Structure–Hydrolyzability Relationships in a Series of Piperidinyl and Tropinyl Esters with Antimuscarinic Activity

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The hydrolysis of a series of antimuscarinic tropinyl and *N*-methylpiperidinyl esters was investigated in 70% dimethyl sulfoxide (DMSO) (0.1 M NaOH) at 25 °C. The hydrolysis followed pseudo-first order kinetics and the piperidinyl esters were hydrolyzed more rapidly than their tropinyl counterparts. Variation in the acyl (R-CO) moiety of the esters generally affected the hydrolysis of piperidinyl and tropinyl esters in a similar manner, but the orientation of the acyl moiety (axial or equatorial) did not influence the hydrolysis rate. The influence of hydrophobic, electronic and steric factors on the hydrolysis was investigated by using appropriate parameters to represent the hydrophobicity ($\log k_w$), size (molecular volume *MV*) and electronic character (Taft's polar substituent constant σ^* and ^{13}C chemical shift difference $\Delta\delta$ of R) of the esters. These were correlated to the rate constants of hydrolysis (pK_1) by a series of regression equations. It was found that the hydrophobic character of the esters could account for 64% of the observed variation in pK_1. However, a combination of σ^* and molecular volume improved the correlation significantly, with $r=0.94$. The regression equation showed that an increase in the electron-withdrawing character of the acyl group R and a decrease in molecular volume of the ester favored hydrolysis.

Key words ester hydrolysis; structure–hydrolyzability relationship; QSAR parameter; hydrophobicity; molecular volume; electronic parameter

There has been considerable interest in the design and synthesis of muscarinic agonists and antagonists following the discovery in the last decade of various muscarinic receptor subtypes (m_1—m_5), some of which (M_1, M_2, M_3) have been pharmacologically defined.[1] The M_1, M_2 and M_3 muscarinic receptors are involved differently in secretory and cardiovascular functions, smooth muscle control and central nervous system transmission, and this has raised hopes that specific interference with one receptor type might have therapeutically useful consequences.

Several *N*-methylpiperidinyl and tropinyl esters which have been synthesized in our laboratory have been shown to possess potent *in vitro* antimuscarinic activity. Since many of these esters are structurally related to the antimuscarinic agent atropine, their chemical stability is a matter of concern, as aqueous solutions of atropine are unstable at elevated temperatures and high pH.[2] Hydrolytic instability in these compounds would severely limit their potential therapeutic usefulness. Thus, the susceptibility of these esters to chemical hydrolysis has been investigated with the aim of determining the contribution of hydrophobic, steric and electronic factors to the hydrolytic process and the application of this knowledge to the design of related compounds.

Experimental

Materials Sixteen *N*-methylpiperidinyl and tropinyl esters were synthesized (Fig. 1). The *N*-methyl-4-piperidinyl and tropinyl esters of phenylacetic acid (NPA, TPA), 2-phenylpropionic acid (NPP, TPP), diphenylacetic acid (NDPA, TDPA), 2,2-diphenylpropionic acid (NDPP, TDPP), cyclohexylphenylacetic acid (NCPA, TCPA) and 2-cyclohexyl-2-phenylpropionic acid (NCPP, TCPP) were synthesized according to standard methods using the respective acid chlorides and *N*-methyl-4-piperidinol/tropine.[3] The *N*-methyl-4-piperidinyl and tropinyl esters of benzilic acid (NBA, TBA) and cyclohexylphenylglycolic acid (NCPG, TCPG) were synthesized by transesterification using the methyl ester of the respective acids as described by Cannon.[4]

The syntheses of *N*-methyl-4-piperidinyl and tropinyl esters of 2-phenylpropionic acid (NPP, TPP), 2,2-diphenylpropionic acid (NDPP, TDPP), cyclohexylphenylacetic acid (NCPA, TCPA), cyclohexylphenylpropionic acid (NCPP, TCPP) and tropine cyclohexylphenylglycolate (TCPG) have not been previously reported. The identity and purity of these compounds were confirmed by elemental analyses, FT-IR and ^1H-NMR spectroscopy, and the relevant data are presented in Table 1.

