# Reactivity of 2-Substituted Cyclohex-1-enylacetic Acids with Diazodiphenylmethane in Various Alcohols

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The reactivities of 2-substituted cyclohex-1-enylacetic acids with diazodiphenylmethane in eleven alcohols has been investigated. The solvent effect is interpreted in terms of the influence of the relative permittivity on the rate constants. The multiple linear correlation of $\log k$ with the Kirkwood function of relative permittivity, Taft $\sigma^*$ value for the alkyl group of the alcohol and the number of $\gamma$-hydrogen atoms in the alcohol $n_{\gamma H}$ was highly successful ($R = 0.9927$). The $\log k$ values for the various acids were correlated by using the appropriate form of the extended Hammett equation involving inductive, resonance and steric parameters.
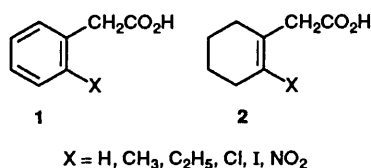
The reaction of cyclohex-1-enylacetic acid with diazodiphenylmethane in eleven alcohols shows a good linear free energy relationship with the corresponding reaction of phenylacetic acid ($R = 0.9793$). The results obtained for 2-substituted cyclohex-1-enylacetic acids were compared with the results for *ortho*-substituted phenylacetic acids under the same experimental conditions.

In connection with our study of the transmission of substituent effects through ring double bonds and delocalized double bonds, 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 various alcohols.

In our previous work [2] the reactivity of 2-substituted cyclohex-1-enylcarboxylic acids with DDM in various alcohols was investigated. The rate data for these acids were correlated with a simple Hammett equation by means of $\sigma_p$ constants. The results have shown that linear free energy relationships are applicable to kinetic data for 2-substituted cyclohex-1-enyl systems. Comparisons are made with the *ortho*-substituted benzoic acid system. The solvent effects on the reactivity of cyclohex-1-enylcarboxylic acid is proportional to its influence on the benzoic acid. Multiple linear correlation with three suitable solvent parameters $f(\varepsilon_r)$, $\sigma^*$, and $n_{\gamma H}$ is quite successful. The ratio $\rho:\rho_0$ has shown that the double bond in the cyclohexene ring is less polarizable than the benzene ring.

In the present work, rate constants have been measured for the reactions at 30 °C of the 2-substituted cyclohex-1-enylacetic acids with DDM in eleven different alcohols. Our object was to investigate the influence of the solvent on the *ortho*-effect of various substituents in a system not subject to the secondary steric effect of *ortho*-substituents which characterize the reactions of 2-substituted cyclohex-1-enylcarboxylic acids and *ortho*-substituted benzoic acids with DDM, examined previously. [2]

According to the structural analogy between *ortho*-substituted phenylacetic acid system 1 and 2-substituted cyclohex-1-enylacetic acid system 2 it seemed of interest to compare the

X = H, CH₃, C₂H₅, Cl, I, NO₂

results of the reaction of these acids with DDM under the same experimental conditions and with identical substituents.

## Results and Discussion

The second-order rate constants for the reaction of 2-substituted cyclohex-1-enylacetic acids with DDM in various alcohols at 30 °C are given in Table 1. The results show (Table 1) that the rate constants increased with increasing polarity of the solvent. This is in accordance with the proposed mechanism of the reaction. [3–5]

All the *ortho*-halogenocyclohex-1-enylacetic acids react more rapidly in all eleven alcohols than does cyclohex-1-enylacetic acid itself, in the order H < Cl < Br < I. The order corresponds qualitatively to that of the Hammett $\sigma_p$ values. [6] *ortho*-Alkylcyclohex-1-enylacetic acids are less reactive than the parent acid because of the electron-releasing character of the alkyl groups. The introduction of the nitro-group into cyclohex-1-enylacetic acid accelerates the reaction.

When values of $\log k$ for the cyclohex-1-enylacetic acid (**2a**) (Table 1) are correlated with the corresponding values for the reactions of phenylacetic acid [7] (**1a**) with DDM at 30 °C (Fig. 1)
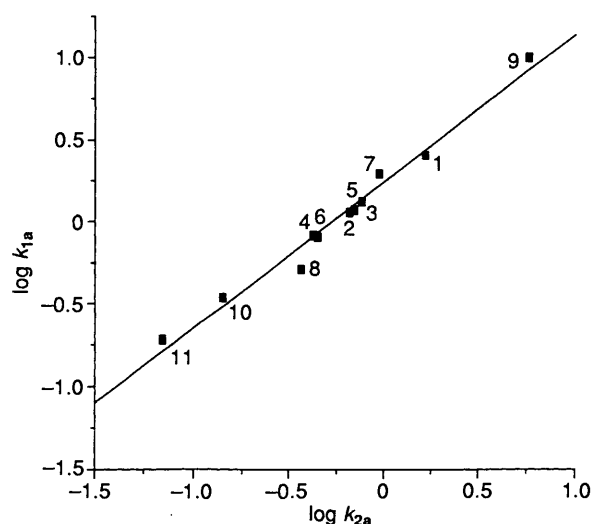


