Table II. $t_{1/2}$ (min) for Inactivation by 3*H*-1,3-Oxazine-2,6-diones

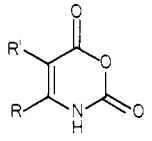
compd	concn, μM	enzyme[a] α-chymotrypsin	enzyme[a] pancreatic elastase
2a	1250	3.5	2.0
	125	85	27
2b	1250	>90	>120
	125	ND[b]	ND[b]
2c	1250	2.3	<1.0
	125	27.5	8.5

[a] Enzymes were incubated and assayed as described in Table I. [b] ND = experiment not done.

results indicate that the species arising from the incubation of α-chymotrypsin with isatoic anhydride or *p*-nitrophenyl anthranilate are equivalent and provide support for the mechanism depicted in Scheme I.

The specificity of **1** for serine and thiol proteases is illustrated in Table I. Incubation of 1250 μM isatoic anhydride with yeast aldehyde dehydrogenase, acetylcholinesterase, creatine kinase, carboxy peptidase A, yeast alcohol dehydrogenase, and pig liver esterase resulted in $t_{1/2}$ for inactivation >25 min. With pancreatic elastase, α-lytic protease, and trypsin, activity returned during the time course of the experiment (<2 h). Only with α-chymotrypsin was the inactivation found to be rapid, stoichiometric, and essentially irreversible.

These results suggested that the simpler 3*H*-1,3-oxazine-2,6-dione ring system (**2**) could also lead to a stable acyl-enzyme.



2a, R = R′ = H
b, R = CH_3; R′ = H
c, R = H; R′ = CH_3

Through modification of the molecule, enhanced selectivity for other serine or thiol proteases might be achieved. Studies in several laboratories have indicated a preference for L-alanine at the p_1 subsite of pancreatic elastase,[5] suggesting that the desired selectivity of action toward pancreatic elastase might be achieved by incorporating a methyl group at C-4 (**2b**) or C-5 (**2c**).

Compounds **2a** and **2b** were prepared from maleic and citraconic anhydride, respectively, by the method of Warren et al.[6] The 5-methyl-3*H*-1,3-oxazine-2,6-dione (**2c**) was prepared by treating citraconimide[7] with sodium hypochlorite as described by Bobek and co-workers.[8]

Table II shows the results obtained with these compounds. These compounds inactivate α-chymotrypsin in a time-dependent process. Inactivation does not proceed as rapidly as with isatoic anhydride, reflecting the enzyme's preference for aromatic residues. Pancreatic elastase was also inactivated. There was no detectable recovery of activity during the course of the experiments, unlike the results with isatoic anhydride. Upon dialysis (0.1 M potassium phosphate, pH 7.5, 48 h, 4 °C), a maximum of 30% recovery of activity with a half-life of approximately 60 h was noted. These results suggest that pancreatic elastase forms a covalent intermediate with **2a**, which hydrolyzes slowly.

A comparison of the results with **2a** and **2c** confirms our hypothesis that the presence of a methyl group enhances the inactivation of pancreatic elastase. The results with **2b** indicate that the orientation of this methyl group, presumably into the hydrophobic pocket, is crucial.

Studies are currently under way to confirm the mechanism of action of these compounds and to expand their specificity to other serine and/or thiol proteases.

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Registry No. 2a, 34314-63-1; **2b**, 51440-82-5; **2c**, 51255-10-8; serine protease, 37259-58-8; isatoic anhydride, 118-48-9; α-chymotrypsin, 9004-07-3; elastase, 9004-06-2; α-lytic protease, 37288-76-9; trypsin, 9002-07-7; papain, 9001-73-4.

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Electronic Absorption Spectra of Polarity-Polarizability Indicators in the Gas Phase

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Most "polarity-polarizability indicators" (PPI) used in solvatochromic studies are polar species,[1-3] sparingly soluble in low polarity-polarizability solvents, and endowed with very small vapor pressures at room temperature. As a consequence, the quantitative analysis of solvent effects on their electronic absorption spectra has long been hampered by the lack of data for these solvents and for the gas phase. This information is of crucial importance in order to unravel the respective contributions from polarity and polarizability effects.[4] Since Brady and Carr[5] have recently succeeded to obtain the UV-visible spectra of a number of PPI's (particularly those used to construct the π* scale of solvent polarity-polarizability[6]) in several perfluorinated solvents, we have decided to meet the most significant challenge left: the determination of gas-phase data.

