desired side of, the barrier between I and Ia.[4] We, therefore, suggested that one might synthesize I by populating the triplet state of II, which lies on the same potential surface as the triplet of I. This approach was made more attractive by the consideration that those triplet states of I which did not decay to ground state I would probably decay to Ia and reopen to II, thus regenerating our starting material. We report the one-step preparation of unsubstituted I *via* the triplet state of II. The product, I, was trapped as the dibromide, III.

Eaton[5] has recently reported the synthesis of a derivative of I, and Wiberg has recently prepared I, itself, by another method.[6]

Solutions of II (0.5–0.74 *M* in ether), to which 0.5 g of Hg was added, were placed in quartz tubes, evacuated and sealed. After irradiation (254 nm) for up to 600 hr at −30°, the tubes were opened and decanted into a flask containing excess Br_2 in ether at 0°. The mixture was slowly (~6 hr) allowed to warm to room temperature. The excess bromine was removed as AgBr. After the inorganic material was removed, a proton nmr spectrum of the organic residue was taken in $CHCl_3$. Most of the peaks in the spectrum could be attributed to bromination products of starting material, II. Indeed, bromination of unreacted II produces a mixture whose proton nmr spectrum contains most of the peaks in that of the irradiated sample. However, a resonance at δ 2.41 appeared in the proton nmr of the irradiated sample that did not appear in that of brominated II. When authentic 1,4-dibromo[2.2.2]bicyclooctane (III), prepared by an established procedure,[7-9] was added to the sample, this peak grew in intensity.

Gas chromatography in a 10% ucon 50 HB 280X column produced a peak with the same retention time as authentic III. Upon addition of III, this peak increased in relative intensity.

Small amounts of the compound corresponding to this peak were trapped using a procedure described elsewhere.[10] The mass spectrum of this compound was shown to be essentially identical with that of authentic III.

Carbon-13 nmr spectra of authentic III showed resonances at −61.5 and −36.5 ppm from TMS. The first of these peaks was also present in the brominated reaction mixture and grew in intensity when authentic II was added, but the second peak was obscured by other stronger resonances. These resonances agree with published spectra of similar compounds.[11]

Mercury sensitization under our conditions is not a very efficient process. The overall yield of I, trapped as III, was only 2–3% after 120 hr and 4–5% after 600 hr irradiation time (as determined by integration of proton nmr spectra). The yield increased with increasing length of irradiation, indicating that the species brominated must have a considerable half-life at −30°. Even after 600 hr of irradiation, the solution remained clear and colorless and no evidence of polymerization was evident. It is, therefore, unlikely that III could be the result of bromination of a diradical such as Ia.

As a control, unirradiated starting material, II, was brominated using the same procedure used for the irradiated reaction mixture (both in the presence and absence of mercury). The peak corresponding to III was absent both from the proton nmr spectrum and the gas chromatogram, indicating that III is not a side product of the bromination of II.

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α-Deuterium Isotope Effect for Displacement of the Nitrate Group

Sir:

The relationship between mechanism and the values of associated α-deuterium effects on the rates of nucleophilic displacement of halides and tosylates is supported by numerous investigations.[1] Maximum values corresponding to limiting mechanisms have been established for the above groups, the relative magnitudes having the order $OTs^- > Cl^- > Br^- > I^-$.[2-5] Fluoride is expected to give a value close to that for the tosylate,[6] but experimental data on these leaving groups are lacking. With one exception[7] no corresponding data giving an estimate of the α-deuterium effect for NO_3^- as a leaving group in solvolytic reactions were available prior to this report. In the course of our investigation of the mechanism of the hydrolysis of certain nitrate esters in water,[8] we have determined the kinetic α-deuterium effects associated with the solvolytic displacement of the nitrate group for a series of benzyl nitrates and isopropyl and cylopentyl nitrates in water. These data are summarized in Table I.