Fig. 1 Plot of $\log k$ for cyclohex-1-enylacetic acid **2a** *vs.* $\log k$ for phenylacetic acid **1a**; 1, methanol; 2, ethanol; 3, propan-1-ol; 4, propan-2-ol; 5, butan-1-ol; 6, butan-2-ol; 7, 2-methylpropan-1-ol; 8, 2-methoxyethanol; 9, benzyl alcohol; 10, 2-methylpropan-2-ol; 11, 2-methylbutan-2-ol

**Table 1** Rate constants ($dm^3$ $mol^{-1}$ $min^{-1}$) for the reaction of 2-substituted cyclohex-1-enylacetic acids with diazodiphenylmethane in various alcohols

| Solvent | Substituent | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| | H | $CH_3$ | $C_2H_5$ | Cl | Br | I | $NO_2$ |
| Methanol | 1.652 | 0.890 | 0.942 | 2.480 | 2.670 | 3.212 | 9.682 |
| Ethanol | 0.659 | 0.350 | 0.362 | 0.963 | 1.080 | 1.270 | 4.230 |
| Propan-1-ol | 0.762 | 0.387 | 0.423 | 1.180 | 1.272 | 1.490 | 5.040 |
| Propan-2-ol | 0.446 | 0.284 | 0.306 | 0.670 | 0.743 | 0.892 | 4.150 |
| 2-Methylpropan-1-ol | 0.940 | 0.627 | 0.643 | 1.665 | 1.790 | 2.070 | 8.460 |
| Butan-1-ol | 0.694 | 0.337 | 0.346 | 1.020 | 1.156 | 1.339 | 4.320 |
| 2-Methoxyethanol | 0.365 | 0.172 | 0.218 | 0.597 | 0.672 | 0.794 | 3.600 |
| Butan-2-ol | 0.424 | 0.221 | 0.230 | 0.637 | 0.716 | 0.868 | 3.650 |
| Benzyl alcohol | 5.740 | 2.96 | 3.18 | 11.40 | 12.04 | 14.16 | 46.72 |
| 2-Methylpropan-2-ol | 0.140 | 0.078 | 0.084 | 0.287 | 0.312 | 0.374 | 1.880 |
| 2-Methylbutan-2-ol | 0.069 | 0.040 | 0.046 | 0.176 | 0.189 | 0.245 | 1.350 |

**Table 2** Solvent parameters for alcohols

| Solvent | $\varepsilon_r{}^a$ | $\sigma^{*b}$ | $n_{\gamma H}{}^c$ |
| --- | --- | --- | --- |
| Methanol | 32.70 | 0 | 0 |
| Ethanol | 24.55 | −0.10 | 0 |
| Propan-1-ol | 20.33 | −0.115 | 3 |
| Propan-2-ol | 19.41 | −0.19 | 0 |
| 2-Methylpropan-1-ol | 17.93 | −0.125 | 6 |
| Butan-1-ol | 17.51 | −0.13 | 2 |
| Butan-2-ol | 16.56 | −0.21 | 3 |
| Benzyl alcohol | 12.80 | +0.215 | 0 |
| 2-Methylpropan-2-ol | 12.47 | −0.30 | 0 |
| 2-Methylbutan-2-ol | 5.82 | −0.31 | 3 |

$^a$ Relative permittivity at 30 °C (ref. 11). $^b$ Taft polar substituent constants of the alkyl groups (ref. 10). $^c$ Number of $\gamma$-hydrogen atoms in the alcohol.

the results conform to the linear free energy relationship, eqn. (1). (Correlation coefficient, $R = 0.9793$; and standard

$$\log k\ \mathbf{1a} = 0.243 + 0.89 \log k\ \mathbf{2a} \qquad (1)$$

deviation of the estimate, $s = 0.069$.)

