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Substituent Effect in Reaction of Dicyclohexylcarbodiimide with Substituted Benzoic Acids

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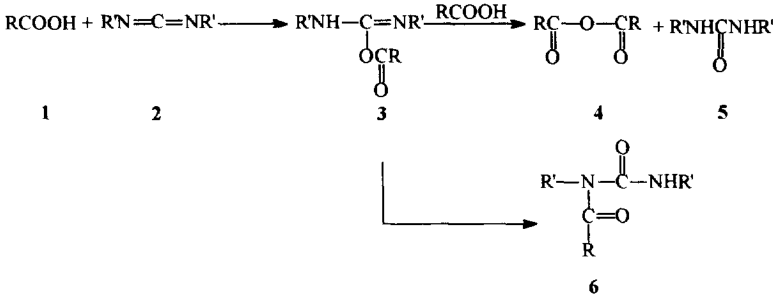
Abstract: A curved Hammett relationship was observed for the reaction of substituted benzoic acids with dicyclohexylcarbodiimide in buffered solution. The reaction is promoted by electon-withdrawing substituents because of larger concentration of the acid anion present in the reaction mixture. On the other hand, electron-donating substituents encourage nucleophilic attack of the acid anion on the protonated carbodiimide.

INTRODUCTION

Carbodiimides rank as one of the most important condensing agents in peptide and nucleotide chemistry. In addition to being used for direct coupling they can be applied to obtain reactive intermediates, such as active esters and symmetrical anhydrides. Carboxylic acids react with carbodiimides to form acid anhydrides and the appropriate N,N'-disubstituted ureas, and N-acyl-N,N'-disubstituted ureas. The mechanism of this reaction suggested by Khorana[1] explains its bi-directional course (Scheme 1). Carbodiimide (**2**) is protonated in the first step and then the acid anion attacks the carbon atom of the cation formed. The very active O-acylisourea (**3**) developed at this stage can in turn react further in two ways. The next acid anion can, after initial protonation of O-acylisourea, attack the carbonyl C atom yielding the acid anhydride (**4**) and urea (**5**). Alternatively, intramolecular O→N migration of the acyl group leads to N-acylurea (**6**).



Scheme 1.

The rate of the reaction and the ratio of the products obtained are affected by a number of factors, for example: the kind of solvent, temperature and the presence of acids or bases. It has been found that the reaction rate increases along with the strength of the carboxylic acid (**1**) used[2,3,4] and the nucleophilicity of its anion[5]. However, mechanistic interpretation of these data is not straightforward because changing the strength of the acids modifies the reaction environment as well. The present investigation was carried out in buffered solution to avoid this disadvantage.

RESULTS AND DISCUSSION

Reactions of the substituted benzoic acids with dicyclohexylcarbodiimide (DCC) were followed using HPLC analysis. N-acyl-N,N'-dicyclohexylureas were the sole products obtained under the applied conditions (tetrahydrofuran, 25.0°C, 0.20 mol/dm^3 tributylamine perchlorate and tributylamine buffer). The observed rate constants were found by numeric fitting of the second-order kinetic equation (2) according to which one molecule of carboxylic acid reacts with one molecule of dicyclohexylcarbodiimide to form N-acyl-N,N'-dicyclohexylurea. The reliability of the calculation procedure was checked by comparing the value of k_{obs} ($R^1 = H$) obtained using it with the one calculated analytically under pseudo-first order conditions [$2.18 \cdot 10^{-3}$ dm^3/(mol·s) and $2.24 \cdot 10^{-3}$ dm^3/(mol·s), respectively]. An example of the results of the numeric procedure is given in Fig. 1 together with the experimental points.

