] In studies of kinetics and mechanism, h.p.l.c. can readily be used as an analytical method to obtain reaction rate constants from quenched aliquot portions. We now report high precision rate–product correlations to illustrate the prospects of h.p.l.c. for mechanistic investigations. Many of our results were obtained by *direct* analysis of the same dilute solutions (10^{-1}—10^{-5} M) as those examined kinetically. Analyses of benzoic acid in aqueous solutions are also reported and illustrate that the method is more convenient than g.l.c. and of wider scope than normal-phase h.p.l.c. or titrimetric methods.

The concept of obtaining mechanistic information from rate–product correlations was developed over 40 years ago. Azide ion, in competition with solvent, can be used as a probe for the presence of very short-lived carbocationic intermediates.[2,3] When more than the expected yield of organic azide product is observed, it is argued that the azide ion is selectively trapping one or more[4] cationic intermediates[2,3] (expected yields of azide are calculated from the observed rate enhancement, corrected for any medium effects, as discussed below). Thus a lack of rate–product correlation provides mechanistic information.

Solvolyses of 1-methylethyl tosylate in 80% ethanol–water, containing added sodium azide, appear to give satisfactory rate–product correlations.[3a] The yield of azide product was correctly predicted from the rate enhancement, provided that no correction for salt effects was made. Counter arguments[3b] assumed a negative salt effect for S_N2 reactions, in contrast to the positive salt effect established for S_N1 reactions.[2] This ambiguity led McLennan[5] to introduce the 'neutral nucleophile stratagem' to reduce substantially the contribution of medium effects to the observed rate enhancements. The same 'strategem' was implicit in earlier studies of the hydrolysis of benzoyl chloride by Gold *et al.*[6] which led to the work we describe here. Our results support the 'neutral nucleophile strategem'. We show that neutral nucleophiles can be studied by h.p.l.c. in low concentrations to reduce further any medium effects and that useful mechanistic information can also be obtained from the presence of rate–product correlations.

In several previous studies[3,5,6] of rate–product correlations and selectivities, a relatively narrow range of concentrations of added nucleophiles was examined (about four-fold). In this work we have examined a much wider range of concentrations (up to 300-fold) to establish whether selectivity varies with concentration of added nucleophile. There is one report[4] of a two-fold variation in selectivity over a 500-fold range of added nucleophiles; in this case only product analyses were carried out, but they required isotope dilution techniques. H.p.l.c. would now be more convenient experimentally.

Results

We studied reactions of neutral nucleophiles (either *o*-, *m*-, or *p*-nitroanilines) with benzoyl chloride in methanol or in acetone–water solutions [equations (1) and (2)]. The competing

$$PhCOCl + ArNH_2 \longrightarrow PhCONHAr + HCl \quad (1)$$

$$PhCOCl + ROH \longrightarrow PhCO_2R + HCl \quad (2)$$

solvolysis [equation (2)] produced benzoic acid from acetone–water [equation (2; R = H)] or methyl benzoate from methanol [equation (2; R = CH_3)]. In the presence of an excess of amine, good first-order kinetics were observed; reaction rates were monitored conductimetrically over at least two half-lives of reaction. HCl (*e.g.* 10^{-3} M) is almost completely ionized even in methanol,[7] and a calibration showed a linear relationship between change in conductance and molar concentration of HCl.[8] The nitroanilines are very weak bases and protonation of *o*-nitroaniline by HCl did not occur in acetone–water.[6]

Preliminary kinetic studies were carried out in acetone–water with added *o*-nitroaniline.[6] Substantial amounts of added amine (*ca.* 10^{-1} M) were required to give readily measurable rate enhancements and this led to difficulties in the product studies; the amine crystallised slowly from some of the stock solutions. This was avoided by changing the solvent to methanol, but crystallisation also occurred *during* h.p.l.c. analysis (the performance of the columns deteriorated rapidly). *p*-Nitroaniline gave readily measurable rate enhancements with 10^{-2} M solutions, but we eventually selected *m*-nitroaniline for our most extensive investigations. Table 1 shows rate and product data for an unusually wide range (300-fold) of concentrations of added nucleophile (*m*-nitroaniline). All the results in Table 1

