Reactions of the dimedone anion with X-benzyl chlorides
Effect of substituents upon the C/O products ratio, and its theoretical interpretation

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Reactions of the dimedone anion with X-benzyl chlorides (X = H, 4-F, 4-Cl, 4-Br, 4-I, 4-CH$_3$, 4-OCH$_3$, 4-NO$_2$, 3-Cl, 3-Br, 3-I, 3-CH$_3$, 3-OCH$_3$) in acetone have been performed. It has been found that the ratio of C- to O-benzyl derivatives formed depends upon the character of the substituent X; log C/O = = f(σ^*). Using the semiempirical CNDO/2 method, the quantum chemical characteristics of X-benzyl chlorides have been calculated. A linear correlation of Hammett σ_p^* constants and charge densities at the electrophilic carbon atom, virtual orbital energies $\varepsilon_{\sigma^*_{C-Cl}}$, and calculated polarities of C—Cl linkages in X-benzyl chlorides have been found.

Были осуществлены реакции аниона димедона с замещенными Х-бензилхлоридами (X = H, 4-F, 4-Cl, 4-Br, 4-I, 4-CH$_3$, 4-OCH$_3$, 4-NO$_2$, 3-Cl, 3-Br, 3-I, 3-CH$_3$, 3-OCH$_3$) в ацетоне. Определилось, что соотношение С- и О-бензилпроизводных изменяется по характеру заместителя Х; было обнаружено, что log C/O = f(σ^*). Семиэмпирическим методом CNDO/2 были вычислены квантовохимические характеристики Х-бензилхлоридов и определена линейная зависимость между константами Гаммета σ_p^* и плотностями заряда на электрофильном углероде, энергиями виртуальных орбиталей $\varepsilon_{\sigma^*_{C-Cl}}$, а также вычисленными полярностями связей С—Cl Х-бензилхлоридов.

Recently, the perturbation MO theory in its qualitative interpretation has been used to explain the reactivity of ambident anions [1]. In its simple form, the method specifies that the ability of an ambident anion to react at its "hard" "soft" nucleophilic centre is given by the magnitude of initial interactions of the two main contributions: the charge and orbital components. In the case of a nucleophilic substitution at a carbon atom the driving force of the reaction is the interaction of an occupied orbital with a localized lone electron pair of the nucleophile, with an unoccupied σ^*_{C-X} orbital of the substrate. For example, nucleophilic substitution of ethyl acetoacetate with various R—X electrophiles affords C/O products the ratio of which decreases in the order of the increasing difference between the energy of the orbitals involved [2]. Accordingly, the C/O ratio decreases in the order

$I > Br > Cl > OTs$ (X = I, Br, Cl, OTs), whereas the $\sigma^*_{\bar{c}-x}$ orbital energy increases in the order $\sigma^*_{\bar{c}-I} < \sigma^*_{\bar{c}-Br} < \sigma^*_{\bar{c}-Cl} < \sigma^*_{\bar{c}-O}$ [3].

We have found previously [4, 5], when studying reactions of the dimedone (5,5-dimethyl-1,3-cyclohexanedione) anion and 2-(1-naphthyl)-1,3-indandione with X-benzyl bromides that the C- and O-product ratio was markedly influenced by the X substituent on the phenyl ring. We have found that $\log C/O = f(\sigma^*)$. Since there was found a relationship between Hammett constants and the $\sigma^*_{\bar{c}-x}$ energy of the lowest unoccupied orbitals [6], and the charge density at the electrophilic carbon atom, we have performed reactions of dimedone anion with X-benzyl chlorides in acetone and have calculated quantum chemical characteristics of X-benzyl chlorides. Thus, it was possible to evaluate the relationship between the calculated $\varepsilon_{\sigma^*_{\bar{c}-Cl}}$ values for X benzyl chlorides and the charge density at the reacting carbon atom, and the reactivity of the carbon and oxygen atoms of dimedone anion.

Experimental

The i.r. spectra (500—3500 cm^{-1}) were measured in Nujol using a Specord spectrophotometer equipped with NaCl optics. The instrument was calibrated against a polystyrene foil.