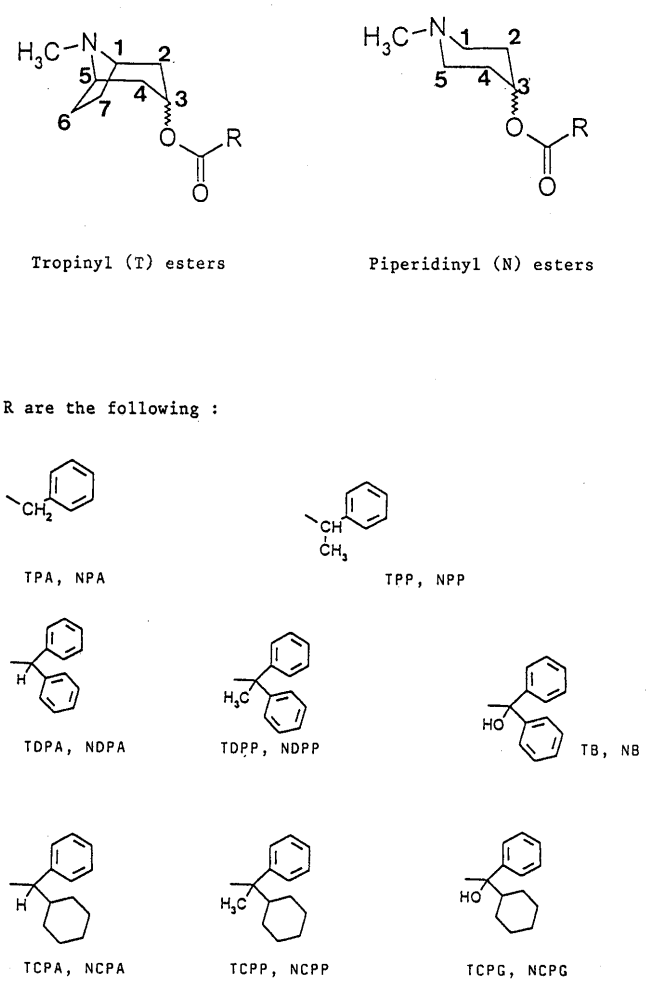

Fig. 1. Structural Formulae of Tropinyl (T) and *N*-Methylpiperidinyl (N) Esters

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Table 1. Physical Data of Synthesized Compounds

Compd.	Method[a]	% yield	mp (°C)[b]	Elemental analysis[c]	Accurate mass[d]	IR (cm^{-1})[e]	^{1}H-NMR (δ ppm)[f]
TPP	A	70	180—183	C, H	273.1728 ($C_{17}H_{23}NO_2$ =273.1729)	1719.08	(CH_3OD) 7.15 (s, 5H, aryl H), 4.89 (t, 1H, C3-H), 3.63 (q, 1H, Ar-CH-CH_3), 3.27—3.30 (m, 2H, C1-H, C5-H), 2.67 (s, 3H, NCH_3), 1.43 (d, 3H, Ar-CH-CH_3)
NPP	A	24	187—189	C, H, N	247.1569 ($C_{15}H_{21}NO_2$ =247.1572)	1721.01	(DMSO-d_6) 7.23—7.36 (m, 5H, aryl H), 4.89 (s, 1H, C4-H), 2.64 (s, 3H, NCH_3), 1.73—3.39 (m, 8H, piperidinyl H), 1.39—1.42 (d, 3H, Ar-CH-CH_3), 1.03—1.10 (q, 1H, Ar-CH-CH_3)
TDPP	A	69	127—129	C, H, N	349.2042 ($C_{23}H_{27}NO_2$ =349.2041)	1713.29	(DMSO-d_6) 7.19—7.40 (m, 10H, aryl H), 5.05—5.06 (t, 1H, C3-H), 3.36—3.48 (m, 2H, C1-H, C5-H), 2.60 (s, 3H, N-CH_3), 1.93 (s, 3H, Ar-C-CH_3), 1.79—2.60 (m, 4H, C6-H, C7-H), 1.06—1.42 (m, 4H, C2-H, C4-H)
NDPP	A	25	128—130	C, H, N	323.1879 ($C_{21}H_{25}NO_2$ =323.1885)	1728.72	(DMSO-d_6) 7.21—7.33 (m, 10H, aryl H), 5.15 (s, 1H, C4-H), 2.63 (s, 3H, NCH_3), 1.72—3.41 (m, 11H, piperidinyl H, Ar-C-CH_3)
TCPA	A	57	210—212	C, H, N	341.2352 ($C_{22}H_{31}NO_2$ =341.2354)	1726.94	(DMSO-d_6) 7.24—7.33 (m, 5H, aryl H), 4.86—4.89 (t, H, C3-H), 2.62 (s, 2H, NCH_3), 0.74—3.76 (m, 22H, tropane and cyclohexy H, CH)
NCPA	A	53	243—246	C, H, N	315.2209 ($C_{20}H_{29}NO_2$ =315.2206)	1724.87	(DMSO-d_6) 7.26—7.33 (m, 5H, aryl H), 4.99 (s, 1H, C4-H), 2.81 (s, 3H, NCH_3), 0.77-3.34 (m, 21H, piperidinyl H, CH)
TCPP	A	57	197—199	C, H	355.2519 ($C_{23}H_{33}NO_2$ =355.2511)	1722.94	(DMSO-d_6) 7.41—7.24 (m, 5H, aryl H), 4.97—4.99 (t, 1H, C3-H), 3.31—3.29 (m, 2H, C1-H, C5-H), 2.69 (s, 3H, NCH_3), 1.53 (s, 3H, Ar-C-CH_3), 2.38—0.93 (m, 19H, cyclohexyl H, C2-H, C4-H, C6-H, C7-H)
NCPP	A	47	226—227	C, H	329.2340 ($C_{21}H_{31}NO_2$ =329.2355)	1721.01	(CH_3OD) 7.45—7.22 (m, 5H, aryl H), 4.96 (s, 1H, C4-H), 3.31—3.20 (m, 4H, C2-H, C6-H), 2.82 (s, 3H, NCH_3), 1.53 (s, 3H, Ar-C-CH_3), 3.31—0.87 (m, 15H, cyclohexyl H, C3-H, C5-H)
TCPG	B	47	143—146	C, H	357.2278 ($C_{22}H_{31}NO_3$ =357.2304)	1728.72	(DMSO-d_6) 7.24—7.56 (m, 5H, aryl H), 4.83—4.86 (t, 1H, C3-H), 3.30—3.32 (m, 2H, C1-H, C5-H), 3.60 (s, 1H, OH), 2.74 (s, 3H, NCH_3), 2.38—0.93 (m, 19H, tropane and cyclohexyl H)