Table 1. Rate constants (k_{obs}) and products for reaction of benzoyl chloride at 25 °C in methanol with added *m*-nitroaniline

Initial concentrations[a]	Rate constants[b]	Product (% amide)		
$10^3[ArNH_2]$/M	$10^3k_{obs}/s^{-1}$	obs.[c]	calc.[d]	10^3S[e]
0[f]	4.50 ± 0.02[g]			
0.36[f]	5.17 ± 0.03	10.6	13.0	8.1
0.36[h]	5.23 ± 0.02[i]	11.5	14.0	8.9
0.63[f]	5.47 ± 0.08	20.2	17.7	9.9
1.00[j]	5.6 ± 0.1[k]	24.5	19.6	8.0
1.36[h]	6.3[l]	30.7	28.6	8.1
2.01[h]	7.67 ± 0.13	41.3	41.3	8.7
3.00[h]	9.05 ± 0.10	48.4	50.3	7.7
3.00[j,m]	8.79 ± 0.10	51.5	48.8	8.7
5.00[m,n]	11.5 ± 0.2	60.9	60.9	7.8
10.00[n]	18.8 ± 0.2	77.0	76.1	8.4
50.0[h,n]	80.3 ± 0.3	94.6	94.4	8.6
100.0[i,n]	144 ± 2	*o*	96.9	
100.0[n]	165 ± 5	*o*	97.3	

[a] [PhCOCl] given in footnotes *f*, *h*, *j*, *m*, and *n* are approximate. [b] Determined conductimetrically in duplicate; errors shown are average deviations. [c] The observed result from response calibrated h.p.l.c. was the average of at least four determinations of the ratio [amide]/[ester]; see also Table 2, footnote *a*. [d] From observed rate constants and equation (4). [e] From observed product ratios and equation (5), with [MeOH] 24.7M. [f] [PhCOCl] *ca.* 5 × 10^{-5}M. [g] Our stock solution of CO_2-free AnalaR methanol gave rate constants 2—5% higher than for independent measurements with other stock solutions. The results in this Table are derived from three independent sets of measurements, (entries: 1—4, 6—8; 5, 9—13; 14), which have been 'normalised' to this slightly higher rate constant for methanolysis. [h] [PhCOCl] *ca.* 1 × 10^{-4}M. [i] Single measurement, error is the calculated standard deviation. [j] [PhCOCl] *ca.* 3 × 10^{-4}M. [k] This rate constant appears to be anomalously low, possibly because an insufficient excess of amine was present. [l] The duplicate measurement gave *k ca.* 7.2 × 10^{-3}, but the same product ratio. [m] [PhCOCl] *ca.* 5 × 10^{-4}M. [n] [PhCOCl] *ca.* 10^{-3}M. [o] The amount of ester could not be obtained with sufficient accuracy because of the large amount of amine.

Table 2. Products for reaction of benzoyl chloride in methanol with added *o*-nitroaniline

Initial concentrations		% Amide[a,b]	S[c]
[PhCOCl]/M	$[ArNH_2]$/M		
1 × 10^{-2}	1.12 × 10^{-2}	0.28[d]	6.2
1 × 10^{-2}	1.12 × 10^{-2}	0.19[e]	
1 × 10^{-3}	1.12 × 10^{-2}	0.27[d,f]	
1 × 10^{-2}	5.6 × 10^{-2}	1.33[d]	5.9
1 × 10^{-2}	5.6 × 10^{-2}	1.38[e]	
1 × 10^{-3}	5.6 × 10^{-2}	1.28[d,f]	
1 × 10^{-2}	1.12 × 10^{-1}	2.52[d]	5.7
1 × 10^{-2}	1.12 × 10^{-1}	2.52[e]	
1 × 10^{-2}	2.24 × 10^{-1}	4.54[d,g]	5.1

[a] Ratio of [amide]/[ester] was determined at 270 nm by h.p.l.c. (eluant 60% v/v methanol–water + 1% v/v acetic acid; flow rate 1.5 ml min^{-1}). [b] Error *ca.* ±2%. [c] Calculated from equation (5), the observed product ratio and the initial concentrations of amine and methanol; error at least ±4%. [d] At 25.0 °C. [e] At 50.0 °C. [f] Duplicate analyses of only *one* sample—probably larger error due to small signal for amide. [g] % amide predicted from equation (4) is 4.9%; k_{obs} = (4.66 ± 0.02) × 10^{-3}, k_{solv} = (4.43 ± 0.02) × 10^{-3}, using 10^{-3}M-benzoyl chloride.

were obtained by kinetic studies followed by product studies of the *same* solutions. Tables 2—4 show mainly product data for *o*-nitroanilines, including comparisons with previous literature data[6] in Table 4.