The values of the α-deuterium effects on the rates of the hydrolysis of the corresponding chlorides are included, where available. The α-deuterated nitrate

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Table I. α-Deuterium Effects on the Rates of Solvolysis in Water of Some Nitrates and Chlorides

Substrate	k_H/k_D at (T, °C)	Av k_H/k_D per D atom	Ref
m-Trifluoromethylbenzyl nitrate	0.975 ± 0.002 (70) 0.977 ± 0.002 (91)	0.988	This work
p-Chlorobenzyl chloride	1.006 ± 0.004 (61) 1.065 ± 0.002 (69) 1.052 ± 0.004 (80)	1.030	*a*
p-Chlorobenzyl nitrate	1.251 ± 0.004 (60) 1.252 ± 0.003 (65) 1.250 ± 0.002 (71)	1.119	This work
m-Methoxybenzyl chloride	1.076 ± 0.003 (56)	1.037	*a*
m-Methoxybenzyl nitrate	1.237 ± 0.002 (62) 1.238 ± 0.002 (56) 1.239 ± 0.002 (46)	1.113	This work
Benzyl chloride	1.091 ± 0.002 (54) 1.093 ± 0.002 (64) 1.095 ± 0.002 (70)	1.045	*a*
Benzyl nitrate	1.249 ± 0.003 (50) 1.238 ± 0.003 (64) 1.233 ± 0.003 (75)	1.114	This work
p-Methylbenzyl chloride	1.282 ± 0.002 (20) 1.280 ± 0.003 (31) 1.278 ± 0.002 (41)	1.131	*a*
p-Methylbenzyl nitrate	1.392 ± 0.003 (24) 1.386 ± 0.003 (30) 1.378 ± 0.003 (45)	1.177	This work
o,o'-Dimethylbenzyl nitrate	1.423 ± 0.003 (10) 1.392 ± 0.003 (20) 1.366 ± 0.003 (25)	1.181	This work
Isopropyl nitrate	1.121 ± 0.003 (80) 1.110 ± 0.003 (90)	1.116	This work
Cyclopentyl nitrate	1.188 ± 0.002 (60) 1.185 ± 0.002 (70)	1.187	This work

[a] K. M. Koshy, R. E. Robertson, and W. M. J. Strachan, *Can. J. Chem.*, in press.

esters were prepared *via* the lithium aluminum deuteride reductions of the appropriate precursors;[9] the deuterium content in each case was judged to be better than 99 atom %. Rate measurements were made by a method described previously.[10]

The relative electron-supplying ability of the substituent in the benzyl series is seen to be paralleled by an increase in the value of k_H/k_D both for the nitrates and for the chlorides, consistent with a decrease in the importance of nucleophilic participation by the solvent as the benzylic cation becomes potentially more stable. The inverse value of k_H/k_D found for the *m*-trifluoromethylbenzyl nitrate would indicate a high degree of nucleophilic interaction and a similar value can be expected for the *p*-nitro member of the series. *m*-Methoxybenzyl, *p*-chloro, and the unsubstituted benzyl nitrates as well as isopropyl nitrate show intermediate values consistent with a "borderline" mechanism. The larger values of k_H/k_D found for *p*-methylbenzyl and the *o,o'*-dimethylbenzyl nitrates and for cyclopentyl nitrates suggest that these compounds solvolyze predominately by an ionizing mechanism. However, it is by no means certain that the values found for the latter two compounds hydrolyzing in water are the maximum values for the displacement of the nitrate group, and there is reason to believe that this maximum will be close to that found for groups such as tresylate[4] and tosylate.[5] Thus it would appear that if the bond which is being broken at the transition state is a C–F or a C–O bond, relatively higher values of α-deuterium effects can be expected than in the case of chlorides, bromides, or iodides. That these limiting values of the kinetic α-deuterium effects parallel the relative electronegativities of the atoms in question in the leaving group appears interesting although the reason for this parallelism is not at once clear.

The comparison of the k_H/k_D values found for the nitrates and the corresponding chlorides in the benzyl series, expressed as ratios of the two values, shows an interesting trend (Table II). The suggestion has been made that this ratio for the two leaving groups should tend toward a maximum at the SN1 limit in a series such as benzyl.[1] While reasonable, this prediction is not in accord with the trend apparent in Table II. Where bond making at the transition state is important, the k_H/k_D values in both series will approximate to unity, while toward the opposite end of the reaction spectrum the ratio will tend to a maximum. In the intermediate region it is apparent that in the NO_3^-/Cl^- comparison, the tendency toward a more ionic transition state becomes apparent sooner for displacement of the nitrate

Table II. Comparison of Kinetic α-Deuterium Effect for Nitrate and Chloride Leaving Groups in the Benzyl Series

Substituent	(α-*d* NO_3)/(α-*d* Cl) (per D atom)	Hammett σ
p-Chloro	1.085	0.23
m-Methoxy	1.073	0.12
p-H	1.066	0.00
p-Methyl	1.041	−0.17

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group, as substitution removes the mechanism from limiting SN2 characteristics. An investigation of the heat capacities of activation associated with the hydrolysis of the above compounds in water[8,11] support the conclusion that by and large the transition state for a nitrate is characterized by a higher degree of ionic character compared to the corresponding chloride. A similar trend in the ratio of isotope effects found for α-phenylethyl chlorides[2] can be understood on the basis of the arguments advanced above.