a) A = Reaction between tropine/*N*-methyl-4-piperidinol using acid chloride as reported in reference 3. B = Transesterification using the methyl ester of the acid as described in reference 4. *b*) Melting point was determined for the HCl salt on a Gallenkamp melting point apparatus without correction. *c*) Elemental analyses were done on a Perkin Elmer 2400 Elemental Analyzer and were within 0.4% of the theoretical values. *d*) Accurate mass values were determined on a VG Micromass 7035 E mass spectrometer with chemical ionization. Values in parentheses are theoretical values for the given formula. *e*) IR spectra were obtained from pressed KBr discs of the HCl salts using a Philips PU 9624 FTIR spectrometer. The position of the $\nu_{C=O}$ band of the ester is indicated. *f*) ^{1}H-NMR spectra were recorded on a Bruker ACF (300 MHz) spectrometer and chemical shifts are reported as ppm relative to tetramethylsilane.

Atropine sulfate was purchased from Sigma Chemical Company (St Louis, Mo.). Other reagents used in the hydrophobicity measurements and hydrolysis studies were of analytical grade.

Chemical Hydrolysis of Esters The rate of hydrolysis was determined by quantifying the amount of carboxylic acid formed over time using a Hewlett Packard 1050 HPLC system, equipped with a variable-wavelength detector set at 254 nm and an integrator. Separation was achieved on a Lichrosorb® 10-RP (10 μM) column using methanol–water–acetic acid (79.5 : 20 : 0.5) (pH 3.2) as the mobile phase. The column temperature was maintained at 25 °C, with the flow rate set at 1.0—1.1 ml/min.

An appropriate amount of the ester was weighed out and dissolved in a solution of 1.0 M NaOH (0.1 ml), dimethyl sulfoxide (DMSO) (0.7 ml), internal standard stock solution in methanol (0.01 M, 0.04 ml) and deionized water (0.16 ml) so as to give a final solution which has a substrate concentration of 0.02 M and an NaOH concentration of 0.1 M. The following compounds were used as internal standards: *m*-chlorobenzoic acid (for atropine, TPA, NPA, TPP, NPP), cyclohexylphenylacetic acid (for TB, NB, NCPG, TCPG) and 2-phenylpropionic acid (for TDPA, NDPA, TDPP, NDPP, TCPA, NCPA, TCPP, NCPP). The solutions were incubated at 25 °C in a shaking water bath. Aliquots (0.05 ml) were then withdrawn at appropriate intervals, and the reaction was quenched by addition of 0.45 ml of the mobile phase. An aliquot (20 μl) of the mixture was injected into the column. The ratio of the peak height of carboxylic acid to that of internal standard was noted and the corresponding concentration of acid was determined from the calibration curve for the acid made under similar conditions. All determinations were carried out in triplicate.