All the product analyses were made with minimum sample manipulation. The low sample concentrations posed no serious problems because of the high ε values for the u.v. detection (≤0.1 A) in h.p.l.c. Gradient elution was avoided by suitable choice of a mixed solvent as eluant. As the solvents used in our products studies and the solvents used as eluants were not identical, solvent peaks were observed. Acetone gave a very large, tailing peak at 270 nm ($\lambda_{max.}$ for benzoic acid). Methanol and water gave sharp positive and negative peaks, both of which tend to disappear in some published chromatograms. These peaks were not sufficiently well resolved from the signal for benzoic acid, unless a small amount of acetic acid was added to the eluant.[9] In some cases the negative peaks led to an incorrect choice of baseline by the electronic integrator; integration was then timed to begin after the negative peak. For studies in methanol, the solvent peak could be avoided by adding water to the sample to match the eluant composition. The ε values for the amides were *ca.* 20 times greater than for benzoic acid or methyl

Table 3. Products for reaction of benzoyl chloride in aqueous acetone with added *o*-nitroaniline

Initial concentrations		% Amide[a]	S[b,c]
10^2[PhCOCl]/M	$10^2[ArNH_2]$/M		
Solvent 80% (w/w) acetone–water at 25 °C			
1	1.00	2.15[d]	20.2
0.1	1.03	1.96[d,e]	
1	5.00	9.9[d]	20.2
1	10.00	18.7[d]	21.1
Solvent 50% (w/w) acetone–water at 25 °C			
1	1.00	1.4	35.4
0.1	1.17	1.5[d,e]	
1	5.00	6.4	34.4
1	10.00	11.8	33.6
At 0 °C			
0.1	1.17	4.40	98.5
0.3	3.69	13.5	105.7
1.0	8.86	25.9	98.5

[a] Calculated from the ratio of [amide]/[acid], determined at 270 nm by h.p.l.c. (hypersil ODS, eluant: 60% v/v acetonitrile–water; flow rate 1.5 ml min^{-1}). [b] Calculated from equation (5), the observed product ratio and the initial concentrations of amine and water. [c] The volume change (a few percentage reduction) on mixing acetone and water was ignored. $[H_2O]$ 25 and 9.2M for 50 and 80% acetone–water, respectively. [d] Duplicate analyses of only one sample. [e] Less reliable because of low initial concentration of benzoyl chloride.

Table 4. Rate–product correlations for published data[a] for reaction of 0.05M-benzoyl chloride in aqueous acetone at 0 °C with added *o*-nitroaniline

Initial concentration 10^2[amine]/M	Rate constant $10^5k/s^{-1}$	Product (% amide) obs.	calc.[b]	S[c]
Solvent 80% (w/w) acetone–water				
0	3.9			
9.1	6.5[d]	35	40.0[d]	54[e]
18.7	8.0	49	51.3	47
28.5	10.0	58	61.0	44.5
Solvent 50% (w/w) acetone–water				
0	27.7			
9.2	32.1	31	13.7	122[e]
18.8	36.3	44	23.7	105
26.6	39.6	54	30.0	102

[a] Ref. 6. [b] From equation (4). [c] See footnotes *b* and *c* of Table 3. [d] Deviation from equation (3). Equations (3) and (4) predict *ca.* 35% amide. [e] No allowance made in our calculations for the *ca.* 20% decrease in [amine] during the reaction. A correction would increase S further.

benzoate; consequently very low yields of amides could be determined remarkably accurately (Table 2). The large excess of highly absorbing amine gave broad peaks which limited the scope of our results (Tables 1—3). We were unable to devise a rapid quantitative ion exchange method to separate the excess of amine prior to h.p.l.c. analysis, partly because the nitroamines appear to be too difficult to protonate. The scope of our results at low concentrations (10^{-5}M) was not reduced by inadequacies in experimental procedures for rates or products.