This relationship (Fig. 1) shows that the same solvent properties act on the reactions of the two acids in 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 $\alpha,\beta$-unsaturated carboxylic acids with DDM in various solvents[1,2] and earlier work of Chapman et al.[8] has established that the solvent effect is best interpreted in terms of the following properties: (i) the behaviour of the solvent as a dielectric in facilitating the separation of opposite charges in the passage from the initial state to the transition state; (ii) the ability of the medium to solvate the molecule of carboxylic acid and thus stabilize the initial state relative to the transition state; and (iii) the ability of a protic solvents to form a hydrogen bond with the negative end of an ion-pair, and thus stabilize the transition state relative to the initial state.

The Kirkwood function[9] of the relative permittivity $\varepsilon_r$, $f(\varepsilon_r) = (\varepsilon_r - 1)(2\varepsilon_r + 1)$ is a suitable measure of ($i$) while ($ii$) and ($iii$) together are governed mainly by the polar effect of the alkyl group of the alcohol, appropriately measured by the Taft polar substituent constant $\sigma^*$.[10] Steric moderation of ($ii$) also occurs, and this is suitably measured by $n_{\gamma H}$, the number of $\gamma$-hydrogen atoms in the alcohol.

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

$$\log k = -2.353 + (5.457 \pm 0.766)f(\varepsilon_r) +$$
$$(3.08 \pm 0.138)\sigma^* + (0.033 \pm 0.009)n_{\gamma H} \qquad (2)$$

$R = 0.9962$ and the standard deviation of the estimate $s = 0.0565$.

The corresponding expression for phenylacetic acid reacting with DDM in the same series of alcohols[7] is eqn. (3) with $R = 0.9927$ and $s = 0.0686$.

$$\log k = -1.234 + (3.528 \pm 0.930)f(\varepsilon) +$$
$$(2.854 \pm 0.167)\sigma^* + (0.036 \pm 0.011)n_{\gamma H} \qquad (3)$$

Chapman, Lee and Shorter[7] have presented correlation analyses of second-order rate constants for the reaction of phenylacetic acid with DDM in the same series of alcohols at 30 °C by eqn. (4).

$$\log k = 1.09 + 3.3f(\varepsilon) + 2.7\sigma^* \qquad (4)$$
$$(R = 0.981 \text{ and } s = 0.103)$$

All regression analyses in this 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-enylacetic acid system is more sensitive to relative permittivity ($\varepsilon_r$) and Taft polar substituent constants $\sigma^*$ changes than the phenylacetic system. This is confirmed by the smaller coefficients of $f(\varepsilon_r)$ and $\sigma^*$ in eqn. (3).

The $n_{\gamma H}$ term is needed to account for the observed rate-enhancing effect of branching at the $\beta$-carbon atom of the alcohol. In this work the $n_{\gamma H}$ term is statistically insignificant in both expressions.

According to Charton's conclusion[12] that the data for non-aromatic unsaturated systems can be correlated with the extended Hammett equation for best results, in this work the rate constants for the reaction of 2-substituted cyclohex-1-enylacetic acids with DDM in various solvents together with literature data for the ortho-substituted phenylacetic acid sets[13] were correlated using the extended Hammett eqn. (5);[12] where

$$Q_X = \alpha\sigma_{I,X} + \beta\sigma_{R,X} + \psi v_X + h \qquad (5)$$

$Q_X$ is the property being correlated (i.e., $\log k_{DDM}$), $h$ is the intercept term, $\alpha$, $\beta$ and $\psi$ define the relative importance of inductive, resonance and steric effects, $\sigma_I$ and $\sigma_R$ represent the localized electronic effects and $v$ is the steric parameter.

The major objectives of this investigation were to determine the composition of the electronic effect and to detect the

**Table 3** Values of $\sigma_I \sigma_R$ and $v$

| Substituent | $\sigma_I$ | $\sigma_R$ | $v$ |
|---|---|---|---|
| H | 0.00 | 0.00 | 0.00 |
| CH$_3$ | −0.01 | −0.16 | 0.52 |
| C$_2$H$_5$ | −0.01 | −0.14 | 0.56 |
| Cl | 0.47 | −0.25 | 0.55 |
| Br | 0.47 | −0.25 | 0.65 |
| I | 0.40 | −0.16 | 0.78 |
| NO$_2$ | 0.67 | 0.10 | 1.39 |

**Table 4** Values of $P_R$

| | $P_R$(%) | |
|---|---|---|
| Solvent | 2-Substituted cyclohex-1-enylacetic acids | ortho-Substituted phenylacetic acids |
|---|---|---|
| Methanol | 49.15 | 36.09 |
| Ethanol | 50.34 | 43.31 |
| Propan-1-ol | 49.33 | — |
| Propan-2-ol | 56.43 | 46.80 |
| 2-Methylpropan-1-ol | 48.74 | 44.42 |
| Butan-1-ol | 50.85 | — |
| 2-Methoxyethanol | 51.34 | — |
| Butan-2-ol | 52.42 | — |
| Benzyl alcohol | 43.39 | — |
| 2-Methylpropan-2-ol | 48.60 | 53.87 |
| 2-Methylbutan-2-ol | 46.50 | 54.66 |