Evaluation of Hydrophobicity The hydrophobicity of the esters was assessed from their capacity factors (k') determined by reversed-phase HPLC on a LiChrosorb® RP-18 (10 μM) stationary phase. The mobile phase consisted of varying concentrations of methanol and a buffer (pH 11.9) prepared from 0.05 M sodium acetate, 0.2 M NaCl and 0.05 M triethylamine in deionized water. Determinations were carried out at 25 °C with the flow rate adjusted to 1.0—1.5 ml/min, depending on the mobile phase composition. Detector wavelength was set at 254 nm.

A stock solution of the ester (10 mg/ml) was prepared in methanol. Equal volumes (20 μl) of the stock solution and an acetone stock solution (10% v/v acetone in the mobile phase) were diluted to 200 μl with the mobile phase. An aliquot (20 μl) was injected and the retention time was determined in triplicate for each mobile phase. At least 4 different mobile phase compositions, varying from 50—85% w/w methanol content, were used for each ester. The capacity factor (k') was determined from $\log k' = \log[(V_s - V_o)/V_o]$, where V_s and V_o are the retention volumes (retention time × flow rate) of the ester and acetone (void volume marker), respectively. Linear regression of $\log k'$ of each compound against mobile phase composition and extrapolation to 100% aqueous phase gave $\log k_w$ of each compound at the prevailing pH of 11.9.

Evaluation of Electronic Parameters The electronic effect of R in the acyl moiety R-CO was assessed by indirect and direct methods. In the indirect method, Taft's polar parameter σ^* for R was obtained from the literature[5] and used as a measure of the electronic effect. In the direct method, ^{13}C-NMR spectroscopy was used to determine the chemical shift of the carbonyl carbon, which is known to be sensitive to the electronic influence of the alkyl/aryl moiety. The ^{13}C-NMR spectra of the esters (4 mM in CD_3OD, tetramethylsilane (TMS) as reference) were determined on a Bruker ACF 300 instrument. $\Delta\delta$, which is used to assess the electronic effect of R, is given by

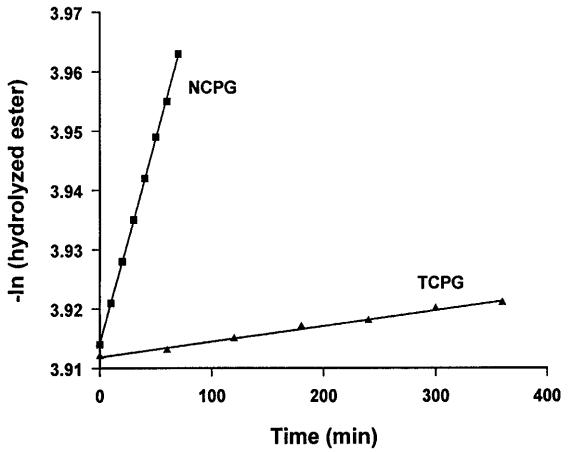

Fig. 2. First-Order Plots for the Hydrolysis of the Cyclohexylphenylglycolate Esters of Tropine (TCPG) and *N*-Methylpiperidine (NCPG) in 70% DMSO (0.1 M NaOH), 25 °C

$$\Delta\delta = \delta_i - \delta_{Me} \quad (1)$$

where δ_i is the chemical shift of the carbonyl carbon of the ester and δ_{Me} is that of the methyl ester of tropine (171.543 ppm) or *N*-methylpiperid-4-ol (170.943 ppm).

Evaluation of Steric Parameters The surface volume of the ester was used as the steric parameter in the present investigation. Surface volumes were determined from the low-energy conformations of the esters obtained by minimization using the SYBYL 6.2[6] Tripos force field (MAXIMIN2); calculation was continued until the r.m.s gradient was less than 0.001 kcal mol^{-1} Å.

Statistical Methods Linear and multiple regression analyses were carried out using SPSS for Windows® (SPSS Inc., Chicago, IL). The following statistical parameters were determined for each regression equation: 95% confidence intervals for the intercept and gradient, the number of points *n*, the correlation coefficient *r*, the significance of the regression model *F* and the standard error S.E.