Here, we report that we have obtained the electronic absorption spectra of the following compounds[7] in the gas phase: 4-nitroanisole (**4**), *N*,*N*-diethyl-4-nitroaniline (**6**), ethyl 4-(dimethylamino)benzoate (**9**), 4-nitroaniline (**14**), ethyl 4-aminobenzoate (**20**), 3-nitroaniline (**28**), 4-nitrophenol (**1b**), and *N*,*N*-dimethyl-3-nitroaniline (**28b**). This was conveniently done by heating a few crystals of these materials at temperatures ranging from 65 to 92 °C in 1-cm silica cells placed in the sample holder of the spectrophotometer.[8] We have also determined the spectra of these compounds in cyclohexane solutions at several temper-

(1) The important solvatochromism of the PPI's is associated with the high polarity of the ground and/or the excited states.[2,3]

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(7) All compounds, except **1b** and **28b**, are numbered as in ref 6.

(8) The measurements were carried out with a Cary 219 spectrophotometer. The slit width was 0.5 nm. The apparatus was cooled by means of a double-loop water circulation at ca. 20 °C while the temperature of the cell holder was kept constant by means of a water circulation provided by a Lauda LS15 ultrathermostat. In all cases, matched 1-cm silica cells fitted with Teflon stoppers were used. In the gas-phase experiments, the cells were allowed to warm for periods of about 1 h before the spectrum was recorded. We also established that the same spectra were obtained when the temperature of the sample was either increased or decreased.

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Table I. Frequencies of the Absorption Maxima for Selected Dipolarity-Polarizability Indicators in the Gas Phase

indicator[a]	$\bar{\nu}_0$[b]	$\bar{\nu}_{gas}$[b,f]	s[c]	π^*_{gas}[d]
1	34.12[c]	36.90[e]	2.410	−1.15
6	27.52[c]	30.39[h,e]	3.182	−0.902
9	33.31[c]	34.84[e]	1.407	−1.07
14	31.10[c]	34.48[e]	3.138	−1.08
20	36.85[c]	38.14[e]	1.297	−0.995
28	28.87[c]	30.90[e]	1.741	−1.17
1b	34.97[c]	37.31[e]	2.171	−1.08
28b	26.18[c]	28.30[e]	2.212[g]	−0.958

[a] Numbered as in ref 6. [b] In kK. [c] See eq 1 and ref 6. [d] Obtained through eq 1; see text. [e] This work. [f] Estimated uncertainty: 0.15 kK. [g] See ref 9. [h] See ref 10.

atures between 25 and 72 °C in order to establish the absence of thermal decomposition and abnormal thermochromism and in "FC 75" (a mixture of the positional isomers of perfluoro-*n*-propyloxane) in order to assess the influence of the medium on the vibrational structure of the spectra. The experimental results are given in Table I. These data can be analyzed in different ways, and in a future paper we shall develop our own approach. Here, we wish to stress the following points:

(1) The gas-phase values, taken together with those from previous works[5,6] on the same PPI's, provide the widest set of medium effects on electronic transitions of polar molecules ever reported.

(2) The PPI's examined herein belong to the family of compounds used to construct the π^* scale. It has been shown[6] that for these indicators, the expression

$$\bar{\nu}_A = \bar{\nu}_0 + s\pi^*_A \quad (1)$$

holds to a high degree of precision. $\bar{\nu}_A$ stands for the wavenumber (in kK) of the near-UV absorption maximum in solvent A; within experimental error, $\bar{\nu}_0$ is the corresponding wavenumber in cyclohexane, taken as a reference ($\pi^*_{c\text{-}C_6H_{12}} = 0$), and s measures the sensitivity of the electronic transition to pority-polarizability effects. Equation 1 can be applied to the above gas-phase data to generate the values for π^*_{gas} given in Table I. Considering the enormous extrapolation involved, the agreement between the different results is quite good, and the average value, $\pi^*_{gas} = -1.06 \pm 0.10$, seems reliable.

