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Reaction Conditions and Mechanism of Electrolytic Reduction of Dibenzoylmethane†

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Electrochemical reduction of dibenzoylmethane was studied on mercury electrode by means of cyclic voltammetry, polarography and potentiostatic measurements in ethanol-water system. In acidic solutions monomeric pinacol was produced by irreversible two-electron process while monomeric and dimeric pinacol were competitively produced by the same process in neutral solution. However, in basic solution the dimeric pinacol was mostly produced through radical by irreversible one-electron transfer process. Mechanisms of the reduction of dibenzoylmethane are deduced from Tafel slope, pH dependence and reaction order with respect to the concentration of dibenzoylmethane in the solution of various pH.

Introduction

Previous investigators¹⁻⁷ have studied the electrochemical reduction of 1,3-diphenyl-1,3-propanedione (or dibenzoylmethane, DBM) by polarographic and coulometric experiments. Evans and Woodbury³ reported that dibenzoylmethane could be reduced in ethanol-water to three kinds of product, via one, two or four electron transfer per a molecule, depending upon the pH of the solutions and the electrode potential. The one-electron product at the first polarographic wave was the dimeric pinacol (1,4-dibenzoyl-2,3-diphenyl-2,3-butanediol) and the two-electron product at the second, the cyclic tetrol (1,2,4,5-tetraphenyl-1,2,4,5-cyclohexanetetrol), however the four-electron product at the third wave was the monomeric diol (1,3-diphenyl-1,3-propanediol).

On the other hand it was recently reported by Chon⁸ that the dimeric and the monomeric pinacols could be obtained by two consecutive one-electron transfer processes on mercury film electrode in basic ethanol-water solvents.

In this paper polarography, cyclic voltammetry and kinetic measurements of the electrochemical reduction of dibenzoylmethane in various pH range of ethanol-water solutions were made in order to elucidate the reduction mechanism against the reaction conditions.

Experimental

Chemicals. Reagent grade dibenzoylmethane (Fisher) was checked for purity by measurements of the melting point, IR and NMR spectra and used without further purification.

†Dedicated to Professor Nung Min Yoon on the occasion of his 60th birthday.

Dibenzoylmethane used in this investigation was found to exist almost entirely in the enol form on comparison with the melting point and the standard spectral data⁹⁻¹¹. All electrolyte solutions were prepared from reagent grade absolute ethanol (James Burrough) and distilled water (50% by volume) with sulfuric acid or citrate buffers as the electrolytes for acidic or moderate solutions and with sodium hydroxide or carbonate buffers for basic solutions. Ionic strength of the solutions were adjusted to 0.10M. All inorganic compounds used herein were reagent grade of Junsei. They were used as received and checked for purity by measurements of the background polarograms.

Apparatus and Measurements. The electrochemical measurements for cyclic voltammetry and polarography were performed with a Princeton Applied Research (PAR) model 264A polarographic analyzer/stripping voltammeter equipped with a PAR 303A static mercury drop electrode (SMDE) and cell system. This cell is suited for sample volume of about 10ml, and the top of the cell allows for introduction of the counter, reference probe, deaeration tube, and a working electrode. The working electrode was SMDE and HMDE which set up by using triply-distilled mercury. The counter electrode was a platinum wire immersed in the test solution, hence it was not separated from the working compartment. The amount of product formed at the counter electrode during a measurement was so small that its presence did not affect the subsequent measurements.

The reference electrode was encased in a bridge tube which made contact with the test solution by means of a fine porosity frit-tip. A Ag/AgCl (sat'd KCl) reference electrode was used and all the potential data given here are referred to this electrode.

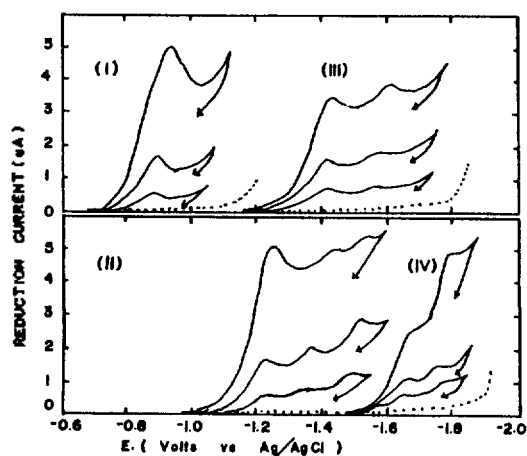


Figure 1. Cyclic voltammograms of 10^{-3} M DBM (solid lines) and base electrolyte (dashed lines) in ethanol-water system at (I) pH = 1.0, (II) pH = 7.0, (III) pH = 11.0, and (IV) pH = 13.0. Scan rates were 500, 50, 5 mV/sec from top to bottom.