Discussion

These competing nucleophilic substitutions fit the rate law shown in equation (3) (see Figure) where k_{obs} is the observed

$$k_{obs} = k_{solv} + k_{am}[ArNH_2] \quad (3)$$

first-order constant for reactions of benzoyl chloride with excess of amine and solvent, k_{solv} is the first-order rate constant for solvolysis of benzoyl chloride in the absence of added amine, and k_{am} is the second-order rate constant for aminolysis of benzoyl chloride (obtained from the slope of the Figure). We can test the validity of two equations (4) and (5), which have been applied to competing nucleophilic substitutions similar to (1) and (2).

$$\text{rate enhancement} = k_{obs}/k_{solv} = 1 + [PhCONHAr]/[PhCO_2R] \quad (4)$$

$$S = k_{am}/k'_{solv} = [PhCONHAr][ROH]/[PhCO_2R][ArNH_2] \quad (5)$$

$$k'_{solv} = k_{solv}/[ROH] \quad (6)$$

Equation (4) summarises the rate–product correlation,[3a] and accurate predictions require that at least four conditions are met: (i) there is a negligible medium effect of added nitroanilines;[5,6] (ii) the nitroanilines participate solely as nucleophiles, not as base catalysts; (iii) the two nucleophilic substitution reactions are independent *e.g.* extra amide is *not* formed by trapping of an intermediate in the methanolysis reaction in competition with direct substitution; (iv) as the nitroanilines are present in excess their concentrations remain constant so that the molar concentration of amide produced is proportional to $k_{am}[ArNH_2][PhCOCl]$.

Equation (5) is derived from condition (iv) above and from the assumption that the molar concentration of ester or acid produced is proportional to $k'_{solv}[ROH][PhCOCl]$, where $k'_{solv} = k_{solv}/[ROH]$.[3e]

Our interest in equation (5) stems from evidence[3e,4] that the selectivity S may be dependent on the molar concentration of added nucleophile. If the solvolysis reaction were not first order in ROH, an appropriately modified version of equation (5) should still lead to a constant value of S. Equation (5) can also be derived from the trapping of an intermediate by the nucleophile in competition with solvent.[3e] Hence equation (5) may fit reactions that do not show the rate–product correlation predicted by equation (4).

The results in Table 1 support the predictions of equation (4) and demonstrate that, within experimental error, there is a rate–product correlation over a 300-fold range in concentration of added nucleophiles. Hence the observed rate enhancements are consistent with the role of amine as nucleophile, not as base catalyst. The selectivity S [equation (5)] varies from 7.7 to 8.9×10^3 for ten of the eleven values; excluding the anomalous value of 9.9×10^3 the average value of S is 8.3×10^3. Also there appear to be no systematic deviations from equation (5) over the wide range of concentration. If the average value of S were used to calculate the observed percentage amide, four of the

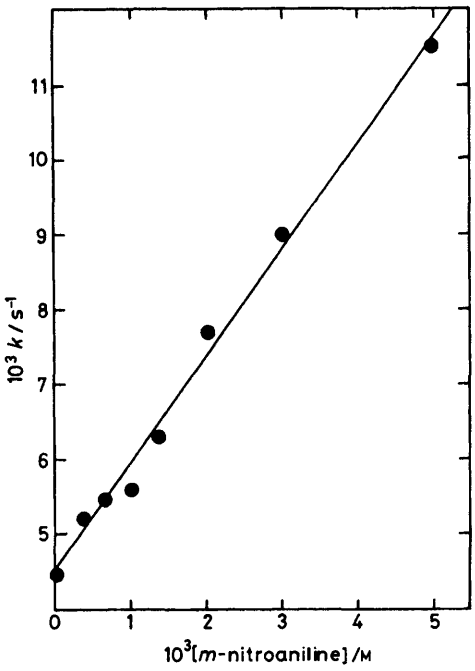

Figure. Observed rate constant (k_{obs}) *versus* initial concentration of *m*-nitroaniline for the first ten entries in Table 1 [slope 1.42 ± 0.05 l mol^{-1} s^{-1} = k_{am} in equation (1); correlation coefficient 0.996]. All 14 entries in Table 1 give k_{am} 1.50 ± 0.03 l mol^{-1} s^{-1}, correlation coefficient 0.997

entries in Table 1 would be 'improved' significantly but four would be worse. Consequently experimental uncertainty in both the rate constants and the product data appears to contribute to the random deviations between the experimentally observed percentage amide and that predicted from equation (4) and the experimentally observed rate constant.

