Preparation and Substituent Effect in the Solvolysis of 1-Ethynylcyclopropyl Tosylates

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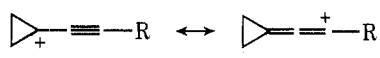
1-(1-propynyl)-, 1-(phenylethynyl)-, and 1-(cyclopropylethynyl)cyclopropyl tosylates **2**, **3**, and **4** have been prepared. Their rates of reaction and the resulting products of solvolysis were determined. The relative rates (k_{rel}) in 50% ethanol (70 °C) follow: **2**, k_{rel} = 1; **3**, k_{rel} = 5.9; and **4**, k_{rel} = 133.4. The kinetic data and the product analysis are consistent with the formation of the stabilized mesomeric cation **1** as intermediate in the solvolysis reactions of 1-(cyclopropylethynyl)cyclopropyl tosylate (**4**).

Upon solvolytic conditions, simple cyclopropyl derivatives usually undergo concerted ionization and disrotatory ring opening into allyl cations.[1] Such a ring opening,[2,3] however, can be prohibited by steric[4] or conjugative interactions;[5] thus 1-cyclopropylcyclopropyl chloride[6] or tosylate[5] leads to partially unrearranged solvolysis products, i.e., 1-cyclopropylcyclopropanols.



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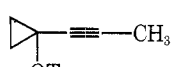
In order to determine the extent to which the mesomeric cation **1** is able to prevent this ring opening by charge delocalization, we are investigating the solvolytic behavior of a variety of substituted 1-ethynylcyclopropyl tosylates; thus, depending on the electron-donating power of the substituent R, a stabilization of the positive charge of **1** can be expected. We report here our initial results with the tosylates **2**, **3**, and **4** and bromide **5**.



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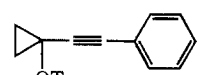

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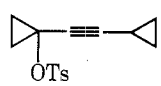

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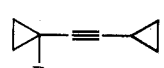

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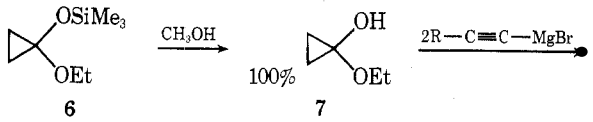
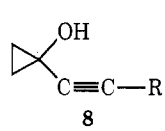
1-Ethoxy-1-trimethylsiloxycyclopropane (**6**), prepared from commercially available ethyl 3-chloropropanoic ester,[7] yielded on simple methanolysis the ethyl hemiketal of the cyclopropanone **7**, which provides a new and more convenient source of this known hemiketal.[8] The reaction of **7**[8] with the suitable acetylenic Grignard reagents led to the 1-alkynylcyclopropanols **8**. The tosylates **2–4** were readily prepared from the cyclopropanols **8** by usual procedures.



6 **7**



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The bromide **5** was prepared from dicyclopropylacetylene as reported by Köbrich.[9]

The reactants **2**, **3**, **4**, and **5** were solvolyzed in 50% aqueous ethanol, buffered with 1.1 equiv of triethylamine in order to avoid any subsequent acid-catalyzed rearrangement of the products.[5] For each run, the products were separated by gas chromatography and their structures unequivocally proven by ir, NMR, and mass spectroscopy (or coupled mass + GC).

As shown in Table I, the products of the solvolysis are strongly dependent upon the nature of the substituent R. The tosylate **2** (R = CH_3) underwent mostly ring opening leading to the allylic alcohol **12**. On the other hand, the tosylate **3** (R = C_6H_5) gave mainly the ethyl ketone **11**, which arose from the well-known homoketonization of cyclopropanols under the conditions used.[3] The tosylate **4** (R = cyclopropyl) is more reactive and underwent very fast the total solvolytic reactions. Direct examination of the NMR spectrum of the crude material shows 81% of the unrearranged alcohol **9** and only 6% of the allylic alcohol **12**. On heating to 100 °C or on gas chromatography it is evident that the ethyl ketone **11** arises exclusively from **9**. There is also a dependency on leaving group: it would seem that the ring opening is less prohibited from the bromide **5**, which yielded 28% of allylic derivatives **11** and **12**, than from the 1-(cyclopropylethynyl)cyclopropyl tosylate **4**, which yielded only 6% of rearranged product.