Table 1. Cyclic Voltammetric Data for 10^{-3} M DBM in Acidic Solution (pH = 1.0)

scan rate (mV/sec)	-Ep (Volts)	Ip (uA)	Ip/v ^{1/2} (uAmV ^{-1/2} sec ^{1/2})
5	0.875	0.38	0.17
10	0.880	0.70	0.22
20	0.885	0.98	0.22
50	0.890	1.63	0.23
100	0.895	2.30	0.23
200	0.900	3.40	0.24
500	0.940	5.00	0.22

The voltammograms were recorded on an x-y recorder when the scan rate was slower than 200 mV/sec. And a storage-type oscilloscope (Hewlett-Packard 1741A) was also employed when it is faster than 200 mV/sec.

The constant potential electrolysis was made with a PAR 273 potentiostat/galvanostat equipped with a PAR 377A coulometric cell system. The cell was a about 30 ml cylindrical glass cell with five connecting joints in teflon top. The five joints provided access for the counter electrode compartment, reference electrode bridge tube, deaeration tube, stirring impeller and the working electrode.

A mercury pool was used as the working electrode during electrolysis. And electric connection to the mercury pool was made by a platinum sealed through the bottom of the cell. The counter electrode was a platinum mesh which encased in

Table 2. Cyclic Voltammetric Data for 10^{-3} M DBM in Neutral Solution (pH = 7.0)

scan rate (mV/sec)	-Ep1	-Ep2	-Ep3	Ip1	Ip2	Ip3	Ip1/v ^{1/2}	Ip2/v ^{1/2}	Ip3/v ^{1/2}
	(Volts)			(uA)			(uAmV ^{-1/2} sec ^{1/2})		
5	1.205	1.330	1.470	0.58	0.18	0.48	0.26	0.08	0.21
10	1.210	1.340	1.480	0.83	0.22	0.50	0.26	0.08	0.16
20	1.215	1.350	1.490	1.10	0.23	0.55	0.25	0.05	0.12
50	1.225	1.370	1.510	1.68	0.28	0.55	0.24	0.04	0.08
100	1.230	1.390	1.520	2.43	0.35	0.58	0.24	0.04	0.06
200	1.235	1.410	1.525	3.35	0.40	0.55	0.24	0.03	0.04
500	1.250	1.440	1.530	5.00	0.43	0.52	0.22	0.02	0.02

Table 3. Cyclic Voltammetric Data for 10^{-3} M DBM in Basic Solution (pH = 11.0)

scan rate (mV/sec)	-Ep1	-Ep2	Ip1	Ip2	Ip1/v ^{1/2}	Ip2/v ^{1/2}	Ip2/Ip1
	(Volts)		(uA)		(uAmV ^{-1/2} sec ^{1/2})		
5	1.395	1.560	0.53	0.18	0.24	0.08	0.34
10	1.400	1.565	0.70	0.25	0.22	0.08	0.36
20	1.405	1.580	0.90	0.35	0.20	0.08	0.39
50	1.410	1.585	1.33	0.60	0.19	0.08	0.45
100	1.415	1.590	1.75	0.80	0.18	0.08	0.46
200	1.420	1.600	2.30	0.95	0.16	0.07	0.41
500	1.430	1.610	3.30	1.18	0.13	0.05	0.36