Tables 2 and 3 emphasise product data [equation (5)] but there is also one satisfactory check of equation (4) (see Table 2, footnote *g*). Again S values appear to be constant within experimental uncertainty over a range (7—20) in amine concentration. Reliable results were obtained for very small percentage amide (especially Table 2). The S values in methanol for *o*-nitroaniline are over 10^3 times smaller than for *m*-nitroaniline; in benzene at 25 °C the corresponding reactivity ratio is *ca.* 150.[10] Temperature changes from 25 to 50 °C (Table 2) and variations in [PhCOCl] over ten-fold (Tables 2 and 3) do not appear to affect S significantly. In contrast there is a marked increase in selectivity with temperature changes from 25 to 0 °C for the reactions in acetone–water (Tables 3 and 4). Our average S value of 101 for 50% acetone–water at 0 °C (Table 3) is in good agreement with two of the three independent measurements (Table 4). Taken together these results indicate a constant value of S (within the range 98—106) over a 30-fold variation in amine concentration, whereas the previously published data might have been taken to indicate a variation in S (range 102—122 or more) over only a three-fold variation in amine concentration.

The absence of rate–product correlation for 50% acetone–water (Table 4) has been explained by competing S_N1 and S_N2 mechanisms,[6] or by an ion-pair mechanism.[3b] The former explanation implies to us that S should vary with concentration of added amine. This is because the rate enhancement is attributed to an extra S_N2 pathway giving some amide, with extra amide being formed by trapping a cation in an S_N1 pathway. Each of these two pathways should then have a 'constant S', but the overall S will vary because the relative proportions of S_N2 and S_N1 pathways will vary with amine

concentration. According to this explanation the extra amide formed by the trapping mechanism would be the difference between the experimentally observed value and the value calculated from equation (4). This difference (Table 4) varies from 17 to only 24% over a three-fold variation in amine concentration, *i.e.* S would not be constant for the proposed S_N1 trapping pathway. Mechanistic analysis is, in this case, complicated by the small medium effect on reactivity (7% change in k with 0.08M nitrobenzene[6]).

Conclusions.—Useful mechanistic and kinetic information can be obtained by reversed-phase h.p.l.c. by studying competitive nucleophilic substitution processes over a wide concentration range. The experimental data can be correlated and interpreted with the aid of equations (3)—(5), which may provide mechanistic information both when the experimental data fit these equations and also when there are deviations from these equations.

Experimental

Chemicals.—Benzoyl chloride was quickly shaken with cold 5% sodium hydrogencarbonate solution, dried with $CaCl_2$, distilled at reduced pressure under nitrogen (b.p. 50 °C at 3 mmHg), and stored in a flask fitted with tap adapter and serum cap.[11] The distilled sample was protected from light by Al foil and was shown to contain <0.1% benzoic acid by h.p.l.c. analysis of a methanolysis reaction (<0.02% water in the methanol). Solutions for kinetic and product studies of methanolyses at low concentrations of benzoyl chloride were prepared using microlitre syringes to prepare dilute stock solutions of benzoyl chloride in dry 1.4-dioxane. Methyl benzoate was washed with 5% sodium hydrogencarbonate solution, then with water, dried, and distilled (b.p. 80 °C at 12 mmHg).

The amines (Aldrich) were recrystallised and checked for purity by h.p.l.c.: *o*-nitroaniline, m.p. 71—73 °C (from aqueous methanol) (lit.,[12] 71.5 °C); *m*-nitroaniline, m.p. 112—114 °C (from 30% ethanol–water) (lit.,[12] 114 °C). The corresponding anilides, prepared from the amines and benzoyl chloride in pyridine, were recrystallised and their purity was checked by h.p.l.c.: 2′-nitrobenzanilide, m.p. 93—94 °C (from toluene) (lit.,[12] 98 or 92 °C); 3′-nitrobenzanilide, m.p. 156—158 °C (from light petroleum) (lit.,[12] 157 °C).