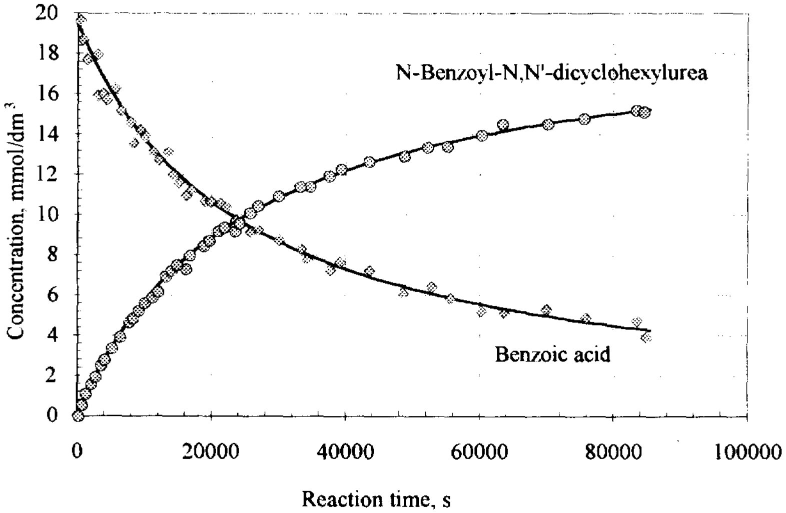


Figure 1. Kinetics of the reaction of C_6H_5COOH with DCC in THF, 0.20 mol/dm^3 $Bu_3NH^+ClO_4^-/Bu_3N$ (1:1) at 25.0°C. The initial concentrations of both C_6H_5COOH and DCC were 0.0190 mol/dm^3. Lines are calculated, points are experimental.

Table 1. The Observed Rate Constants for Reaction of $R^1C_6H_4COOH$ with DCC in THF. The reactions were carried out in 0.20 mol/dm^3 buffer $Bu_3NH^+ClO_4^-/Bu_3N$ (1:1). The initial concentrations of $R^1C_6H_4COOH$ and DCC were 0.019 mol/dm^3.

R^1 =	p-NO$_2$	m-Cl	p-Cl	m-MeO	H	p-MeO
σ^a =	0.78	0.37	0.23	0.12	0.00	-0.27
$10^3 \cdot k_{obs}{}^b$ = dm^3/(mol·s)	2.03	2.60	2.79	2.86	2.18^c	1.61

[a] derived from ionisation constants in water[6]

[b] precision of k_{obs} was better than ±0.05·10^{-3} dm^3/(mol·s)

[c] k_{obs} = 2.07·10^{-3} dm^3/(mol·s) was found in 0.10 mol/dm^3 buffer (ionic strength maintained with $Bu_4N^+ClO_4^-$)

Reactions of the series of substituted benzoic acids with DCC did not obey simple Hammett equation (Tab. 1). Instead, a curved line of $\lg(k_{obs}/k^0_{obs})$ *versus* the substituent constant σ was observed. This type of deviation from linearity in the Hammett relationship is characteristic for the reactions in which the rate limiting step is preceded by an equilibrium[7]. The reaction was not susceptible to variation in the buffer concentration, that is the reaction is subjected rather to specific than general acid catalysis. Therefore, the consecutive reaction mechanism shown in Scheme 2 was adopted. According to it, the reaction is initiated by protonation of DCC by a solvated proton.

$$\mathrm{RCOOH} \xrightleftharpoons{K_a} \mathrm{RCOO}^{\ominus} + \mathrm{H}^{\oplus}$$

$$\mathrm{DCCH}^{\oplus} \xrightleftharpoons{K_c} \mathrm{DCC} + \mathrm{H}^{\oplus}$$

$$\mathrm{RCOO}^{\ominus} + \mathrm{DCCH}^{\oplus} \xrightarrow{k_1} \mathrm{AIU} \xrightarrow{k_2} \mathrm{NDCU}$$

Scheme 2.

Although the O-acylisourea (AIU) intermediate has not been so far isolated from the reaction mixture, studies on its intramolecular analogue have supported its existence[8]. Later on, stable O-benzoyl-N,N-dimethyl-N'-(N-methyl-2,4-dinitroanilino)isourea was obtained and its transformation to N-acylurea and hydrolysis was observed[9]. These findings indicate that O-acylisourea is a very reactive intermediate undergoing fast conversion to the product, hence its formation is the rate limiting process. On the steady-state assumption for O-acylisourea one obtains:

$$\frac{d[\mathrm{NDCU}]}{dt} = k_1[\mathrm{RCOO^-}][\mathrm{DCCH^+}] \qquad (1)$$