Results and Discussion

The hydrolysis of the esters in 70% v/v DMSO (0.1 M NaOH) at 25 °C was found to follow pseudo first-order kinetics. The pseudo first-order rate constant (K_1) was obtained from the slope of the plot of $\ln[E_o - X]$ *versus* time t (Eq. 2), where E_o = concentration of ester at time t_o and X is the concentration of acid formed at time t. All plots were linear, with correlation coefficients (r) of not less than 0.992. A representative first-order plot is shown in Fig. 2.

$$\ln[E_o - X] = K_1 t - \ln[E_o] \quad (2)$$

The measured rate constants for hydrolysis (pK_1) of the esters are listed in Table 2. The hydrolyses of NCPP and TCPP were not detected under the present experimental conditions.

As can be seen from Table 2, the piperidinyl esters were more rapidly hydrolyzed (10 to 1000 ×) than their tropinyl counterparts. In keeping with the observations of other investigators,[7,8] variation of the acyl part of the ester affected the hydrolysis rates significantly. It is interesting to note that acyl group variation gave rise to very similar trends for both tropinyl and piperidinyl esters, *viz.* rates decreased in the order phenylacetate > benzilate > phenylpropionate > diphenylacetate > cyclohexylphenylglycolate > cyclohexylphenylacetate > diphenylpropionate > cyclohexylphenylpropionate. An exception was noted for the piperidinyl ester of diphenylacetic acid (NDPA), which was hydrolyzed at a slightly more rapid rate than the phenylpropionate ester (NPP).

Table 2. Values of Rate Constants (pK_1) for Hydrolysis, and Hydrophobic ($\log k_w$), Steric ($\log MV$, Orientation of Acyl Side Chain) and Electronic Parameters (σ^*, $\Delta\delta$) of Tropinyl and *N*-Methylpiperidinyl Esters

Ester	pK_1	σ^*	$\Delta\delta$	$\log k_w$	$\log MV$	Acyl group orientation[a]
TPA	2.38	0.215	0.226	1.55	2.38	A
TPP	3.79	0.105	2.987	1.98	2.40	A
TB	2.41	0.980	2.568	2.41	2.49	A
TDPA	4.04	0.405	1.137	2.94	2.48	A
TDPP	6.49	0.305	3.751	3.04	2.50	E
TCPG	4.58	0.705	3.488	2.46	2.52	A
TCPA	6.34	0.155	2.282	2.89	2.51	A
TCPP	—[b]	0.055	4.161	3.28	2.54	E
NPA	0.41	0.215	0.066	1.36	2.33	A
NPP	1.97	0.105	2.720	1.79	2.36	A
NB	1.10	0.980	1.712	2.01	2.46	A
NDPA	1.88	0.405	2.104	2.47	2.45	A
NDPP	4.58	0.305	2.734	2.69	2.47	A
NCPG	3.15	0.705	2.837	2.26	2.49	A
NCPA	4.50	0.155	2.046	2.68	2.48	E
NCPP	—[b]	0.055	4.811	3.04	2.50	A
Atropine	1.67	—	—	1.28	2.42	A

a) A = axial, E = equatorial. *b*) No hydrolysis was apparent under the present experimental conditions.

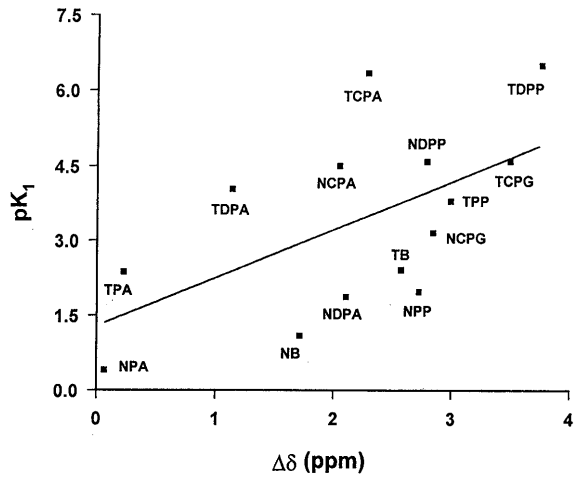

Fig. 3. Plot of the Negative Logarithm of the Hydrolysis Rate Constant (pK_1) *versus* the Chemical Shift Parameter $\Delta\delta$ (Eq. 4, $n = 14$)

Esters with an α-OH group (TB, NB, TCPG, NCPG) were hydrolyzed at faster rates than the corresponding esters with α-H (TDPA, NDPA, TCPA, NCPA). The increase in rate (as much as 100 fold) is particularly marked among the tropinyl esters (TB, TCPG). A possible factor accounting for this rate acceleration is the neighboring group effect of the α-OH function.[9] The proximity of the α-OH group would allow the formation of an intramolecular H-bond between the carbonyl O and OH, which would, in turn, make the carbonyl C more susceptible to nucleophilic (OH^-) attack and, therefore, hydrolysis.