Methanol, purified as described previously,[13] gave virtually the same rate constants as commercial dried and distilled (Fisons; 0.01% water). For kinetic work requiring $< 3 \times 10^{-4}$M-benzoyl chloride, the methanol was distilled from soda lime and then from molecular sieves and protected from carbon dioxide.

Kinetic Methods.—Rate constants were determined conductimetrically at least in duplicate by the method recently described in detail.[13] For half-lives > *ca.* 1 min, a Wayne–Kerr model B331 autobalance conductance bridge was used. Calculations were carried out on a Prime 750 computer using the LSKIN first-order kinetics program.[14]

Product Studies.—Solutions of amines in methanol were prepared by accurate dilutions of stock solutions of known concentration. An accurately known volume (±5%) of the benzoyl chloride in dioxane was injected rapidly into the well shaken, thermostatted methanol solution, and product analyses were performed after at least ten half-lives of reaction. The products were shown to be stable to the reaction conditions. All solutions were analysed at least twice (see below) and solutions were usually prepared in duplicate.

Liquid Chromatography.—Qualitative measurements were made on a h.p.l.c. system comprising an Altex 110A solvent metering pump (without pulse dampening), Rheodyne 7125 injection valve (supplied with a 20 μl sample injection loop and fitted with a 0.15 mm bore stainless steel tube for the connection to the column, not the wider bore tubing supplied), a 25 cm × 1/4 in column (5 mm bore), and a Cecil 272 u.v. monitor usually operated at 254 or 270 nm and typically 0.1 A. The recorder was a Servoscribe 541; baselines much better than specification were obtained by leaving the u.v. monitor switched on overnight between periods of daily use. The connection from the end of the column to the 8 μl flow cell in the detector was made with 0.15 mm bore PTFE tubing and the positions of the ferrules were adjusted so that there was negligible dead volume both at the top and the bottom of the column.

The columns (25 cm; Jones Chromatography) were packed with 5 μm Hypersil ODS (*ca.* 3.5 g; Shandon) using the Shandon column packing instrument and the recommended procedure. A check on efficiency and sensitivity was carried out using a standard mixture, at the beginning of each day after the baseline had stabilised. (A detailed guide to care of h.p.l.c. columns has been published.[15]) Column efficiencies (N) were calculated from the peak width at half height of a strongly retained peak. As the usual formula for N makes no allowance for the volume of liquid eluted between injection and detection (*ca.* 3 ml), it is not suitable for peaks of short retention volume. Satisfactory columns had $N > 5\,000$ plates. The qualitative h.p.l.c. system was also used to obtain capacity factors (k') and hence α values for the required separation. Because of the large variation in the relative amounts of each sample and hence large variation in relative peak sizes (band ratio), it was useful to calculate the expected separation from the resolution (R_S) of the two adjacent peaks.[16] At this stage it may have been decided that a new column of greater N was required or that alternative chromatographic conditions were needed. As the equations implied above do not take account of peak broadening at the base due to tailing (the equations idealise the shapes of the peaks as Gaussian), columns with significantly higher than predicted N values were used. (For very large variations in band ratios, incomplete resolution led to integration by peak skimming.)

Quantitative measurements were made on an LDC h.p.l.c. system comprising a Constametric III pump, a Rheodyne 7125 injector, and a Spectromonitor III u.v. detector fitted with a 12 μl flow cell. The baseline noise level was slightly lower than for the Altex system, principally because the noise from the pump was reduced. Peak areas were calculated by electronic integration (LDC 308 or HP 3090A). Standard solutions were prepared to match closely the expected peak ratios of 'unknowns', and relative response factors were obtained from linear calibration graphs.

Eluting solvents were acetonitrile (Fisons h.p.l.c. grade), methanol (Fisons or B.D.H. AnalaR grade), water (distilled and stored in glass apparatus), and acetic acid (AnalaR grade). Solvents were filtered through a Grade 5 sintered disc (down to 2μ) and the solvent was also filtered before it entered the pump (Series 6500 solvent filter; Jones Chromatography). Solvents were degassed by ultrasonic treatment (125 W bath) accompanied by warming.

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