Ascribing total concentration of the acid and the carbodiimide as $[\mathrm{RCOOH}]_t = [\mathrm{RCOO^-}] + [\mathrm{RCOOH}]$ and $[\mathrm{DCC}]_t = [\mathrm{DCCH^+}] + [\mathrm{DCC}]$, the equation (1) can be rewritten in the form incorporating protonation equilibria:

$$\frac{d[\mathrm{NDCU}]}{dt} = k_{obs}[\mathrm{RCOOH}]_t[\mathrm{DCC}]_t \qquad (2)$$

where

$$k_{obs} = \frac{k_1 K_a [H^+]}{(K_a+[H^+])(K_c+[H^+])} \tag{3}$$

Among the constant values in equation (3) only k_1 and K_a depend on the nature of the substituent in the phenyl ring of benzoic acid. Accordingly, the Hammett linear free energy relationship applied to k_{obs} leads to:

$$\lg\left(\frac{k_{obs}}{k^o_{obs}}\right) = \lg\left(\frac{k_1}{k^o_1}\right) + \lg\left(\frac{K_a}{K^o_a}\right) - \lg\left(\frac{K_a+[H^+]}{K^o_a+[H^+]}\right) \tag{4}$$

The last term in the equation (4) can be rewritten as:

$$\lg\left(\frac{k_{obs}}{k^o_{obs}}\right) = \lg\left(\frac{k_1}{k^o_1}\right) + \lg\left(\frac{K_a}{K^o_a}\right) - \lg\left\{\frac{(K_a+[H^+])}{K^o_a} \cdot \frac{K^o_a}{(K^o_a+[H^+])}\right\} \tag{4a}$$

which is equal to:

$$\lg\left(\frac{k_{obs}}{k^o_{obs}}\right) = \lg\left(\frac{k_1}{k^o_1}\right) + \lg\left(\frac{K_a}{K^o_a}\right) - \lg\left(\frac{K_a}{K^o_a} + \frac{[H^+]}{K^o_a}\right) + \lg\left(1 + \frac{[H^+]}{K^o_a}\right) \tag{4b}$$

Applying the Hammett's notation gives equation (5):

$$\lg\left(\frac{k_{obs}}{k^o_{obs}}\right) = (\rho_1 + \rho_a)\sigma - \lg\left(10^{\rho_a \sigma} + \frac{[H^+]}{K^o_a}\right) + \lg\left(1 + \frac{[H^+]}{K^o_a}\right) \tag{5}$$

Numeric fitting of the curve (5) to the experimental data by varying values of the reaction constants ρ_1 and ρ_a, and the ratio $[H^+]/K_a^o$ gave the regression line displayed in Fig. 2. The values of observed rate constants for *meta*-substituted benzoic acids apparently deviate from the predicted line (multiple correlation coefficient $R = 0.915$ and 0.991 with and without *meta*-substituents, respectively). However, the enhanced *para*-substituent values σ^+ and σ^- applied instead of simple substituent constants σ have not improved the correlation. The rules of error propagation imply that uncertainty of $\lg(k_{obs}/k^o_{obs})$ should not exceed 0.03 if only the error of k_{obs}-value is less than $5 \cdot 10^{-5}$ dm^3/(mol·s). Thus the values of ρ_1 and ρ_a in equation (5) can be determined merely with limited precision but this does not restrain the general relationship and the conclusion derived from it.

The reaction constants ρ_a and ρ_1 are of significant magnitude, almost equal in absolute values but of opposite signs. The ρ values of similar order were observed for reactions in which entire charge is developed or lost at the reaction centre, for example: $\rho \sim 3.5$ for acid dissociation of arylammonium cations in dioxane/water mixtures[10] and $\rho \sim -4.2$ for nucleophilic attack of arylamines on fluorodinitrobezene in ethanol[11]. In both instances the reaction centre is adjacent to the phenyl ring that is not exactly the case in the investigated reaction but the ρ_a and ρ_1 values suggest strong transmission of the substituent effect to the carboxyl group. Moreover, dipolar aprotic solvents poorly solvating the anion increase the sensitivity of dissociation of benzoic acids to substituent influences (ρ by definition equal to unity in water rises to 2.29 in acetone)[12]. The same impact, even to a greater extent, may be expected for the investigated reaction in tetrahydrofuran.