Hydrophobic, steric and electronic parameters have been widely cited as the key parameters influencing the hydrolysis of esters.[10-12] In order to evaluate the relative importance of these factors in the present series of

Table 3. Correlation (r) Matrix for Independent Variables Used in Regression for $n=14$ Esters

	σ^*	$\Delta\delta$	$N-3$	$\log k_w$	$\log MV$
σ^*	1.000	0.159	0.656	0.069	0.455
$\Delta\delta$	0.159	1.000	0.778	0.535	0.578
$N-3$	0.656	0.778	1.000	0.540	0.737
$\log k_w$	0.069	0.535	0.540	1.000	0.864
$\log MV$	0.455	0.578	0.737	0.864	1.000

esters, appropriate parameters representing hydrophobicity ($\log k_w$), size (molecular volume MV) and electronic character (Taft's polar substituent constant σ^* and ^{13}C chemical shift difference $\Delta\delta$) have been determined (Table 2) and correlated to the rates of hydrolysis.

Electronic Character Taft's polar substituent constant σ^* is a measure of the inductive effect of the group R. Base-catalyzed hydrolysis of esters is particularly sensitive to such inductive effects.[5] Thus, an electron-withdrawing R would increase the positive charge on the carbonyl carbon making it more susceptible to nucleophilic attack by OH^-. However, a very poor correlation is obtained when σ^* values of R were regressed against pK_1.

$$pK_1 = -1.60\ (\pm 1.64)\ \sigma^* - 4.06\ (\pm 0.83) \quad (3)$$
$$n=14,\ r=0.27,\ s=1.83,\ F=0.94$$

In view of the poor correlation, the chemical shift difference $\Delta\delta$ was considered as an alternative electronic parameter. Regression of $\Delta\delta$ against pK_1 resulted in an improved correlation (Eq. 4, Fig. 3):

$$pK_1 = 0.96\ (\pm 0.39)\ \Delta\delta + 1.29\ (\pm 0.95) \quad (4)$$
$$n=14,\ r=0.58,\ s=1.55,\ F=6.04$$

Unlike σ^* values, $\Delta\delta$ was determined directly. However, $\Delta\delta$ does not lead to mechanistic insights in the same way as σ^*. This is because the chemical shift difference may result from a complex mixture of electronic and steric factors.[12] In order to establish the various factors contributing to $\Delta\delta$, the latter was regressed against the following parameters: $\log MV$, $\log k_w$, σ^* and $[N-3]$, where N is the number of hyperconjugable α-H atoms in the acyl moiety R-CO. The correlation coefficients of these regressions are given in Table 3.

$\Delta\delta$ is seen to be poorly correlated to σ^* but reasonably well correlated to hydrophobic ($\log k_w$) and size ($\log MV$) parameters. A surprisingly good correlation was found between $\Delta\delta$ and $[N-3]$. Theoretically, the number of α-H in R would determine the extent of stabilization of the reactant relative to the transition state. A large N (maximum 3) would result in greater stabilization of the ester and a slower rate of hydrolysis. The esters TPA, NPA, TDPA and NDPA have one or more α-H in their acyl components and, by this reasoning, should show slower hydrolytic rates. But this was not the case. In fact, their experimentally determined rates were among the fastest observed. Not surprisingly, $[N-3]$ was poorly correlated to pK_1 ($r=0.343$). A possible reason could be the presence of the aromatic rings, which may compete for the delocalized σ electrons from hyperconjugation. As $[N-3]$ is reasonably correlated to several parameters

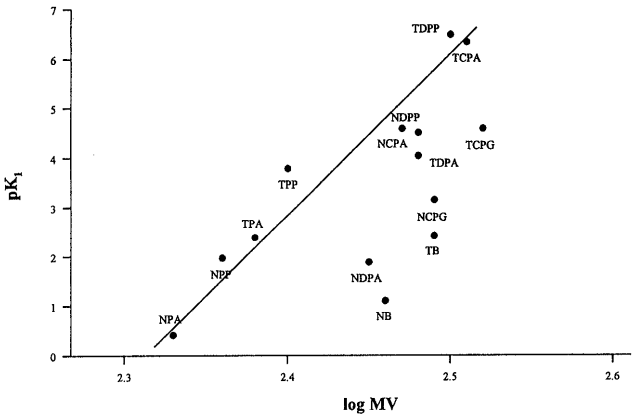

Fig. 4. Plot of the Negative Logarithm of the Hydrolysis Rate Constant (pK_1) *versus* the Logarithm of Molecular Volume ($\log MV$) (Eq. 5, $n=14$)

such as $\Delta\delta$, $\log MV$ and σ^* (Table 3), it is reasonable to assume that it makes an indirect contribution to hydrolysis.