Reactions of the dimedone anion with X-benzyl chlorides

A mixture of dimedone (5 mmol), acetone (50 ml), and anhydrous potassium carbonate (15 mmol), contained in a three-neck flask equipped with a stirrer and a thermometer, was stirred for 10 min, and then treated with X-benzyl chloride (10 mmol, X = H, 4-F, 4-Br, 4-Cl, 4-I, 4-CH$_3$, 4-OCH$_3$, 4-NO$_2$, 3-Cl, 3-Br, 3-I, 3-CH$_3$, 3-OCH$_3$). The mixture was heated with stirring at 40 ± 1°C for 4 1/2 h, filtered, concentrated, and the residue was extracted with benzene (3×30 ml).

The benzene-insoluble material was dissolved in water (50 ml) and the solution was acidified (HCl). The precipitate was chromatographed on a column of silica gel (chloroform—ethanol 10:1) and the two substances eluted were identified as unreacted dimedone and 2-X-benzyl-5,5-dimethyl-1,3-hexanedione.

The benzene solution was concentrated to 30 ml and chromatographed on a column of alumina (Brockmann, Reanal, Budapest) with benzene—chloroform 1:1. First eluted was 2,2-di-(X-benzyl)-5,5-dimethyl-1,3-cyclohexanedione (IV). The mixture of 2-(X-benzyloxy)-5,5-dimethyl-2-cyclohexane-2-one (II) and 2-(benzyl-3-benzyloxy)-5,5-dimethyl-2-cyclohexen-1-one (III), eluted was rechromatographed on alumina with benzene—petroleum ether (20:1). The analytical data for the formed benzylation products agree with those given in our previous work [4]. In that work the pertinent data for all substances, except those formed from 4-fluorobenzyl chloride (see below), can be found.

2-(4-Fluorobenzyl)-5,5-dimethyl-1,3-cyclohexanedione (I), m.p. 175—177°C.

For C$_{15}$H$_{17}$FO$_2$ (248.2) calculated: 72.48% C, 6.85% H; found: 72.39% C, 6.93% H. ν(CO) (cm^{-1}): 1744, 1712.

3-(4-Fluorobenzyloxy)-5,5-dimethyl-2-cyclohexene-1-one (*II*), m.p. 47—49°C.

For $C_{15}H_{17}FO_2$ (248.2) calculated: 72.48% C, 6.38% H; found: 72.18% C, 6.76% H. ν(CO) (cm^{-1}): 1649, 1620.

2-(4-Fluorobenzyl)-2-(4-fluorobenzyloxy)-5,5-dimethyl-2-cyclohexene-1-one (*III*), m.p. 82—83°C.

For $C_{22}H_{22}F_2O_2$ (356.3) calculated: 74.23% C, 6.18% H; found: 74.39% C, 5.96% H. ν(CO) (cm^{-1}): 1650; ν(C=C):1620.

2,2-Di-(4-fluorobenzyl)-5,5-dimethyl-1,3-cyclohexanedione (*IV*), m.p. 126—128°C.

For $C_{22}H_{22}F_2O_2$ (356.3) calculated: 74.23% C, 6.18% H; found: 74.36% C, 6.33% H. ν(CO) (cm^{-1}). 1706, 1738.

Results and discussion

Reactions of the dimedone anion with X-benzyl chlorides in acetone were carried out at $40\pm1°C$. Based on the reaction with *p*-nitrobenzyl chloride which was the slowest of the reactions performed, the reaction time was prolonged from 3 to 4 1/2 h, as compared with the reactions involving X-benzyl bromides. All reactions were monitored by t.l.c. on silica gel. The dimedone anion was generated by treating dimedone with potassium carbonate. Four products were formed (see Experimental and Scheme 1) in all reactions, except in that carried out with
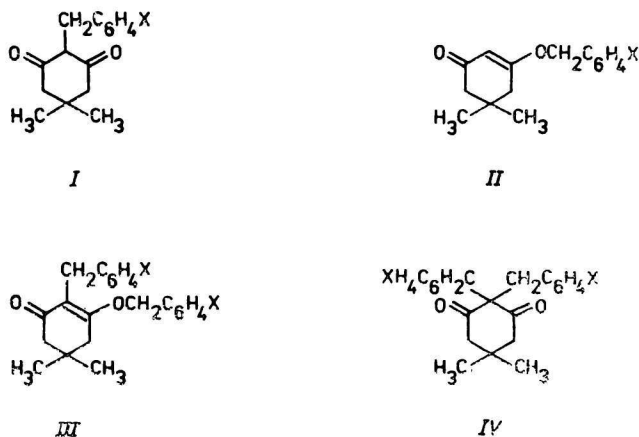
Scheme 1