The solvolysis rates of the tosylates and bromide **2–5**, measured by automatic continuous titration, are given in Table II. They increase with the increasing electron-releasing ability of the substituent R: the tosylate **3** (R = C_6H_5) reacted 5.9 times faster than **2** (R = CH_3). Strongly marked is the stabilization of the electron deficiency by the cyclopropyl group; **4** reacted 133.4 times faster than **2**.

Discussion

Although a carbon–carbon double bond stabilizes an adjacent electron deficiency by allylic resonance, it has been shown that a triple bond is highly destabilizing by a factor greater than 10^3.[10,11]

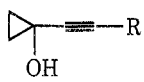
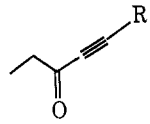
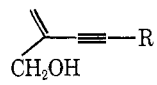
On the other hand, the solvolysis rate data on the cyclopropyl tosylates **14**, **15**, and **16**,[5] shown in Table II, evidence the very large accelerating effect of an *adjacent* cyclopropyl group compared to an isopropyl group or even an allyl group.

14, R = *i*-Pr
15, R = vinyl
16, R = cyclopropyl

The data in Table II show clearly the stabilizing effect of the "substituted triple bond" in the solvolytic transition state. The higher reactivity of the tosylate **4** compared to **2** and **3** reflects in this case the superior efficiency of the cyclopropyl group, particularly relative to the phenyl group,[12] in the stabilization of the electron deficiency.

The generation of the vinyl cations **17**, **18**, and **19** from

Table I. Solvolysis Products (%) of 1-Ethynylcyclopropyl Tosylates 2, 3, and 4 and Bromide 5 Buffered with 1.1 Equiv of Triethylamine in 50% Aqueous Ethanol

Compd	Temp, °C	Reaction time, h	 9	 10	 11	 12	 13	Unknown
2 R = CH_3	100	72				90		10[a]
3 R = C_6H_5	100	72	8	21	62	7	2	
4	60	2	81	9		6		4
R = 	100	0.5		9	81	6		4
5 R =	100	72	4	39	20	21	7	7[b]

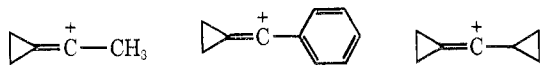
[a] As dimer of 12 from GC + mass spectra. [b] As starting bromide.

Table II. Solvolysis Rates of the Substituted 1-Ethynylcyclopropyl Tosylates and Bromide 2–5 in Aqueous Ethanol

Compd	Solvent[a]	Temp, °C	$k \times 10^4$, s^{-1} [b]	Rel rate 50E, 70 °C	m
2	50E	70.0 ± 0.1	0.141 ± 0.007	1.0	
	50E	75.0	0.230 ± 0.002		
3	50E	70.0	0.838 ± 0.017	5.94	0.60
	50E	75.0	1.320 ± 0.006		
	80E	70.0	0.090 ± 0.003		
4	50E	50.0	2.860 ± 0.015		
	50E	70.0	18.810 ± 0.015	133.40	0.64
	80E	70.0	1.797 ± 0.019		
5	50E	70.0	0.107 ± 0.001		
14[c]	50E	70.0	0.183	1.0	
15[c]	50E	70.0	1.883	10.3	
16[c]	50E	70.0	2 915	15 929	0.77

[a] 50E refers to 50% aqueous ethanol, v/v before mixing. [b] The errors reported were determined by means of a least-squares computer program. [c] From ref 5. At 70 °C, for 2 E_a = 23.38 kcal/mol; for 3, E_a = 21.69 kcal/mol; for 4, E_a = 20.87 kcal/mol.

the solvolytic reaction of the corresponding 1-bromomethylenecyclopropanes was recently reported by Hanack et al.[13]

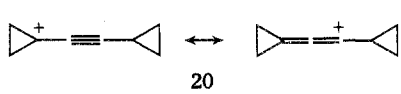


17 18 19

The solvolysis products are dependent upon the substituent in the 1 position of the (bromomethylene)cyclopropane: while 17 rearranges almost completely with formation of the cyclobutane derivatives, 18 and 19 yield mostly the nonrearranged cyclopropyl ketones. The relative solvolysis rates (k_{rel}) for the formation of 17 in 80% aqueous ethanol at 100 °C follow: k_{rel} = 1; for 18 k_{rel} = 2.5; and for 19 k_{rel} = 100.

