The Reactivity of 2-Substituted Cyclohex-1-enecarboxylic Acid With Diazodiphenylmethane in Various Alcohols

Gordana S. Uščumlić, Vera V. Krstić and Milan D. Muškatirović
Department of Organic Chemistry, Faculty of Technology and Metallurgy of Beograd, Karnegijeva 4, P.O. Box 494, YU-11000 Belgrade, Yugoslavia

The reactivities of 2-substituted cyclohex-1-enecarboxylic acids with diazodiphenylmethane in several alcohols were investigated. The rate data for these acids were correlated with a simple Hammett equation by means of the σ_p constants. The transmission of polar effects through the double bond, in terms of polar susceptibility constant ρ, has been discussed. For the reactions of a given acid in the various alcohols, the log *k* and ρ values were correlated through multiple regression on appropriate solvent parameters. The results obtained for 2-substituted cyclohex-1-enecarboxylic acids were compared with the results for *ortho*-substituted benzoic acids under the same experimental conditions.

In connection with our study of the transmission of polar effects through the double bond, we now in this paper extend our previous work[1,2] on the reactivity of α,β-unsaturated carboxylic acids to their reaction with diazodiphenylmethane (DDM) in ethanol.

The transmission of substituent effects through three types of double bonds: in a ring, open chain, and delocalized double bonds, were previously investigated in the case of 2-substituted cyclohex-1-enecarboxylic acids,[1] (*Z*)- and (*E*)-3-substituted acrylic acids[3,4] and *ortho*-substituted benzoic acids[5,6] reacting with DDM in ethanol.

Bowden[3] has previously studied the reactivity of both (*Z*)- and (*E*)-3-substituted acrylic acids in their reaction with DDM in three solvents and their ionization in water. The effect of substitution was assessed by use of linear free energy relations and the results obtained were compared with the results for *ortho*-substituted benzoic acids.[6] Bowden has shown that the polar effect of a substituent is found to be approximately the same from the *cis*- or *trans*-position and that the transmission of the polar effect in 3-substituted acrylic acids and *ortho*-substituted benzoic acids is twice that of the *meta*- or *para*-substituted benzoic acids.[3]

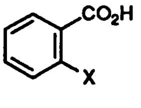
In our previous work[1] the reactivity of 2-substituted cyclohex-1-enecarboxylic acids with DDM in ethanol was investigated. The rate data for these acids were correlated with a simple Hammett equation by means of σ_p constants and with the extended Hammett equation to detect the presence or absence of steric effects as well as the composition of the electronic effect. The results obtained for 2-substituted cyclohex-1-enecarboxylic acids were compared with the results for (*Z*)-and (*E*)-3-substituted acrylic acids[3] and *ortho*-substituted benzoic acids[6] under the same experimental conditions. The results have shown that there are small differences in the composition of the electronic effect depending on the type of double bond through which the effects are transmitted. Starting from the assumption of similarity in the polar interaction of the substituents with the reaction centre and proximity effects, these differences were ascribed to the different polarizability of the investigated double bonds.

The identical ρ values obtained for 2-substituted cyclohex-1-enecarboxylic acids (ρ = 1.672) and (*E*)-3-substituted acrylic acids (ρ = 1.671) and the similar values of reaction constants for (*Z*)-3-substituted acrylic acids (ρ = 1.772) and *o*-substituted benzoic acids (ρ = 1.889) suggests the same mode for the transmission of the electronic effect in these systems.[1]

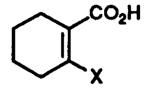
The previous results of the correlations of the rate data for the reaction of 2-substituted cyclohex-1-enecarboxylic acids with DDM in ethanol, by the extended Hammett equation, have shown that this reaction is free of steric interaction. The composition of the electronic effect showed the importance of a resonance effect.[1]

In the present work rate coefficients have been measured for the reactions at 30 °C of the 2-substituted cyclohex-1-enecarboxylic acids with DDM in eight different alcohols. The solvent effect was interpreted in terms of the influence of the relative permittivity on log *k* and on polar susceptibility constant σ. The second-order rate constants for the reaction of 2-substituted cyclohex-1-enecarboxylic acids with DDM were obtained by studying substituents of moderate steric bulkiness, *i.e.* in the absence of secondary steric effect which could cause deconjugation of carboxyl group and cyclohex-1-ene ring.