**Table 5** Summary of physicochemical data for 2-substituted cyclohex-1-enylacetic acids

| | | | Found (%) | | Calc. (%) | |
|---|---|---|---|---|---|---|
| Substituent | B.p./°C (mmHg) | Yield (%) | H | C | H | C |
|---|---|---|---|---|---|---|
| H | 138–140 (17)[a] | 80 | 8.24 | 68.42 | 8.57 | 68.57 |
| CH$_3$ | 148–150 (17)[b] | 60 | 8.86 | 69.14 | 9.09 | 70.13 |
| C$_2$H$_5$ | 150–152 (17) | 40 | 9.64 | 72.00 | 9.52 | 71.42 |
| Cl | 168–169 (17) | 40 | 6.34 | 55.12 | 6.30 | 55.00 |
| Br | 172–174 (17) | 50 | 4.88 | 41.19 | 5.02 | 43.83 |
| I | 186–188 (17) | 30 | 3.92 | 34.28 | 4.13 | 36.09 |
| NO$_2$ | 175–176 (17) | 50 | 6.08 | 52.13 | 5.94 | 51.89 |

[a] Ref. 19. [b] Ref. 30.

presence or absence of steric effects. The correlations of the kinetic data were carried out by means of multiple linear regression analysis.[14] The $\sigma_I$ and $v$ values were generally taken from the compilation of Charton[15] and $\sigma_R$ values were obtained from eqn. (6) using the $\sigma_P$ constants of McDaniel and

$$\sigma_R = \sigma_P - \sigma_I \qquad (6)$$

Brown.[16] The values of $\sigma_I$, $\sigma_R$ and $v$ are given in Table 3.

The results of the correlations have been deposited under the Supplementary publication scheme.*

The results of the correlation by eqn. (5) have shown that there is a high level of reliability with which the data comply with this equation in all cases. The values of $R$ are 0.9906–0.9989 for 2-substituted cyclohex-1-enylacetic acids and 0.9905–0.9994 for ortho-substituted phenylacetic acids. The values of $s$ are 0.024–0.057 for 2-substituted cyclohex-1-enylacetic acids and 0.008–0.029 for ortho-substituted phenylacetic acids.

* For details of the scheme, see 'Instructions for Authors', J. Chem. Soc., Perkin Trans. 2, 1994, issue 1 [Supp. Pub. No 57017 (3 pp.)].

Of the two systems correlated with eqn. (5) in various solvents, one set of 2-substituted cyclohex-1-enylacetic acids gave a confidence level (CL) of 80.0%, six a CL of 50.0% and four a CL of 20.0% for the 'student t' test for the significance of $\psi$ and for the ortho-substituted phenylacetic acids four gave a CL of 50.0% and two a CL of 20.0% for the 'student t' test for the significance of $\psi$.

Examination of the $\psi$ values for the 2-substituted cyclohex-1-enylacetic and ortho-substituted phenylacetic acids shows that the steric effect is not significant in these systems. These results are in accordance with the conclusion of Chapman et al.[13] that the phenylacetic acid system shows a small primary steric effect of ortho substituents in certain solvents.

The composition of the electronic effect is defined by the percent of the resonance effect: $P_R = \beta \times 100/(\alpha + \beta)$. The values of $P_R$ for the investigated series are given in Table 4.

Values of $P_R$ obtained range from 43.39 to 56.43 for 2-substituted cyclohex-1-enylacetic sets and from 36.09 to 54.66 for ortho-substituted phenylacetic sets. Of the two systems correlated with eqn. (5) in six solvents, four sets of 2-substituted cyclohex-1-enylacetic acids show a greater percentage of the resonance effect than for the ortho-substituted phenylacetic systems. These results are in accordance with the conclusion of Charton[17] that the resonance contribution in aliphatic unsaturated systems is greater than that for benzene derivatives, as might be expected in a less extended unsaturated system.

The regression coefficient of $\sigma_I$ varies from 1.070 to 1.610 for 2-substituted cyclohex-1-enylacetic acids and from 0.347 to 0.675 for ortho-substituted phenylacetic acids. The $\sigma_R$ terms obtained range from 1.164 to 1.467 for 2-substituted cyclohex-1-enylacetic systems and from 0.196 to 0.814 for ortho-substituted phenylacetic systems. The regression coefficients of $\sigma_I$ and $\sigma_R$ tend to increase with a decrease in the polarity of the solvent. This corresponds approximately to the variation with solvent polarity of the Hammett $\rho$ value for the reaction of these acids with DDM.