(3) To our knowledge, the only scale covering the same range of medium effects hitherto available was Allerhand and Schleyer's G[11a] based on IR frequency shifts. We find that the already reported excellent correlation between π^* and G can be extended to the gas phase. Thus, if hydrogen-bonding acids are excluded, the following expression is obtained:

$$G = 51.52 + 51.53\pi^* \text{ cm}^{-1}$$

with number of points $n = 13$ (including the gas phase),[11b] a correlation coefficient, $r = 0.9941$, and a standard deviation $\sigma = 3$ cm^{-1}. Obviously, the extension of the scale is not detrimental to its correlational power.

(4) Finally, it is important to consider that this method can be applied to a large number of polar compounds having relatively high boiling and melting points. This opens many interesting possibilities in different fields.

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Registry No. 1b, 100-02-7; **4**, 100-17-4; **6**, 2216-15-1; **9**, 10287-53-3; **14**, 100-01-6; **20**, 94-09-7; **28**, 99-09-2; **28b**, 619-31-8.

(9) Estimated from the data for *N,N*-dimethyl-4-nitroaniline (**13**), **14**, **6**, **3**, and *N,N*-diethyl-3-nitroaniline (**2**).

(10) The near-UV spectra of solutions of **6** show a broad, flat maximum. In the gas phase and in FC 75, this maximum is resolved into a doublet. For the sake of consistency with solution data, we have taken $\bar{\nu}_{gas}$(**6**) at the center of the doublet.

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Total Synthesis of (±)-Chorismic Acid[1]

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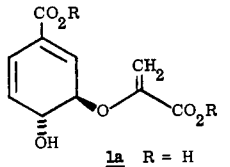
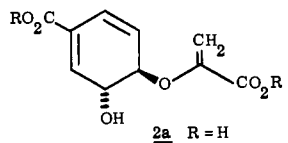
The metabolism of shikimic acid in microorganisms and plants produces an exquisite array of biochemically important natural products.[2] Among them chorismic acid (**1a**) occupies a strategic



1a R = H
1b R = CH_3



2a R = H
2b R = CH_3

position in the shikimate pathway as the key branch point intermediate governing the biosynthesis of aromatic amino acids, isoprenoid quinones, bacterial growth promoters, and other vital compounds.[3] For some time we have been interested in the chemistry of chorismic acid[4] and in processes that affect its metabolism[5] because of the promising potential in this area for designing bacterial and plant growth regulators. We now report an efficient, stereoselective total synthesis[6] of **1a** that is suitable for preparing isotopically labeled material. Its unnatural isomer, pseudochorismic acid **2a**, has also been synthesized to probe the specificity of the enzyme chorismate mutase, which promotes the facile in vivo Claisen rearrangement of **1a**.[2a]

Bicyclic allylic alcohol **3** (Chart I) was prepared in four steps and 35% yield from 1,4-dihydrobenzoic acid.[4a] Protection of the hydroxyl as its MEM ether **4**, saponification, and esterification produced hydroxy ester **8** as a stable oil in 64% yield from **3**.[4b] Attachment of the enol pyruvate side chain proved to be difficult but was eventually achieved in stepwise fashion as follows. Coupling of **8** with dimethyl diazomalonate (1.2 equiv) was smoothly catalyzed by rhodium acetate (C_6H_6, 65 °C, 2.5 h)[7] and afforded alkoxy malonate **9** as a waxy solid (75%, mp 35–37 °C).[8] Heating unpurified **9** in moist benzene with *p*-TsOH hydrolyzed the MEM group and cyclized the malonyl side chain in one operation to bicyclic lactone **10** (mixture of epimers, 35% after flash CC). Attempts to alkylate **10** using Eschenmoser's salt [$CH_2{=}{}^+N(CH_3)_2I^-$][9] with or without triethylamine caused aromatization, probably initiated by iodide attack on the ring. The problem was circumvented by employing Potier's salt [$CH_2{=}{}^+N(CH_3)_2CF_3CO_2^-$],[10] which furnished a 4:1 mixture of Mannich base **11** and methyl *m*-enolpyruvylbenzoate. Quaternization of the amine (FSO_2OCH_3, $CDCl_3$, NMR monitoring) afforded **12**, which could be purified by extraction into H_2O (37% from **10**).

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