According to structural analogy between *ortho*-benzoic (**1**) and cyclohex-1-ene (**2**) systems it seemed of interest to compare the results of the reaction of these acids with DDM under the same experimental conditions and with identical substituents.



1



2

X = H, CH_3, C_2H_5, Cl, Br, I

Results and Discussion

Values of second-order rate coefficients for the reaction of 2-substituted cyclohex-1-enecarboxylic acids with DDM in various alcohols at 30 °C are given in Table 1. The results obtained show that the rate constants increased with increasing polarity of the solvent. This is in accordance with the proposed mechanism of the reaction.

When values of log *k* for the cyclohex-1-enecarboxylic acids (Table 1) are correlated with the corresponding values for the reactions of benzoic acids[7] with DDM at 30 °C (Fig. 1) the results conform to the linear free energy relationship eqn. (1).

$$\log k_{(\text{benzoic acid})} = 0.496 + 1.353 \log k_{(\text{cyclohex-1-enecarboxylic acid})} \quad (1)$$

(Correlation coefficient *r* = 0.9689 and standard deviation of the estimate s = 0.034).

Table 1 Rate coefficients (dm^3 mol^{-1} min^{-1}) for the reaction of 2-substituted cyclohex-1-enecarboxylic acids with DDM in various alcohols

Substituent	Methanol	Ethanol	Propan-1-ol	2-Methyl-propan-1-ol	Butan-2-ol	2-Methoxy-ethanol	Cyclo pentanol	Pentan-1-ol
H	0.817	0.417	0.503	0.582	0.339	0.327	0.349	0.319
CH_3	0.567	0.264	0.305	0.417	0.239	0.142	0.198	0.178
C_2H_5	0.583	0.278	0.328	0.462	0.248	0.192	0.240	0.199
Cl	2.244	1.130	1.395	1.785	1.028	0.846	1.090	0.994
Br	2.321	1.279	1.512	2.160	0.169	0.950	1.112	1.046
I	2.614	1.470	1.732	2.456	1.356	1.185	1.328	1.316

Table 2 Solvent parameters for alcohols

Solvent	ε_r ^{a}	σ^{*b}	$n_{\gamma H}$ ^{c}
Methanol	32.70	0.00	0
Ethanol	24.55	−0.10	0
Propan-1-ol	20.33	−0.115	3
2-Methylpropan-1-ol	17.93	−0.125	6
Butan-2-ol	16.56	−0.210	3
Cyclopentan	15.80	−0.150	0
Pentan-1-ol	13.90	−0.135	3

^{a} Relative permittivity at 30 °C. ^{b} Polar substituent constant of alkyl group. ^{c} Number of γ-hydrogen atoms.

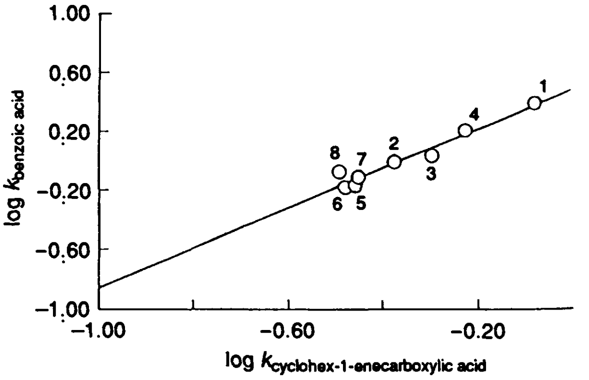


Fig. 1 Plot of log *k* for cyclohex-1-enecarboxylic acid *vs.* log *k* for *ortho*-benzoic acid. 1, Methanol; 2, ethanol; 3, propan-1-ol; 4, 2-methylpropan-1-ol; 5, butan-2-ol; 6, 2-methoxyethanol; 7, cyclopentanol; 8, pentan-1-ol.

This relationship shows that the same solvent properties act on the reactions of the two acids in the various alcohols, and the influence of a given property in one reaction is proportional to its influence in the other.