Table 4. Cyclic Voltammetric Data for 10^{-3} M DBM in Basic Solution (pH = 13.0)

scan rate (mV/sec)	-Ep1	-Ep2	Ip1	Ip2	Ip1/v ^{1/2}	Ip2/v ^{1/2}	Ip2/Ip1
	(Volts)		(uA)		(uAmV ^{-1/2} sec ^{1/2})		
5	*	1.73	0.37	0.03	0.17	0.01	0.08
10	*	1.73	0.50	0.05	0.16	0.02	0.10
20	1.64	1.73	0.65	0.10	0.15	0.02	0.15
50	1.65	1.74	1.00	0.30	0.14	0.04	0.30
100	1.66	1.75	1.28	0.70	0.13	0.07	0.55
200	1.67	1.76	1.58	1.48	0.12	0.07	0.94
500	1.67	1.78	2.42	2.40	0.10	0.11	0.99

* Combined reduction wave (see the cyclic voltammogram in Figure 1)

a tube terminating with a fine fritted disk.

Results and Discussion

Cyclic Voltammetry. Figure 1 illustrates typical cyclic voltammograms of 10^{-3} M DBM under various conditions of pH in 50% ethanol-water solution. In the cyclic voltammograms obtained by potential sweeping in acidic solutions there was only one reduction wave, whereas in neutral and basic solutions there were three and two reduction waves respectively. However, any oxidation waves corresponding to each reduction were not observed in all solutions used here. It seems that the electrochemical reduction of DBM is occurring by irreversible electron transfer. To suggest reversibility more clearly the cyclic voltammetric data at various scan rates were collected and the results of pH = 1.0, 7.0, 11.0 and 13.0 were summarized in Table 1, 2, 3, and 4, respectively.

For all the solutions tested here, the reduction peak-potentials (Ep) were negatively shifted and the peak-currents

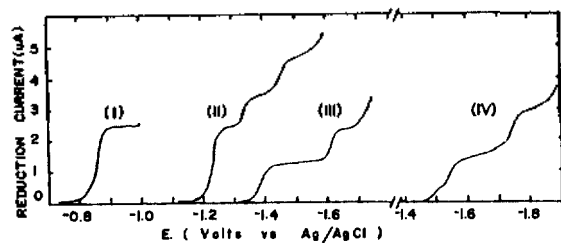


Figure 2. Typical polarograms of 10^{-3} M DBM in ethanol-water system at (I) pH=1.0, (II) pH=7.0, (III) pH=11.0, and (IV) pH=13.0.

Table 5. Polarographic data of 10^{-3} M DBM in 50% Ethanol Water System

Parameter	Acidic (pH = 1.0)	Neutral (pH = 7.0)			basic solution			
	1st wave	1st	2nd	3rd	pH = 11.0	pH = 13.0	1st	2nd
-E (V)	0.88	1.23	1.38	1.54	1.40	1.61	1.55	1.75
Id (uA)	2.3	2.4	—	—	1.2	1.1	1.2	1.5
slope (mV)	50	50	—	—	80	—	—	—

(ip) were increased with increasing scan rates. However the current functions ($ip/v^{1/2}$) in acidic and neutral solutions were observed to be nearly constant, while those in basic solutions were slightly decreased with increasing scan rates. It is speculated that the irreversible electron transfer processes were being affected by a preceding chemical step¹² in more basic solutions than $pK = 10.4^8$ of DBM but not in acidic solutions within the range of the scan rate conducted in this study.

Furthermore, the current ratio between two reduction waves (ip_2/ip_1) in basic solution (pH = 13.0) was increased up to 1.0 with increasing scan rates. It seems that the second reduction step was occurring with a competitive chemical reaction as previous reported⁹.

Polarography. Typical polarograms for the reduction of 10^{-3} M DBM under various conditions of 50% ethanol-water solution are given in Figure 2, and the polarographic data are summarized in Table 5.

In acidic solutions one well-defined polarographic wave was obtained and αn was 1.08 from the plot of $\log((id-i)/i)$ vs E. If this polarographic wave is irreversible as mentioned above, the αn value of 1.08 suggests that DBM was reduced by two-electron transfer to a product which may give monomeric pinacol or dimeric pinacol. However, the monomeric pinacol may be favorably produced, because TLC analysis revealed only one species and the concentration of proton was much higher than that of reactant molecule (refer to mechanism section).