4-methoxybenzyl chloride where the product of the primary C benzylation was not isolated. 2-X-Benzyl-5,5-dimethyl-1,3-cyclohexanediones (*I*) are the products of primary C benzylation, 3-X-benzyloxy-5,5-dimethyl-2-cyclohexene-1-ones (*II*) are those of primary O benzylation, 2-X-benzyl-3-X-benzyloxy-5,5-dimethyl-2-cyclohexene-1-ones (*III*) and 2,2-di-X-benzyl-5,5-dimethyl-1,3-cyclo-

hexanediones (*IV*) are the products of C benzylation, and of the secondary C,O benzylation (Table 1). The composition of the reaction mixture altered according to the nature of the substituent X. It can be seen from data in Table 2 that the C/O ratio, determined according to $C + CC + CO/O$, depends upon the substituent X: compounds bearing electron-donating and electron-withdrawing substituents gave higher yields of O and C benzylation, respectively. It was found by statistical evaluation that $\log C/O = f(\sigma^*)$. However, statistically important dependence was found only with primary substitution where $\log C/O = 0.250\sigma^* + 0.465$, $r = 0.902$. No such linear correlation was found for the secondary benzylation, as from *m*-derivatives more of the O compound was formed than would be expected for a linear dependence. The formation of a greater amount of the O product in the secondary benzylations with *m*-substituted X-benzyl chlorides can be explained by steric factors that prevent C benzylation. A comparison of benzylations with X-benzyl chlorides *vs.* similar reactions involving X-benzyl bromides [4] shows that, as expected, more of the O benzylation product was formed in reactions with the former derivatization agent; in benzylations with benzyl iodides a less of O benzylation products was formed [6]. Thus in agreement with the perturbation MO theory it can be concluded that also in the case of reactions of benzyl halides with the dimedone anion the increase of the orbital energy σ^*_{C-X} (X = I, Br, Cl), $\varepsilon_{\sigma^*_{C-I}} < \varepsilon_{\sigma^*_{C-Br}} < \varepsilon_{\sigma^*_{C-Cl}}$, makes the reaction at the "harder" nucleophilic centre more feasible, as a result of the more pronounced contribution of the charge component [7]. The calculated values $\varepsilon_{\sigma^*_{C-Cl}} = 4.027$ eV and $\varepsilon_{\sigma^*_{C-Br}} = 3.837$ eV for benzyl chloride and benzyl bromide, respectively, are in good agreement with the above-mentioned assumption.

We have also attempted to theoretically interpret the effect of substituents upon the C/O ratio of the formed products of benzylation. For this purpose the quantum chemical indices of the substituted benzyl chlorides were calculated using the semiempirical CNDO/2 method in its original parametrization [8]. The used geometry was that following from experimental data for benzyl chloride and substituted benzenes [9]. The data in Table 3 show that the substituent on the phenyl ring affects both the $\varepsilon_{\sigma^*_{C-Cl}}$ value and the electron density Q_C at the electrophilic carbon atom. Electron donating and withdrawing substituents increase and decrease, respectively, the σ^*_{C-Cl} energy, as compared with unsubstituted benzyl chloride. The effect of the substituent is, of course, different in the *meta* and *para* position. While a linear correlation (correlation coefficient $r = 0.919$) of calculated $\varepsilon_{\sigma^*_{C-Cl}}$ values and Hammett σ^* constants was observed for *p*-X-benzyl chlorides, the correlation impaired by including into calculations also the *m*-derivatives. Similarly, a linear dependence between the charge densities Q_C at the electrophilic carbon atom and σ^* constants of the substituents has been observed. A better correlation was again observed for the *p*-substituted benzyl chlorides ($r = 0.911$).