Our previous investigations of the reactivity of α,β-unsaturated carboxylic acids with DDM in various solvents[8] and earlier work of Chapman *et al.*[9] have established that the solvent effect is best interpreted in terms of the following properties: (a) the behaviour of the solvent as a dielectric in facilitating the separation of opposite charges in the formation of the activated complex; (b) the ability of the medium to solvate the carboxylic proton; (c) the ability of a protic solvent to form a hydrogen bond with the negative end of an ion-pair. Both (b) and (c) stabilize the transition state relative to the initial state. The Kirkwood function[10] of the relative permittivity ε_r, $f(\varepsilon_r) = (\varepsilon_r - 1)/(2\,\varepsilon_r + 1)$ is a suitable measure of (a), while (b) and (c) together are governed mainly by the polar effect of the alkyl group of the alcohol, appropriately measured by the Taft polar substituent constant σ^*.[11] Steric moderation of (b) also occurs, and this is suitably measured by $n_{\gamma H}$, the number of γ-hydrogen atoms in the alcohol.

Solvent parameters are shown in Table 2. Multiple linear regression of log *k* for cyclohex-1-enecarboxylic acid with $f(\varepsilon_r)$, σ^* and $n_{\gamma H}$ gives expression (2) with the multiple correlation

$$\log k = -2.922 + 5.911\,f(\varepsilon_r) + 1.797\,\sigma^* + 0.032\,n_{\gamma H} \qquad (2)$$
$$(\pm 2.928) \quad (\pm 0.451) \quad (\pm 0.010)$$

coefficient $R = 0.9400$ and the standard deviation of the estimate, s = 0.0515.

The corresponding expression for benzoic acid reacting with DDM in the same series of alcohols is eqn. (3), with $R = 0.9706$ and s = 0.0495.

$$\log k = -1.508 + 3.936\,f(\varepsilon_r) + 3.034\,\sigma^* + 0.043\,n_{\gamma H} \qquad (3)$$
$$(\pm 2.816) \quad (\pm 0.433) \quad (\pm 0.0098)$$

Chapman and his coworkers[9] have presented correlation analyses of second-order rate constants for the reactions of *ortho*-substituted benzoic acids with diazodiphenylmethane in 10 different alcohols at 30 °C by eqn. (4):

$$\log k = -1.555 + 4.075\,f(\varepsilon_r) + 3.185\,\sigma^* + 0.050\,n_{\gamma H} \qquad (4)$$
$$(\pm 0.520) \quad (\pm 0.101) \quad (\pm 0.007)$$
$$R = 0.998 \qquad s = 0.038$$

All regression analyses in the work were carried out with the ICL Statistic Analysis Package Mark 2XDS3. All the above correlations are significant between 99% and 99.9% confidence limits.

Eqns. (2) and (3) show that the cyclohex-1-enecarboxylic acid system is more sensitive to relative permittivity (ε_r) changes than the benzoic system. The cyclohex-1-ene system is also less sensitive to Taft polar substituent constant σ^* changes than the benzoic system. This is confirmed by the smaller coefficient of $f(\varepsilon_r)$ and by the larger coefficient of σ^* in eqn. (3).

The data from Table 1 have been correlated with the simple Hammett equation by means of σ_p constants[12] and the reaction constants ρ have been determined. The results are shown in Table 3 together with the literature data for the *ortho*-substituted benzoic acids[7] obtained under the same experimental conditions.

Charton has previously correlated a number of reactions of *ortho*-substituted systems using *para*-σ values.[13] Our study of the application of the Hammett equation to the 2-substituted cyclohex-1-ene series has shown that in these series the σ_p constants provide an adequate representation of the electronic effects of *ortho*-substituents.

The higher values of the reaction constants for *ortho*-substituted benzoic acids rather than 2-substituted cyclohex-1-enecarboxylic acids in all investigated solvents (Table 3) have shown that the susceptibility to polar effects of substituents is greater for the *ortho*-benzene than for the 2-substituted cyclohex-1-ene systems.

The ratio ρ/ρ_0 has been used to evaluate the transmission of electronic effects by relevant groups, where ρ_0 is the reaction constant of the reference system (*p*-substituted benzoic acids)[14] at the same temperature and the same solvent. These ratios are given in Table 4.