In neutral solutions three polarographic waves were appeared and the first wave was very similar to that of acidic solutions, except that the half-wave potential was negatively shifted by 58 mV per pH. These data are indicative that the reduction at the potential region of the first wave in neutral solutions may be the same process as that in acidic solutions. Based on TLC analysis two kinds of product was obtained during electrolysis under the potential region of the first wave in neutral solution, and one of them was the same product as in acidic solution. It seems that the monomeric and dimeric pinacol could be produced via two electron transfer. Thus the second and third reduction waves could be the

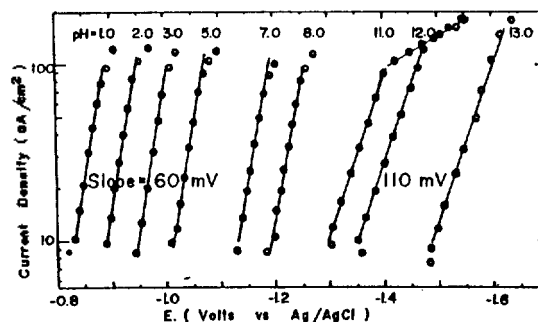


Figure 3. Steady state polarization curves of 10^{-3} M DBM in various conditions of ethanol-water system.

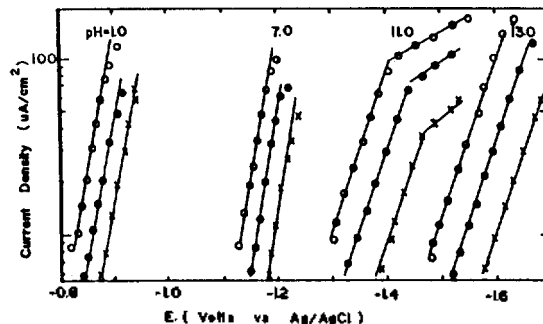


Figure 4. Effects of polarization curves on the concentration of DBM in various pH's: ●●● 10×10^{-4} M, ●●● 5.0×10^{-4} M, xxx 1.0×10^{-4} M.

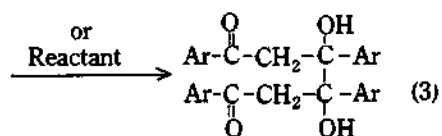
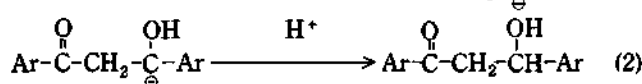
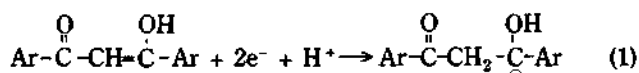
reduction of dimeric and monomeric pinacols, respectively.

In basic solutions two polarographic reduction waves were obtained, and they were well defined at pH = 11.0 and ill defined in at pH = 13.0. Furthermore, the diffusion current ratio of the second wave to the first was about 1.0. And the value of αn was 0.68 from the plot of $\log((id-i)/i)$ vs E. From the cyclic voltammograms all of the reduction processes were irreversible. Thus, the first reduction process in basic solutions may be occurring via one-electron transfer. The TLC analysis showed the same pattern as in the case of the neutral solution, during electrolysis under the potential region of the first wave. Therefore, it seems that the reduction products in the basic solutions were also monomeric and dimeric pinacols.

Polarization Curves. The steady state current-potential relationships for the reduction of dibenzoylmethane in the solutions of various pH by potentiostatic method are shown in Figure 3. At lower polarization region which controlled by charge transfer rates, Tafel slopes were about 60 mV for both acidic and neutral solutions but 110 mV for basic solutions. As can be seen from Figure 3 the pH dependance at the constant-current density, $(dE/dpH)_i$, was observed to be -60 mV in acidic and neutral solutions, which implies the first order reaction about the concentration of proton. However, the pH dependance in basic solutions was observed to be -95 mV and 0 mV at the lower and higher polarization, respectively. It can therefore be assumed that the reaction order with respect to the concentration of proton is nearly the first at the lower and the zeroth at the higher polarization in basic solutions. In Figure 4, it is shown that the reduction rate of dibenzoylmethane was dependent on its concentration and the reaction orders, $d(\log i)/d(\log(\text{DBM}))$, for all the solutions used here were observed to be 1.0 within the experimental error.