The similarity of the effect of substituents in the generation of the vinyl cations 17–19 and in the generation of the intermediate ion derived from the tosylates 2–4 (comparison of the results shown in Tables I and II with Hanack's data) would seem to suggest the occurrence of the mesomeric cation 1 in the solvolytic reactions of 1-ethynylcyclopropyl derivatives.

Indeed, the stabilization by an adjacent cyclopropyl group of the vinyl cations 19 and 20 appears clearly of the same order: they both give mostly the nonrearranged derivatives and the rate ratio k cyclopropyl/k methyl is 100 and 133.4, respectively.



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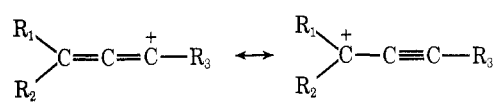
This hypothesis seems to be confirmed by two other findings: the solvent effect and the leaving group effect.

As expected the tosylate 4 solvolyzes faster in solvents of higher ionization strength; e.g., at 70 °C, 4 reacted 10.5 times faster in 50% aqueous ethanol than in 80% ethanol corresponding to a Winstein–Grünwald m value of 0.64. For the mesomeric cation 21 obtained by Schiavelli et al. from triarylhaloallene solvolysis in aqueous acetone at 26 °C an m value of 0.69, highly comparable, was reported;[14a] while for the solvolysis of the cyclopropyl tosylate itself in aqueous ethanol at 25 °C the reported m value is only 0.50.[15]



21

A comparison of the rates of solvolysis of the tosylate 4 and bromide 5 yields a leaving group effect k_{OTs}/k_{Br} = 176; although a direct comparison is not available, it is interesting to note that an element effect k_{Br}/k_{Cl} = 56 was reported for mesomeric cations such as 21.[14b]

Furthermore, the extensive electronic delocalization of mesomeric cations 21 has been recently determined by Olah[16] from ^{13}C NMR chemical shifts; when $R_1 = R_2 = CH_3$ and $R_3 = C_6H_5$ the results indicate that the charge localization at the allenyl end (which is a secondary benzylic vinyl cation) is equal to that of the propargyl end (tertiary carbenium center). It has been noted, however, that the charge distributions are not reflected in the subsequent reactions of such ions, since the nucleophilic attack by the solvent occurs exclusively at the propargylic position.[14,16]

In the mesomeric cation 20, the allenyl cation form is a secondary vinyl cation with an adjacent cyclopropane ring;

it is well established that such carbenium centers are specially favored.[17] Moreover, if, as suggested, methylenecyclopropane and cyclopropyl cation ring strain effects are comparable,[18] then the relative contribution of the allenyl cation form must be important too in **20**. The lack of carbonyl absorption in the ir and of vinylic proton absorption in the NMR spectra of the crude solvolytic products would seem to indicate that the propargylic position is also relatively more reactive in the mesomeric cation **20**. This is understandable if one considers the expected delocalization of the charge at the allenyl end by the adjacent cyclopropane ring.[17]

In conclusion, from all these data, it seems reasonable to consider that the stability of the cation formed from 1-(cyclopropylethynyl)cyclopropyl tosylate **4** solvolysis should be derived chiefly from the delocalization of positive charge over the three-carbon system (see **20**), thereby allowing further delocalization into the two adjacent cyclopropane rings.