Table 3 Hammett reaction constants

	2-Substituted cyclohex-1-enecarboxylic acids			*Ortho*-substituted benzoic acids		
Solvent	ρ_1	r^a	n^b	ρ_1	r^a	n^b
Methanol	1.545	0.992	6	1.956	0.948	6
Ethanol	1.687	0.994	6	1.984	0.958	6
Propan-1-ol	1.710	0.996	6	—	—	6
2-Methylpropan-1-ol	1.729	0.983	6	2.021	0.963	6
Buthan-2-ol	1.723	0.988	6	2.183	0.966	6
2-Methoxyethanol	1.908	0.996	6	2.050	0.983	6
Cyclopentan	1.825	0.995	6	2.064	0.975	6
Pentan-1-ol	1.922	0.996	6	2.024	0.970	6

[a] Correlation coefficient. [b] Number of substituents studied.

Table 4 Ratio of reaction constants ρ/ρ_0

Solvent	2-Substituted cyclohex-1-ene carboxylic acids	*Ortho*-substituted benzoic acids
Methanol	1.747	2.212
Ethanol	1.787	2.101
Propan-1-ol	1.729	—
2-Methylpropan-1-ol	1.849	2.161
2-Methoxyethanol	1.617	1.737

Starting from the assumption of similarity in the transmitting cavities for the 2-substituted cyclohex-1-ene and *ortho*-benzoic acids the differences in the transmission of substituent effects through the benzene ring and the double bond in the cyclohexene ring were ascribed to the different polarizability of the investigated double bonds. The double bond in the ring is less polarizable than the benzene ring.

The results given in Table 3 have shown that the ρ values are decreased by increasing the relative permittivity. This may be interpreted in two ways. Firstly the transmission of the polar effects of the substituents through the medium increases in importance relative to transmission through the molecular cavity as ε_r is decreased. Secondly, at high relative permittivities the energy necessary to bring about the charge separation in the transition state is relatively small, and this gives rise to a low susceptibility to the polar effects of substituents. The ρ value thus increases as the energy necessary to achieve the charge separation increases as ε is decreased. It is thus reasonable to correlate ρ_1 and ρ_2 with $f(\varepsilon_r)$, σ^* and $n_{\gamma H}$ as for log *k*. For the 2-substituted cyclohex-1-enecarboxylic acids eqn. (5) holds

$$\rho_1 = 7.493 - \underset{(\pm 1.696)}{12.447 f(\varepsilon_r)} - \underset{(\pm 0.262)}{0.047\sigma^*} - \underset{(0.006)}{0.008 n_{\gamma H}} \quad (5)$$

with $R = 0.9789$ and $s = 0.029$ and for *ortho*-substituted benzoic acids eqn. (6) with $R = 0.8623$ and $s = 0.0468$.

$$\rho = 0.542 + \underset{(\pm 2.708)}{2.209 f(\varepsilon_r)} - \underset{(\pm 0.418)}{1.316\sigma^*} - \underset{(\pm 0.0095)}{0.0006 n_{\gamma H}} \quad (6)$$

Eqns. (5) and (6) show that the 2-substituted cyclohex-1-ene carboxylic acid system is more sensitive to solvent changes than the *ortho*-substituted benzoic system. The relative values of the coefficients of $f(\varepsilon_r)$ in eqns. (2) and (3) compared with the corresponding values in (5) and (6) show that the dielectric term plays a relatively more important role in governing ρ than it does in governing log *k* for the parent acid.

On the basis of all the information presented, it may be concluded that linear free energy relationships are applicable to kinetic data for 2-substituted cyclohex-1-ene systems. The solvent effect on the cyclohex-1-enecarboxylic acid is proportional to its influence on the benzoic acid. Multiple linear correlation with three suitable solvent parameters $f(\varepsilon_r)$, σ^* and $n_{\gamma H}$ is quite successful. Comparisons are made with the *ortho*-substituted benzoic acid system. The ratio ρ/ρ_0 has shown that the double bond in the cyclohexene ring is less polarizable than the benzene ring.