Reaction Mechanism in Acidic and Neutral Solutions. The Tafel slope for the reduction of dibenzoylmethane, 60 mV as obtained from Figure 3, suggests an irreversible two-electron transfer in the rate-determining step. And the pH dependence of -60 mV/pH means that one proton is involved in the rate determining step. In Figure 4 the reaction order with respect to DBM seems to be first, therefore, the rate is directly proportional to the concentration of DBM. And from this dependence, the electrode reaction can be reasonably assumed to take place with a non adsorbed species. Chon⁸ previously found that the pKa of DBM is 10.4 by a combined experiment of pH-metry and conductometry. Thus, if pH of the solution is much lower than 10.4, the enol form of DBM is probably dominant over the enolate.

Therefore, the following mechanism is assumed:



Writing the rate of step (1), $r = k(\text{DBM})(\text{H}^+) \exp(-2\alpha\text{FE}/\text{RT})$. Thus, the current for the reduction of DBM is

$$i = 2Fk(\text{DBM})(\text{H}^+) \exp(-2\alpha\text{FE}/\text{RT}) \quad (4)$$

where α is the transfer coefficient of reaction (1) and F is the Faraday constant. With $T = 298$ K, equation (4) is rewritten in the logarithmic form

$$\log i = \log(\text{const.}) - p(\text{DBM}) - \text{pH} - 2\alpha E/0.0592 \quad (5)$$

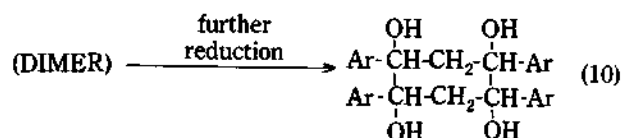
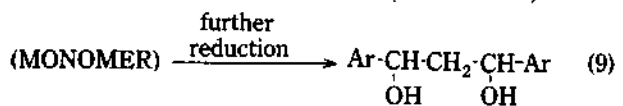
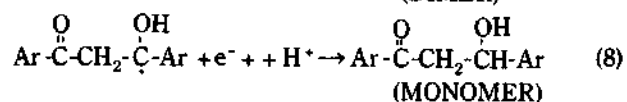
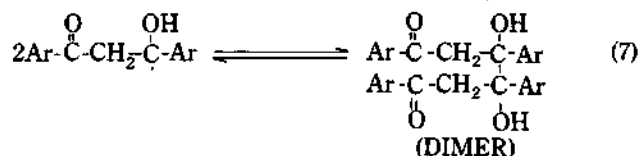
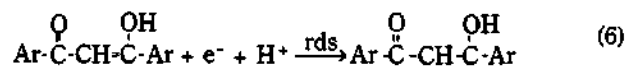
If α is assumed to be about 1/2 as usual¹³⁻¹⁶, the Tafel slope, pH dependence and reaction order will be 60 mV, -60 mV and 1, respectively. The observed values in Figure 3 and 4 are in good agreement with this prediction within the experimental error.

The reaction (2) and (3) are considered to be prevalent in acidic condition while the reaction (3) will be favored in basic. In strongly acidic solutions^{17,18} the concentration of DBM is much lower than proton, thus the carbanion produced by the reaction (1) is immediately converted to a pinacol through the reaction (2). However, in neutral or moderate solution the relative concentration of proton and DBM will affect the relative reaction rates of (2) and (3). Therefore, the second and the third polarographic wave could be observed due to reduction of the two-kinds of product via reaction (3) and (2).

Reaction Mechanism in Basic Solutions. If the pH-value of a solution is higher than pKa value of DBM, 10.4, the enolate species will be probably dominant over the enol species of DBM. However, it has been proposed that the neutral enol species is more electroactive than the anionic enolate^{4,19}.

The Tafel slopes, 110 mV as shown in Figure 3, suggest a single electron transfer in the rate determining step. And then the pH-dependance shown in Figure 3 and the reaction order in Figure 4 at the lower polarization, seem to be the first order, therefore, one proton and one DBM molecule are involved in the rate determining step.

The following mechanism is assumed:



The electrochemical reactions of (6) and (8) are occurring in series, but the rate of (8) will be interrupted by the competing chemical step (7). At the higher polarization the chemical process (7) seems to be faster than (8) due to the higher coverage of the radical that produced by the reaction (6). On the contrary at lower polarization the rate of (7) could be competing with that of (8). And it may be assumed that the rate constant of (8) is faster than (6) because of the unstability of radical. Thus, the reduction rate may be determined by the reaction (6).