Certainly doubts, which are present when a limited number of substituents are used in multiple regression analysis, have to be kept in mind when dealing with the results presented in this paper.

On the basis of all the information presented, it may be concluded that the extended Hammett equation is applicable to kinetic data for the 2-substituted cyclohex-1-enylacetic system. Comparisons are made with the ortho-substituted phenylacetic acid system. The electronic effect is predominant in both systems. The composition of the electronic effect shows the importance of the resonance effect.

## Experimental

*Materials.*—Cyclohex-1-enylacetic acid was prepared by the method of Sugasawa and Saito[18] from cyclohexanone with cyanoacetic acid and ammonium acetate. The obtained cyclohex-1-enylacetonitrile was hydrolysed with KOH to the acid; b.p. 138–140 °C/17 mmHg (ref. 19, 139 °C/17 mmHg).

2-Substituted cyclohex-1-enylacetic acids were prepared by a Reformatsky reaction with ethyl bromoacetate and the corresponding 2-substituted cyclohexanone followed by saponification and dehydration of the resulting hydroxy esters.[20] 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.* Commercially available (Fluka).

*2-Ethylcyclohexanone.* This ketone was prepared by the procedure described for 2-phenylcyclohexanone.[21] 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 ethyl bromide and 28 g of magnesium in 250 cm$^3$ of diethyl ether. After one half the diethyl ether had been removed by distillation, 100 cm$^3$ of benzene was added and the mixture was refluxed for 2 h and then hydrolysed with an ice-cold solution of ammonium chloride. The ketone was distilled at 73 °C/14 mmHg, $[\alpha]_D^{20}$ 1.4488 (ref. 22, b.p. 67 °C/13 mmHg, $[\alpha]_D^{20}$ 1.4528).

2-*Chlorocyclohexanone.* The ketone was prepared by chlorination of cyclohexanone according to the usual procedure,[23] b.p. 90–91 °C/14–15 mmHg. (Ref. 23; b.p. 67 °C/13 mmHg, $[\alpha]_D^{20}$ 1.4528).

2-*Bromocyclohexanone.* A mixture of 60 g of cyclohexanone, 40 cm$^3$ of water and 30 g of CaCO$_3$ was stirred continuously and bromine was added dropwise over 1 h. The crude product was then extracted with diethyl ether, the solvent was removed and the ketone was distilled at 95–105 °C/17 mmHg (ref. 24; b.p. 95–105 °C/22 mmHg).

2-*Iodocyclohexanone.* This ketone was prepared by the method of Cantacuzene et al.[25] from *trans*-2-iodocyclohexanol which was prepared by the method of Winstein.[26] A solution of 1.1 g of CrO$_3$ in 28 cm$^3$ of acetic acid was added slowly with stirring to a 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 mmHg (ref. 27; b.p. 54 °C/1 mmHg).

2-*Nitrocyclohexanone.* A mixture of 12.6 cm$^3$ of 70% HNO$_3$ and 28 g of cyclohexanone enol acetate[28] in 61 g of acetic anhydride at 18–20 °C was stirred continuously over 1 h. The crude product distilled at 10–40 mmHg gave 28 g yellow oil containing 95% 2-nitrocyclohexanone, m.p. 36–38 °C (ref. 29; 35–38 °C).

*Diazodiphenylmethane* was prepared by Smith and Howard's method,[31] stock solutions of *ca.* 0.06 mol dm$^{-3}$ were stored in a refrigerator and diluted before use.

Solvents were purified as described in the literature.[3] Methanol was purified by Lund and Bjerrum method[33] and ethanol by the Smith method:[32] propan-1-ol, propan-2-ol, butan-1-ol, butan-2-ol and 2-methylpropan-1-ol were dried by methods analogous to the Smith's method for ethanol. 2-Methylpropan-2-ol dried over potassium carbonate, was refluxed over and distilled from sodium. 2-Methylbutan-2-ol was conveniently dried by fractional distillation, water being removed as an azeotrope of b.p. 88 °C.

2-Methoxyethanol and benzyl alcohol were kept over freshly ignited potassium carbonate for some days and then treated with molecular sieve (linde type 4 Å) for at least 3 days. The solvents were then distilled 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-enylacetic acids with DDM were determined as reported previously by the spectroscopic method of Roberts and his coworkers[34] using a 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 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 within 3% of the mean.

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