Experimental

Materials.—2-Substituted cyclohex-1-enecarboxylic acids were prepared by the method of Wheeler and Lerner[15] from corresponding 2-substituted cyclohexanone cyanohydrin which was dehydrated to 2-substituted 1-cyanocyclohexene. The nitrile was hydrolysed with phosphoric acid to the corresponding 2-substituted cyclohex-1-ene carboxylic acids. The yields and other data for these acids are presented in Table 5. The preparation of the corresponding substituted ketones is presented separately. IR, UV and ^{1}H NMR spectra were determined for all prepared acids. Cyclohexanone and 2-methylcyclohexanone were commercially available (Fluka).

2-*Ethylcyclohexanone.* This ketone was prepared by the procedure described for 2-phenylcyclohexanone.[16] A solution of 32 g of 2-chlorocyclohexanone in 80 cm^3 of diethyl ether was added slowly with stirring to an ice solution of the Grignard reagent prepared from 141 g of ethylbromide and 28 g of magnesium in 250 cm^3 of ether. After one half the ether had been removed by distillation, 100 cm^3 of benzene was added and the mixture was refluxed for two h, and then hydrolysed with an ice cold solution of ammonium chloride. The ketone was distilled at 73 °C at 17 mmHg, n_D^{20} = 1.4488 [Ref. 17. b.p. 67 °C (13 mmHg), n_D^{20} = 1.4528].

2-*Chlorocyclohexanone.* The ketone was prepared by chlorination of cyclohexanone according to the usual procedure,[18] b.p. 90–91 °C at 14–15 mmHg [Ref. 18. b.p. 67 °C (13 mmHg), n_D^{16} = 1.4528].

2-*Bromocyclohexanone.* A mixture of 60 g of cyclohexanone, 40 cm^3 of water and 30 g of CaCO$_3$ was stirred continually and bromine was added dropwise over 1 h. The crude product was then extracted with ether, the solvent was removed and the ketone was distilled at 95–105 °C (17 mmHg) [Ref. 19. b.p. 95–105 °C (22 mmHg)].

2-*Iodocyclohexanone.* This ketone was prepared by the method of Cantacuzene *et al.*[20] from *trans*-2-iodocyclohexanol which was prepared by the method of Winstein.[21] A solution of 1.1 g of CrO$_3$ in 28 cm^3 of acetic acid was added slowly with stirring to solution of 2.26 g 2-iodocyclohexanol in 25 cm^3 of acetic acid over 4 h at 20 °C. The crude product was then extracted with CCl$_4$, the solvent was removed at −10 °C and the ketone was distilled at 28 °C (0.5 mm) [Ref. 22. b.p. 54 °C (1 mmHg)].

Diazodiphenylmethane was prepared by Smith and Howard's

Table 5 Summary of physical data for 2-substituted cyclohex-1-enecarboxylic acids

Substituent	Melting point/°C Obsd.	Melting point/°C Lit.	Yield %	Solvent
H	38	37[a]	80	pentane
CH_3	85–87	87[b]	80	methanol–water
C_2H_5	71	71–72[b]	60	methanol–water
Cl	104	105–106[b]	40	methanol–water
Br	110	—	30	methanol–water
I	121–122	—	30	methanol–water

[a] Ref. 23. [b] Ref. 24. [c] Solvent for purification.

method.[25] Stock solutions of *ca.* 0.06 mol dm^{-3} were stored in a refrigerator and diluted before use. Commercial absolute ethyl alcohol was treated with metallic sodium by the Smith method.[26] Methanol was purified by Lund and Bjerrum's method.[27] Propan-1-ol was dried by methods analogous to Smith's method for ethanol, by using sodium and the appropriate dialkyl phthalate.

2-Methoxyethanol was kept over freshly ignited potassium carbonate for some days and then treated with molecular sieve for at least three days. The solvent was then distilled under reduced pressure.

Cyclopentanol and pentan-1-ol were dried (K_2CO_3) for several days and then over molecular sieve (Linde type 4Å) for three days before fractional distillation under reduced pressure. All the solvents used for kinetic studies were examined by GLC and no impurities were detected.