Table 1

Yields (%) of the reaction of 5,5-dimethyl-1,3-cyclohexanedione anion with X-benzyl chlorides in acetone

X	Overall yield	C derivative (I)	O derivative (II)	C,O derivative (III)	C,C derivative (IV)
p-NO₂	72.5	15.0	30.0	7	48
p-Br	68.0	15.5	28.5	10	36
p-F	64.0	28.0	31	8	33
p-Cl	65.0	24.0	27.0	12.5	36.5
p-CH₃	39.5	18.5	45.0	12.0	25
p-OCH₃	51.0	—	62.0	18	20
H	69.0	25.0	29.0	10	36
m-Cl	81.0	37.0	28.0	17.0	18.0
m-Br	79.0	35.0	26.0	19.0	20.0
m-CH₃	38.5	23.0	46.0	19.0	13.0
m-OCH₃	47.0	30.0	37.5	14.0	18.5

Table 2

C/O ratio (primary reaction) and the CC/CO ratio (secondary reaction) in the reaction of 5,5-dimethyl-1,3-cyclohexanedione with X-benzyl chlorides

X	C/O	log C/O	CC/CO	log CC/CO	σ^*
p-NO₂	3.5	0.54407	6.0	0.77815	0.80
p-F	2.2	0.34242	3.1	0.49136	−0.07
p-Cl	2.7	0.43136	2.9	0.46240	0.15
p-Br	2.6	0.41497	3.6	0.55630	0.11
p-CH₃	1.2	0.07918	2.1	0.32227	−0.31
p-OCH₃	0.6	0.77815 − 1	1.1	0.04139	−0.78
H	2.4	0.38021	3.6	0.55630	0.00
m-Cl	2.6	0.41497	1.1	0.04139	0.39
m-Br	2.7	0.43136	1.0	0.00000	0.39
m-CH₃	1.2	0.07918	0.7	0.84510	−0.09
m-OCH₃	1.8	0.25527	1.3	0.11394	0.12

Table 3

Calculated virtual-orbital energies ($\varepsilon^*_{\sigma^*_{C-Cl}}$), charge densities at the electrophilic carbon atom (Q_C), and differences between charge densities at carbon and chlorine atoms ($Q_C - Q_{Cl}$) for the studied X-benzyl chlorides

X	$\varepsilon_{\sigma^*_{C-Cl}}$/eV	Q_C	ΔQ
p-NO$_2$	3.4366	0.0967	0.2463
p-F	3.8964	0.1072	0.2691
p-Cl	3.8693	0.1052	0.2659
p-Br	3.9019	0.1052	0.2666
p-CH$_3$	4.0733	0.1064	0.2715
p-OCH$_3$	4.0652	0.1095	0.2755
H	4.0271	0.1045	0.2680
m-Cl	3.7686	0.1018	0.2598
m-Br	3.5563	0.1021	0.2600
m-CH$_3$	4.0597	0.1038	0.2679
m-OCH$_3$	3.9863	0.1019	0.2628

Assuming an S_N2 mechanism of the reaction under investigation, the nucleophilic substitution of benzyl chlorides may be described by an index as a measure of the extinction of the C—Cl linkage. We have found a linear correlation between the Wiberg index W_{C-Cl} and σ^* constants for p-substituted benzyl chlorides ($r = 0.936$). Another quantum chemical index that describes the C—Cl linkage polarity is the difference between charge densities at the electrophilic carbon atom and the chlorine atom. The thus calculated ΔQ values are in good linear correlation with σ^* constants for all derivatives studied ($r = 0.937$).

It can be concluded that the nucleophilic substitution reaction of X-benzyl chlorides with the ambient dimedone anion can be described by the following CNDO/2 quantum chemical characteristics: virtual orbital energy σ^*_{C-Cl}, charge density at the electrophilic carbon atom Q_C, and the C—Cl linkage polarity ΔQ. Benzyl chlorides showing low $\varepsilon_{\sigma^*_{C-Cl}}$, Q_C, and ΔQ values (*e.g.* p-NO$_2$ derivative) predominantly react with the "softer" nucleophilic centre — carbon atom; the more increase these quantum chemical indices the more increases also the significance of O benzylation, which becomes the main reaction for the derivative showing the highest $\varepsilon_{\sigma^*_{C-Cl}}$, Q_C, and ΔQ values (p-OCH$_3$ derivative). In order to characterize the studied reaction in a greater detail attempts were made to find a correlation between the quantum chemical parameters and experimental C/O values. The correlation, however, was not as clear as with Hammett constants. In order to find such correlations exact kinetic measurements would be required, taking into account also the effect of solvents upon the studied reactions. The outlined problem will be the objective of a subsequent investigation.

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