Steric Considerations The rate of hydrolysis of esters has been shown to depend on the size of the acyl (R-CO) moiety.[7,8] A large acyl group would increase steric repulsion in the tetrahedral intermediate of hydrolysis, resulting in a higher energy for the latter and a slower rate of hydrolysis.

For the present series of esters, the axial or equatorial orientation of the acyl group may have some bearing on their rates of hydrolysis. It has been noted that axially oriented steroidal esters are normally hydrolyzed at a slower rate than their equatorial counterparts because of increased steric crowding in the transition state.[13] To see if similar steric considerations apply to the present series of compounds, the axial/equatorial orientation of the acyl moiety in the esters was assessed from the energy-minimized conformations of the esters. This method gives only an approximation of the preferred conformation, which would be better determined by an experimental method.

As shown in Table 2, there is a general preference for the axial orientation among the tropinyl and piperidinyl esters. Thus acyl group orientation is unlikely to contribute to the differences in pK_1.

In this study, the molecular van der Waals volume (MV) of the ester has been used as the steric parameter. Regression of $\log MV$ against pK_1 gave the following equation:

$$pK_1 = 20.49\ (\pm 6.38)\ \log MV - 46.84\ (\pm 15.64) \quad (5)$$
$$n=14,\ r=0.68,\ s=1.40,\ F=10.32$$

Examination of the pK_1 *vs.* $\log MV$ plot reveals that several esters (TB, NB, TDPA, NDPA, TCPG, NCPG) are obvious outliers (Fig. 4). Removal of these esters from the regression analysis resulted in an improved correlation:

$$pK_1 = 28.84\ (\pm 3.36)\ \log MV - 66.27\ (\pm 8.16) \quad (6)$$
$$n=8,\ r=0.96,\ s=0.79,\ F=73.75$$

Equation 5 shows that pK_1 values of approximately half of the investigated esters can be accounted for by their molecular volumes. Large esters such as TCPA are hy-

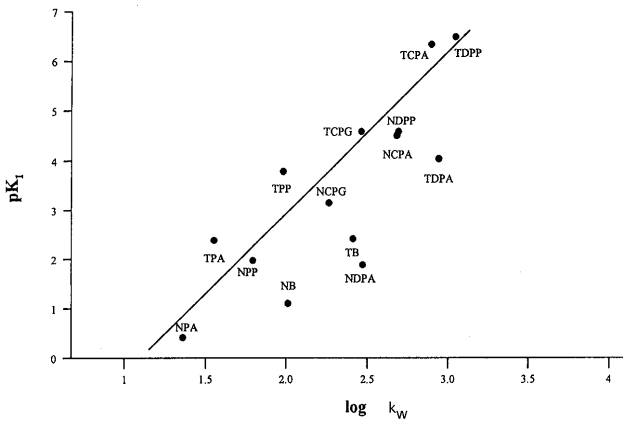

Fig. 5. Plot of the Negative Logarithm of the Hydrolysis Rate Constant (pK_1) *versus* the Logarithm of Capacity Factor at 100% Aqueous Phase ($\log k_w$) (Eq. 7, $n=14$)

drolyzed about 10^4 times more slowly than small esters such as TPA. In the case of the esters classified as outliers, their rates of hydrolysis appear to be faster than would be expected for their size.

Hydrophobicity of Esters The experimentally determined $\log k_w$ values of the esters showed a good correlation to the theoretical $C\log P$ values determined using SYBYL[6] ($r=0.91$). $\log k_w$ values also showed a good correlation ($r=0.86$) to the molecular volumes of the esters (Table 3). This is not unexpected, as the hydrophobicity of a molecule generally increases with size. Thus, increased hydrophobicity in an ester can be expected to slow down its hydrolysis. Besides size considerations, the presence of hydrophobic acyl groups could also slow down hydrolysis by creating a non-polar environment which would hinder the approach of the attacking nucleophile OH^- and thus the formation of the polar transition state. The regression of $\log k_w$ *versus* pK_1 gave the best correlation obtained so far for all 14 esters (Eq. 7):

$$pK_1 = 2.81\ (\pm 0.60)\ \log k_w - 3.13\ (\pm 1.43) \quad (7)$$
$$n=14,\ r=0.80,\ s=1.13,\ F=21.88$$