Experimental Section

Synthesis of 1-Ethoxycyclopropanol (7). A solution of 17.4 g (0.1 mol) of 1-ethoxy-1-trimethylsiloxycyclopropane[7] in 150 ml of CH_3OH was stirred at room temperature for 8 h. The solvent was removed slowly at room temperature on a rotary evaporator and a short-path distillation yielded 9.5 g (93%) of the pure 1-ethoxycyclopropanol (**7**): bp 59 °C (17 mm) [lit.[8] bp 60–62 °C (20 mm)]; the NMR spectrum was identical with those reported.[19]

1-(1-Propynyl)cyclopropanol (8a, R = CH_3). To 10.9 g (8.15 × 10^{-2} mol) of ethylmagnesium bromide in 100 ml of tetrahydrofuran was added slowly, at 0 °C with stirring, propyne following the known procedure.[20] To propynylmagnesium bromide (8.15 × 10^{-2} mol) was added with stirring at 0 °C 4.15 g (4.08 × 10^{-2} mol) of the hemiketal **7**. The mixture was stirred at room temperature for 3 h and heated under reflux for 2 h. The cold mixture was hydrolyzed and extracted with ether. The organic layer was dried over magnesium sulfate and concentrated to yield a light yellow oil. Distillation at reduced pressure gave 2.95 g (75%) of 1-(1-propynyl)cyclopropanol (**8a**): bp 26–27 °C (0.07 mm); ir (neat) 3090 (ν_{C-H} cyclopropane) and 2240 cm^{-1} ($\nu_{C\equiv C}$); NMR (CCl_4) δ 0.90 (m, 4 H), 1.80 (s, 3 H), 3.90 ppm (s, 1 H); MS M^+ *m/e* (rel intensity) 96 (68), 95 (31), 81 (14), 67 (100), 55 (29).

1-(Phenylethynyl)cyclopropanol (8b, R = C_6H_5). The cyclopropanol **8b** can be prepared analogously to **8a** by the reaction of phenylacetylene magnesium bromide[21] with the hemiketal **7**. After the usual work-up the cyclopropanol **8b** was obtained in 86% yield (liquid): bp 97.5 °C (0.035 mm); ir (neat) 3080 (ν_{C-H}) and 2215 cm^{-1} ($\nu_{C\equiv C}$); NMR (CCl_4) δ 1.10 (m, 4 H), 3.90 (m, 1 H), and 7.25 ppm (m, 5 H); MS M^+ *m/e* (rel intensity) 158 (53), 157 (12), 129 (100), 115 (24), 102 (21), 78 (22), 75 (22), 55 (25).

Synthesis of 1-(Cyclopropylethynyl)cyclopropanol (8c, R = Cyclopropyl). Cyclopropylacetylene. To a stirred mixture of 50 g (0.45 mol) of potassium *tert*-butoxide and 110 g of dimethyl sulfoxide, a solution of 33 g (0.22 mol) of 1-cyclopropyl-1,1-dichloroethane[22] and 20 ml of dimethyl sulfoxide was added at such a rate to maintain the temperature below 40 °C. Then the mixture was stirred at room temperature for 2 h under nitrogen. A Claisen was adapted to the flask immersed in an oil bath at 110 °C and the distillate collected to 80 °C. A careful distillation of the crude material through a spinning band column yielded 6.8 g (94%) of cyclopropylacetylene: bp 52 °C (760 mm) (lit.[23] bp 51.5–52.5 °C); ir (neat) ν_{C-H} 3080 and $\nu_{C\equiv C}$ 2110 cm^{-1}; NMR (CCl_4) δ 0.75 (m, 4 H), 1.30 (m, 1 H), and 1.58–1.6 ppm (d, 1 H).

1-(Cyclopropylethynyl)cyclopropanol (8c). A solution of 8 g (0.121 mol) of cyclopropylacetylene in 15 ml of tetrahydrofuran was added to 15.85 g (0.121 mol) of ethylmagnesium bromide at room temperature with stirring and the mixture was heated to reflux for 2 h.