Kinetic Measurements.—Second-order rate constants k_2, for the reaction of 2-substituted cyclohex-1-enecarboxylic acids with DDM were determined as previously reported by spectroscopic method of Roberts and his coworkers[28] using Unicam SP 600 spectrophotometer. Optical density measurements were performed at 525 nm with 1 cm cells at 30 ± 0.05 °C.

The second-order rate constants for all investigated compounds were obtained by dividing the pseudo-first-order rate constants by the acid concentration (the concentration of acid was 0.06 mol dm^{-3} and of DDM 0.006 mol dm^{-3}). Three to five rate determinations were made on each acid and in every case the individual second-order rate constants agreed to within 3% of the mean.

Acknowledgements

The authors acknowledge the financial support of the Research Fund of Serbia, Belgrade.

References

1 G. S. Uščumlić, V. V. Krstić and M. D. Muškatirović, *J. Serb. Chem. Soc.*, 1989, **54** (3), 119.
2 G. S. Uščumlić, V. V. Krstić and M. D. Muškatirović, *Quant. Struct.-Act. Relat.*, 1991, **10**, 216.
3 K. Bowden, *Can. J. Chem.*, 1965, **43**, 3354.
4 M. Charton, *J. Org. Chem.*, 1965, **30**, 974.
5 M. Charton, *Can. J. Chem.*, 1960, **38**, 2493.
6 N. B. Chapman, J. Shorter and J. H. P. Utley, *J. Chem. Soc.*, 1962, 1824.
7 M. H. Aslam, A. G. Burden, N. B. Chapman, J. Shorter and M. Charton, *J. Chem. Soc., Perkin Trans. 2*, 1981, 500.
8 G. S. Uščumlić and M. D. Muškatirović, *J. Serb. Chem. Soc.*, 1991, **56** (2), 707.
9 N. B. Chapman, D. Newman and J. Shorter, *J. Chem. Soc. B*, 1976, 847.
10 J. G. Kirkwood, *J. Chem. Phys.*, 1934, **2**, 351.
11 R. W. Taft in *Steric Effects in Organic Chemistry*, ed. M. Newman, Wiley, New York, 1956, p. 13.
12 D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, 1958, **23**, 420.
13 M. Charton, *Can. J. Chem.*, 1960, **38**, 2493.
14 A. Buckley, N. B. Chapman, M. R. Dack, J. Shorter and H. M. Wall, *J. Chem. Soc. B*, 1968, 631.
15 O. H. Wheeler and I. Lerner, *J. Am. Chem. Soc.*, 1956, **78**, 63.
16 S. M. Newman and D. M. Farbman, *J. Am. Chem. Soc.*, 1944, **66**, 1550.
17 J. R. Dice, L. E. Loveless and H. L. Cates, *J. Am. Chem. Soc.*, 1949, **71**, 3546.
18 L. I. Smith and K. L. Howard, *Org. Synth., Coll. Vol. III*, 1955, 188.
19 M. Plant, *J. Chem. Soc.*, 1930, 1595.
20 J. Cantacuzene, R. Jantzen and D. Ricard, *Tetrahedron*, 1972, **28**, 733.
21 S. Winstein, E. Grunwald, R. E. Buckles and C. Hanson, *J. Am. Chem. Soc.*, 1948, **70**, 820.
22 G. Cardillo and M. Shimizu, *J. Org. Chem.*, 1977, **42**, 4268.
23 E. A. Braude and J. A. Coles, *J. Chem. Soc.*, 1950, 2014.
24 L. L. McCoy and E. E. Riecke, *J. Am. Chem. Soc.*, 1973, **95**, 7404.
25 L. I. Smith and K. L. Howard, *Org. Synth., Coll. Vol. III*, 1955, 351.
26 A. I. Vogel, *Practical Organic Chemistry*, 3rd edn., Longman Green, London, 1956, p. 168.
27 H. Lund and J. Bjerrum, *Ber.*, 1931, **64**, 210.
28 J. D. Roberts, E. A. McElhill and R. Armstrond, *J. Am. Chem. Soc.*, 1949, **71**, 2923.

Paper 2/03938I
Received 22*nd July* 1992
Accepted 4*th January* 1993