Inspection of the pK_1 *versus* $\log k_w$ plot (Fig. 5) suggested that omission of some outlying esters (NB, TB, NDPA, TDPA) would improve the correlation, and this was found to be so (Eq. 8):

$$pK_1 = 3.11\ (\pm 0.38)\ \log k_w - 3.25\ (\pm 0.88) \quad (8)$$
$$n=14,\ r=0.95,\ s=0.81,\ F=68.57$$

It is interesting to note that the outlying esters (NB, TB, NDPA, TDPA) are the same esters whose rates correlated poorly with their molecular volumes. In contrast, the pK_1 values of NCPG and TCPG, which were also poorly accounted for by their molecular volumes, now show a good correlation to their hydrophobic character.

Structure–Hydrolyzability Relationships Although $\log k_w$ alone could account for the hydrolytic rates of about two-thirds of the esters (Eq. 7), a better correlation may be obtained if a combination of steric, hydrophobic and electronic parameters is considered in the regression equation. Thus a multiple regression analysis was carried out, using no more than 2 variables for the 14 esters. The regressions of the electronic parameter (σ^* or $\Delta\delta$) and $\log MV/\log k_w$ against pK_1 are given in the following equations:

$$pK_1 = -1.94\ (\pm 0.89)\ \sigma^* + 2.89\ (\pm 0.53)\ \log k_w - 2.52\ (\pm 1.28) \quad (9)$$
$$n=14,\ r=0.86,\ s=0.99,\ F=16.68$$

$$pK_1 = -4.33\ (\pm 0.68)\ \sigma^* + 30.49\ (\pm 3.45)\ \log MV - 69.59\ (\pm 8.35) \quad (10)$$
$$n=14,\ r=0.94,\ s=0.67,\ F=42.43$$

$$pK_1 = 0.35\ (\pm 0.34)\ \Delta\delta + 2.42\ (\pm 0.71)\ \log k_w - 2.99\ (\pm 1.43) \quad (11)$$
$$n=14,\ r=0.82,\ s=1.13,\ F=11.52$$

$$pK_1 = 0.46\ (\pm 0.43)\ \Delta\delta + 15.63\ (\pm 7.76)\ \log MV - 35.95\ (\pm 18.50) \quad (12)$$
$$n=14,\ r=0.72,\ s=1.39,\ F=5.82$$

A combination of hydrophobic and electronic (σ^* or $\Delta\delta$) parameters (Eqs. 9, 11) did not improve the correlation as compared to the hydrophobic parameter alone (Eq. 7). It would appear that the contribution made by the electronic nature of R is minimal and the hydrolytic rates are largely dependent on the hydrophobicity of the esters. In contrast, a combination of the electronic parameter σ^* (but not $\Delta\delta$) and molecular volume resulted in a marked improvement in the correlation (Eq. 10). This is somewhat surprising, as neither parameter has been shown to be significantly correlated to pK_1 (Eqs. 3, 5). Equation 10 shows that an increase in the electron-withdrawing character of R and a decrease in molecular volume of the ester would result in a more rapid rate of hydrolysis.

It has been mentioned that omission of some esters (TB, NB, TCPG, NCPG, TDPA, NCPA) from the regression equation 5 resulted in an improved correlation (Eq. 6). These esters were found to have pK_1 values which were low in relation to their molecular volumes. Interestingly many of these esters, such as TB, NB, TCPG and NCPG, have large σ^* values which indicate strong electron-withdrawing character. Thus, the inclusion of the electronic parameter σ^* in the regression equation brought about an improvement in the correlation. Only the pK_1 values of TDPA and NDPA remain poorly accounted for by the electronic, steric and hydrophobic parameters used in this study.

Conclusions

Hydrophobic, size and electronic characteristics have been considered in the structure–hydrolyzability relationships of a series of piperidinyl and tropinyl esters. Of the observed variance in hydrolysis rates, 88% could be accounted for by the Taft's polar substituent constant σ^* of the acyl R and the molecular volume of the esters (Eq. 10).

With the exceptions of NPA and NB, the piperidinyl and tropinyl esters were found to be more stable than atropine under the present conditions of chemical hydrolysis. It would be of interest to see if these esters are also resistant to metabolic hydrolysis by esterases *in vivo*.

Should such stability be observed, the combination of metabolic stability and potent antimuscarinic activity of some of these esters would make them interesting lead compounds for new drug development.

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