Then the cyclopropylacetylene magnesium bromide was treated with the hemiketal **7** analogously to the preparation of **8a**. After the usual work-up and removal of the solvent the residue was distilled to give 5.50 g (62%) of 1-(cyclopropylethynyl)cyclopropanol (**8c**): bp 38 °C (0.06 mm); ir (neat) 3090 (ν_{C-H} cyclopropane), 2235 cm^{-1} ($\nu_{C\equiv C}$); NMR (CCl_4) δ 0.55–1.00 (m, 8 H) and 1.10–1.45 ppm (m, 1 H); MS M^+ *m/e* (rel intensity) 122 (75), 93 (31), 91 (56), 79 (100).

1-(1-Propynyl)-1-tosyloxycyclopropane (2). The tosylate **2** was obtained by conventional means through the reaction of the alcohol **8a** with tosyl chloride in pyridine (dried over molecular sieves) at −10 °C. Two recrystallizations from pentane gave the pure 1-(1-propynyl)-1-tosyloxycyclopropane (**2**): mp 48.7 °C; NMR ($CDCl_3$) δ 1.10–1.50 (m, 4 H), 1.60 (s, 3 H), 2.45 (s, 3 H), and 7.30–7.95 ppm (9, 4 H).

Anal. Calcd for $C_{13}H_{14}O_3S$: C, 62.38; H, 5.64; O, 19.17; S, 12.80. Found: C, 61.98; H, 5.65; O, 19.27; S, 12.85.

1-(Phenylethynyl)-1-tosyloxycyclopropane (3). The tosylate **3** was obtained from **8b** and tosyl chloride in pyridine. Two recrystallizations from pentane gave the pure 1-(phenylethynyl)-1-tosyloxycyclopropane (**3**): mp 116.3 °C; NMR (CCl_4) δ 1.15–1.70 (m, 4 H), 2.30 (s, 3 H), and 7.10–7.90 ppm (m, 9 H).

Anal. Calcd for $C_{18}H_{16}O_3S$: C, 69.21; H, 5.16; O, 15.36; S, 10.26. Found: C, 69.33; H, 5.14; O, 15.29; S, 10.16.

1-(Cyclopropylethynyl)-1-tosyloxycyclopropane (4). The tosylate **4** was obtained from **8c** and tosyl chloride in pyridine for 10 days at 0 °C (92%). Two recrystallizations from pentane gave the pure 1-(cyclopropylethynyl)-1-tosyloxycyclopropane (**4**): mp 61.3 °C; NMR (CCl_4) δ 0.35–1.20 (m, 8 H), 1.35–1.70 (m, 1 H), 2.45 (s, 3 H), and 7.20–7.80 (q, 4 H).

Anal. Calcd for $C_{15}H_{16}O_3S$: C, 65.19; H, 5.83; O, 17.36; S, 11.60. Found: C, 64.93; H, 5.92; O, 17.57; S, 11.21.

Description of a Typical Product Analysis. The tosylate **2** (2.50 g, 0.01 mol) was dissolved in 40 ml of EtOH–H_2O (50:50) mixture containing 1.11 g (1.1 equiv) of triethylamine as buffer. The mixture was heated in a sealed tube at 100 °C for 3 days. After cooling the tube was opened and the solvent was removed on a rotary evaporator. The residue mixed with concentrated aqueous NaCl solution was extracted with pentane three times. The pentane extract was dried over $MgSO_4$ and concentrated on a rotary evaporator. The remainder of the pentane phase was worked up by preparative gas chromatography and each product was identified by combined GC and MS analysis.

The other solvolysis reactions were run in the same way under the conditions reported in Table I.

2-Methylene-3-pentyn-1-ol (12, R = CH_3). NMR (CCl_4) δ 1.95 (s, 3 H), 3.95 (m, 2 H), 5.30 (m, 1 H), and 5.40 ppm (m, 1 H); ir (neat) ν_{O-H} 3360, $\nu_{C\equiv C}$ 2220, $\nu_{C=C}$ 1610 cm^{-1}; MS M^+ *m/e* (rel intensity) 96 (92), 95 (52), 81 (100), and 65 (81).