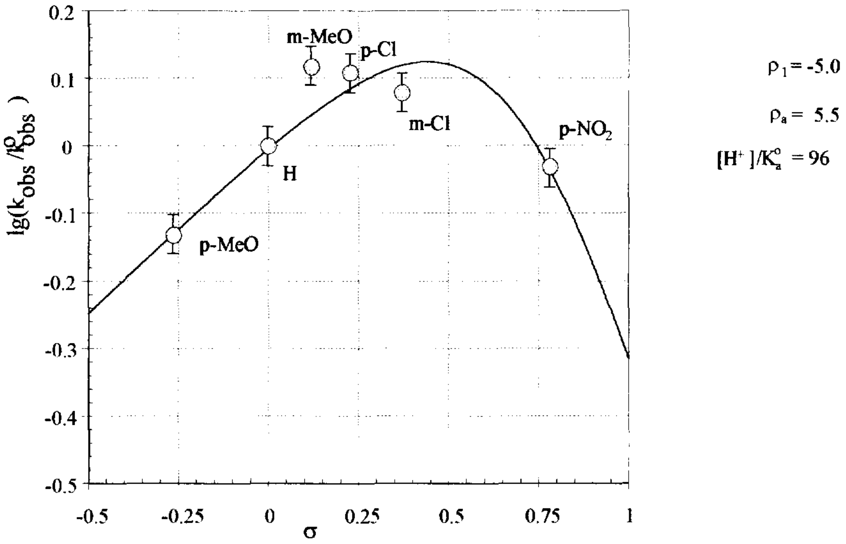


Figure 2. LFER curve fitting according to equation (5).

The curvature in LFER is a consequence of diverse effects exerted by substituents on different reaction steps. Both the acid dissociation and nucleophilic attack of the acid anion on the protonated carbodiimide are susceptible to changes of σ-values but in opposite directions. The more electon-withdrawing is the substituent the greater is the dissociation of the benzoic acid analogue ($\rho_a = 5.5$). Thus the reaction is promoted because of larger concentration of the acid anion present in the reaction mixture. On the other hand, electron-donating substituents encourage a nucleophilic attack of the acid anion on the protonated carbodiimide ($\rho_l = -5.0$) and a changeover in the rate limiting step is observed as the nature of the substituent changes. The acid to carbodiimide proton transfer may be crucial in the case of non buffered solutions and the second of the above mentioned influences may be masked. This is probably why the phenomenon has not been so far observed although dependence of the reaction of carbodiimides with carboxylic acids on proton activity is well recognised[9,13,14,15].

EXPERIMENTAL

Reagents. The substituted benzoic acids (Aldrich Chemical Co.) were used as obtained. The appropriate HPLC standards of N-acyl-N,N'-dicyclohexylureas were obtained as previously described[16] and were positively characterised by elemental analysis and physical constants. Tributylamine (Aldrich Chemical Co.) was distilled under reduced pressure (bp 97-98°C/14 mmHg). Tributylammonium perchlorate (mp 93-93.5°C form *sec*-butanol/diethyl ether) was synthesised from tributylamine and 60% perchloric acid according to Werner and Keller[17]. Tetrabutylammonium perchlorate (mp 214-215°C) was obtained from tetrabutylammonium hydroxide (40% in water, Serva Int.) and perchloric acid. The purity of dicyclohexylcarbodiimide (Chemical Dynamics Co.) was checked[18] to be at least 98%. Tetrahydrofuran (Polskie Odczynniki Chemiczne) was freshly distilled over sodium-potassium alloy. It is very important to use freshly distilled THF, otherwise the reaction deteriorates.

Kinetic measurements. The reactions were carried out in a thermostated vessel with magnetic stirring. The kinetics of the reaction was studied by taking samples of the reaction mixture at suitable intervals and injecting them right onto the separation column. A Hewlett-Packard model 1050 liquid chromatograph equipped with UV detector operated at 270 nm was employed. Separation of the reaction products was accomplished using 250 x 4.6 mm column packed with Nucleosil C_{18} 100-5 (Machery-Nagel) and a mixture of methanol and water (70 + 30)v/v as the mobile phase at flow rate of 1.0 cm^3/min.

Calculations. The reaction rate equation (2) and the LFER equation (4) were numerically fitted to the experimental data by varying constant k_{obs} in equation (2), and values of ρ_1, ρ_a and $[H^+]/K^o_a$ in equation (4). The Solver package in Excel® program under the condition of minimisation of the sum of squares $SS = \sum(x_{calc} - x_{expl})^2$ was used. In the case of kinetic calculation SS was estimated using $x = [AOH]_t + [NDCU]$. The concentrations of reactants, $[AOH]_t$, $[DCC]_t$ and [NDCU], were computed in the intervals proportional to the reaction time. For the LFER estimation an calculation step $\Delta\sigma = 0.01$ and $x = \lg(k_{obs}/k^o_{obs})$ were used.

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