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The Application of Pattern Recognition to Screening Prospective Anticancer Drugs. Adenocarcinoma 755 Biological Activity Test

Sir:

Pattern recognition[1] has been introduced to the chemical literature as a general tool which can be used by the chemist to reduce masses of experimental data to relevant information. Perhaps more importantly, it provides connections between raw, multivariant data and sought-for information without making restrictive assumptions about the underlying statistics of the data. The general problem has been stated as follows. Given a collection of objects and a list of measurements made on each object, is it possible to find and/or predict a property of the objects that is not directly measurable but is known to be related to the measurements *via* some *unknown* relationship? The only assumption made is that similarities and dissimilarities among objects are reflected in at least some of the measurements.

The above stated problem is general indeed, and pattern recognition can and has been used to solve problems in several diverse areas of science and engineering. Of particular interest to chemistry is the somewhat less general problem of learning something about a collection of objects when the objects are chemical compounds and the measurements are physical and/or structural properties of the molecules. Several possibilities exist. A chemist may want to determine the cause of a manufacturing problem by using pattern recognition to detect the discriminatory property or combination of properties between acceptable and unacceptable products. Material problems such as this have been solved by pattern recognition,[2] or, more fundamentally, one might wish to draw a relationship between the structure of a molecule and its activity (reactivity, response, etc.) in some system.

In this communication, a novel example of the latter pattern recognition application is presented. Potential anticancer drugs are screened for their chemotherapeutic activity by applying pattern recognition to 20 selected structural properties (Table I) of 200 drugs previously tested by the National Cancer Institute for activity in the solid tumor Adenocarcinoma 755 (CA 755) screening system.[3] In this test, the drug is administered to small animals with solid tumors, and tumor growth is measured. If the tumor weight inhibition (TWI) is greater than 70%, then the drug is considered positive and reproducible as an antineoplastic agent. Toxic molecules were not included in this study. Of the 200 drugs in this study, 87 had values above 70% and were included in the "positive" category, and 113 had values less than 50% (39 were 0%) and were included in the "negative" category. Some of the drugs in the study are currently in clinical chemotherapeutic use.

Table I. Features Used for the CA 755 Study

Feature no.	Feature	Variance wt	Rank	Correlation
1	Number of oxygens/number of atoms	1.36	9	−
2	Number of phosphorus/number of atoms	0.88	19	−
3	Number of sulfurs/number of atoms	3.99	1	+
4	Number of halogens/number of atoms	1.48	6	+
5	Number of carbons/number of atoms	1.48	5	+
6	Number of C—S bonds/number of carbons	3.86	2	+
7	Number of C=C bonds/number of carbons	1.53	4	+
8	Number of C—N bonds/number of carbons	1.27	12	−
9	Number of C—O bonds/number of carbons	1.39	8	−
10	Number of C=O bonds/number of carbons	1.08	14	−
11	Number of N—H bonds/number of nitrogens	1.34	10	−
12	Number of O—H bonds/number of oxygens	1.29	11	−
13	Number of PO_4 groups	0.88	20	−
14	Number of S—H bonds	2.35	3	+
15	Purine derivative	1.00	16	+
16	Pyrimidine derivative	1.00	17	−
17	Number of oxygens in rings	1.09	13	−
18	Number of nitrogens in rings	1.05	15	+
19	Number of phenyl groups	1.45	7	+
20	Substitution at the primary nitrogen in purine or pyrimidine	0.97	18	−

In order to limit the number of drugs studied in early experiments, it was decided to study a particular class of drugs instead of selecting drugs at random. The purine and pyrimidine nucleoside derivatives form a class of drugs that have produced several drugs of clinical interest. From a summary[3] of compounds in this class, 50 structural properties were extracted from the 200 drugs mentioned above. Preliminary data analysis was performed in order to eliminate several of the structural features from the study. First, 14 features were eliminated because of their scarcity in the 200 structures. Then 16 more were eliminated because they contained little or no useful information relating to biological activity in CA 755 as determined by variance weighting.[1] The remaining 20 structural features used in the study are listed in Table I.

Each of the 20 features was autoscaled[1] for the first stage of preprocessing. Autoscaling weights all of the features equally by producing new variables with zero mean and unit standard deviation. Then, the variance

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