1-Ethoxy-1-(phenylethynyl)cyclopropane (10, R = C_6H_5). NMR (CCl_4) δ 1.00 (m, 4 H), 1.17 (t, 3 H, J = 7 Hz), 3.80 (q, 2 H, J = 7 Hz), and 7.25 ppm (m, 5 H); ir (neat) $\nu_{C\equiv C}$ 2220 cm^{-1}; MS M^+ *m/e* (rel intensity) 186 (0.6), 171 (1), 158 (11), and 129 (100).

1-Phenyl-1-pentyn-3-one[24] (11, R = C_6H_5). NMR (CCl_4) δ 1.18 (t, 3 H, J = 7.5 Hz), 2.60 (q, 2 H, J = 7.5 Hz), and 7.35 ppm (m, 5 H); ir (neat) $\nu_{C\equiv C}$ 2200 and $\nu_{C=O}$ 1670 cm^{-1}; MS M^+ *m/e* (rel intensity) 158 (90), 141 (52), 127 (100), and 115 (31).

2-Methylene-4-phenyl-2-butyn-1-ol (12, R = C_6H_5). NMR (CCl_4) δ 3.92 (m, 2 H), 5.48 (m, 2 H), and 7.20 ppm (m, 5 H); ir ν_{OH} 3420, $\nu_{C\equiv C}$ 2200 cm^{-1}; MS M^+ *m/e* (rel intensity) 158 (100), 129 (79), 128 (53), and 115 (37).

1-Ethoxy-3-methylene-4-phenyl-3-butyne (13, R = C_6H_5). NMR (CCl_4) δ 1.20 (t, 3 H, J = 7.5 Hz), 3.60 (t, 2 H, J = 7.5 Hz), 4.00 (m, 2 H), 5.50 (m, 2 H), and 7.20 ppm (m, 5 H); ir $\nu_{C\equiv C}$ 2200 cm^{-1}; MS M^+ *m/e* (rel intensity) 186 (2), 171 (10), 158 (81), and 157 (100).

1-Ethoxy-1-(cyclopropylethynyl)-1-cyclopropane (10, R = Cyclopropyl). NMR (CCl_4) δ 0.80 (m, 8 H), 1.10 (m, 1 H), 1.20 (t, 3 H), 3.65 (q, 2 H); ir $\nu_{C\equiv C}$ 2220 cm^{-1}; MS M^+ *m/e* (rel intensity) 150 (2), 135 (4), 122 (55), 107 (43), 91 (84), and 79 (100).

1-Cyclopropyl-1-pentyn-3 one (11, R = Cyclopropyl). NMR (CCl_4) δ 0.95 (m, 4 H), 1.10 (t, 3 H), 9.30 (m, 1 H), and 2.40 ppm (q, 2 H); ir (neat) ν_{C-H} 3090, $\nu_{C\equiv C}$ 2200, and $\nu_{C=O}$ 1670 cm^{-1}; MS M^+ *m/e* (rel intensity) 122 (3), 107 (3), 93 (100), and 65 (33).

4-Cyclopropyl-2-methylene-3-butyn-1-ol (12, R = Cyclopropyl). NMR (CCl_4) δ 0.80 (m, 4 H), 1.10 (m, 1 H), 3.90 (m, 2 H), 5.20 (m, 1 H), and 5.35 ppm (m, 1 H); ir (neat) ν_{OH} 3380, ν_{C-H} 3090, $\nu_{C\equiv C}$ 2210, and $\nu_{C=C}$ 1610 cm^{-1}; MS M^+ *m/e* (rel intensity) 122 (10), 121 (9), 106 (12), 91 (25), 79 (100), and 77 (53).

Kinetic Procedures. The solutions used during the kinetic runs were prepared with absolute ethanol and distilled water. The solvolysis rates were measured by means of a Combi titrator 3D (Metrohm AG CH-9100, Herisau, Switzerland).