Writing the rate of step (6), $r = k(\text{DBM})(\text{H}^+) \exp(-\alpha\text{FE}/\text{RT})$, the current due to the sequence of the above steps at lower polarization becomes

$$i = 2Fk(\text{DBM})(\text{H}^+) \exp(-\alpha\text{FE}/\text{RT}) \quad (11)$$

where α is the transfer coefficient of the reaction (6). With $T = 298$ K, equation (11) is rewritten in the logarithmic form,

$$\log i = \log(\text{const.}) - p(\text{DBM}) - \text{pH} - \alpha E/0.0592 \quad (12)$$

If the α is considered to be 1/2 as in the case of acidic or neutral solution, the Tafel slope will be 120 mV which close to the observed 110 mV in Figure 3. And the pH dependence of potential, $(dE/d\text{pH})_i$, and the reaction order will be -120 mV, and 1, respectively. The observed values in Figure 3 and 4 are in agreement with this prediction.

The higher polarization curves whose slopes were observed to be 520 mV could not be denoted by the charge-transfer control, but by the diffusion control, owing to the dimerization on the electrode surface through reaction (7).

The cyclic voltammetry data of Figure 1, and Tables 3 and 4 can be also interpreted by the reaction scheme (6) to (8), and (9) or (10). If the first reduction wave corresponds to (6), and (8) as the above-mentioned, the second reduction process would occur by the step (9) or (10). Although the reduction product under the potential region of the second wave, was not confirmed, the current ratios between two reduction waves are to indicate that the reaction (9) is presumably favored over (10).

When the reduction of monomer (reaction (9)) is taking place over the region of the second reduction, the relative

current ratio (i_{p2}/i_{p1} , refer to Table 4) increases with increasing scan rate because the chemical dimerization of radical (reaction (7)) is fast enough. Furthermore, when the potential sweeping rate is very slow the coverage of monomer is much lower than that of dimer on the electrode surface, the current ratio (i_{p2}/i_{p1}) is thus probably close to zero. On the other hand, when the rate is fast enough, the coverage of monomer is much higher and the current ratio approaches to unity.

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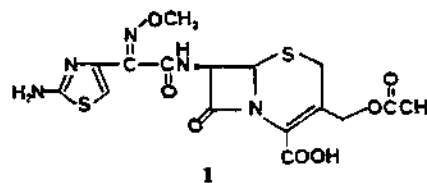
Synthetic β -Lactam Antibiotics II. Synthesis and Antibacterial Activity of 7 β -[2-(2-Aminothiazol-4-yl)-2-(methoxyimino)acetamido]-3-[1-(halosubstitutedphenyl)-1H-tetrazol-5-yl]thiomethyl-cephalosporins

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Syntheses of cefotaxime analogs with halosubstituted phenyltetrazolthiomethyl at the C₃-position are described. Their *in vitro* potency was established. The compounds exhibited a broad antibacterial spectrum. Some of these compounds showed activity against Gram-positive bacteria superior to the parent cefotaxime. Against Gram-negative bacteria, these compounds are less effective than cefotaxime.

Recently, a number of β -lactamase-stable, extended-spectrum cephalosporins referred to as third generation cephalosporins have been developed for clinical use. Among them, cephalosporins bearing (Z)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetyl group at the C₇ position of a cephem nucleus, such as cefotaxime(1),^{1,2} ceftizoxime,^{3,4} cefmenoxime⁵ and ceftriaxone^{6,7} are characterized by their excellent activity and marked resistance to β -lactamases. They are, however, relatively weak in Gram-positive activity, especially in anti-Staphylococcal activity as compared to older cephalosporins such as cephalothin.^{8,9} Also only a few exhibit substantial activity against *Pseudomonas* species.¹⁰



For the continuous work of extensive study on the development of broad spectrum cephalosporins, the primary aim in the present work was to prepare cefotaxime analogs by varying the C₃-substituent with enhanced potency against Gram-positive bacteria and *Pseudomonas* species, and high