The pH of the solution was adjusted to 7.00. About 70 ml of the solvent mixture was transferred to the reaction vessel, which was placed in a constant temperature bath adjusted to the appropriate temperature within a range of ±0.1 °C. After the stirred solution had reached thermal equilibrium, about 25 mg (~0.1 mmol) of

reactant (2–5) was added to it. The solvolysis proceeded with continual stirring. The *p*-toluenesulfonic acid (or HBr) liberated during the solvolysis was automatically neutralized with 0.1 N NaOH solution. The titre was registered automatically on a graph, and the data was gathered in such a way that the Guggenheim method[25] could be employed for calculation of the rate constants.

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Registry No.—**2,** 57951-59-4; **3,** 57951-60-7; **4,** 57951-61-8; **5,** 39225-19-9; **6,** 27374-25-0; **7,** 13837-45-1; **8a,** 57951-62-9; **8b,** 57951-63-0; **8c,** 57951-64-1; **10** (R = C_6H_5), 57951-65-2; **10** (R = cyclopropyl), 57951-66-3; **11** (R = C_6H_5), 19307-74-5; **11** (R = cyclopropyl), 57951-67-4; **12** (R = CH_3), 57951-68-5; **12** (R = C_6H_5), 57951-69-6; **12** (R = cyclopropyl), 57951-70-9; **13** (R = C_6H_5), 57951-71-0; propynyl bromide, 2003-82-9; phenylacetylene bromide, 42560-90-7; cyclopropylacetylene, 6746-94-7; 1-cyclopropyl-1,1-dichloroethane, 40459-85-6; cyclopropylacetylene bromide, 57951-72-1; tosyl chloride, 98-59-9.

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Structure–Activity Relationships in Papain–Ligand Interactions

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Quantitative structure–activity relationships have been formulated for two sets of ligands (XC_6H_4O-$COCH_2NHSO_2Me$ and $XC_6H_4OCOCH_2NHCOC_6H_5$) binding to papain. The data of Williams and co-workers are analyzed to show that K_m is correlated with electron withdrawal by inductive-field effect by X and by the polarizability of X as measured by the molar refractivity of X. It is suggested that one part of the ligand interacts with a hydrophobic pocket via desolvation and that a second part binds in a polar area without desolvation.

We have been interested in developing quantitative structure–activity relationships (QSAR) for enzyme–ligand interactions. Our work,[1–4] taken with that of others,[5–9] provides convincing evidence that the use of a multiparameter approach, based on substituent constants and regression analysis, enormously extends one's ability to cast enzymic structure–activity relationships in numerical terms. Early QSAR studies with enzymes often attempted to rationalize substituent effects on enzyme–ligand interactions with the simple Hammett equation, generally by omitting those substituents which were not well fit. More recently, more comprehensive treatments have been based on electronic, steric, and hydrophobic[10] constants for substituents. However, there has been a long-standing interest in the use of polarizability of substituents to rationalize the affinity they impart to a parent molecule for interaction with a biomacromolecule. Pauling and Pressman[11] appear to be the first to have attempted the correlation of binding constants of haptens and antibodies with molar refractivity of substituents. They showed, with certain assumptions, that one could expect a linear relationship between log K and MR where K is an equilibrium binding constant and MR is defined by the Lorentz–Lorenz equation:

$$MR = \frac{n^2 - 1}{n^2 + 2}\frac{MW}{d} \quad (1)$$

In eq 1, n is the refractive index, MW the molecular weight, and d the density of a molecule. MR is an additive property of organic compounds and extensive tables of its values for substituents have been compiled.[12] While Pauling and Pressman did not obtain a high correlation between binding constants of haptens and antibodies (this was later shown to be controlled by steric effects of substituents),[13] their basic idea appears sound.

We have found two parameters (π and MR) in our studies of QSAR of enzymes for nonspecific interactions of substituents to be necessary to correlation work. A large amount of evidence has accumulated to establish the importance of hydrophobic regions in enzymes and log P or π (from octanol–water partition coefficients)[14] appear to correlate substituent interactions in these regions.[1–10]

One must also consider the "other space" which is not hydrophobic. This nonhydrophobic space must be polar in nature; hence, one would not expect desolvation of a substituent interacting with such space to play an important role in the interaction. Pauling and Pressman envisioned