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Unexpected Double Benzylation of Acetophenone under Phase Transfer Catalysis Conditions. Acidity or π–π Interaction Effect?

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Abstract. A π–π interaction in the transition state of the benzylation of 1,3-diphenyl-1-propanone, the monobenzylation product of acetophenone, is proposed according to chemical, kinetic and theoretical approaches. Evidence for the existence of this kind of interaction in a transition state has been provided for the first time. The results obtained cannot be explained solely by the increased acidity but by considering the existence of a π–π interaction.

In the course of our studies[1] on selective alkylation of active methylenes under phase transfer catalysis in solvent-free conditions, an unexpected result was obtained in the benzylation of acetophenone **1**. The expected benzylated derivative (1,3-diphenyl-1-propanone, **2a**) was not obtained, with the double benzylation product 2-benzyl-1,3-diphenyl-1-propanone **3a**, being the only product under most of the reaction conditions.

Although it is known[2] that 1,3-diphenyl-1-propanone **2a** and other C-alkylated acetophenones are slightly more acidic than acetophenone **1**, the exclusive dibenzylation could not be explained by considering the acidity difference alone. Given the existence of π moieties on each of the reactants, a π–π interaction between the aromatic systems of benzyl halide and the ketone **2** in the transition state could be also considered as an additional contributing factor.

Interactions between π systems (aromatic and non aromatic) have been invoked to explain structural arrangements and selectivities observed in several reactions. Thus, π-interactions are known to control various

phenomena such as: the double helical structure of DNA,[3] drug interactions with DNA,[4] binding properties of polyaromatic macrocycles,[5] aggregation of porphyrins,[6] the tertiary structure of proteins,[7] host-guest systems,[8] the packing of aromatic molecules in crystals,[9] the resolution of racemic compounds by liquid-liquid chromatography,[10] diastereoselection in enolate alkylation,[11] enantioselection in addition to ketones,[12] Diels-Alder reactions,[13] and a wide range of phase transfer catalysed reactions using quaternary ammonium salts bearing phenyl moieties.[14] The p-p interactions are also essential for the control of asymmetric synthesis where induction achieved with chiral auxiliaries and chiral catalysts is enhanced by π-stacking effects.[15]

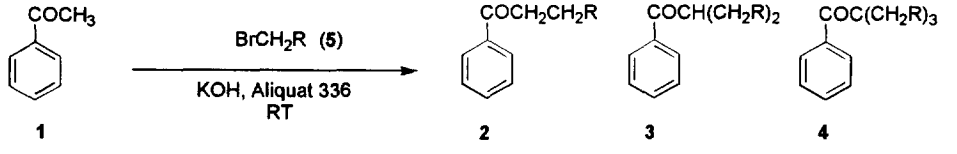
Theoretical approaches to explain the nature of π–π interactions have been reported.[16] Two main effects are present in a π–π interaction: charge transfer and coulombic (polar-π) effects. Examples of the predominance of charge transfer[17] and coulombic[18] effects have also been reported.

In all cases reported to date, the π–π interaction takes place between the aromatic moieties of two different molecules (structural arrangements, blocking one face in stereoselective reactions) and between the π-moieties of a molecule (conformational studies, selectivity in Diels-Alder reactions). In one case a π–π interaction in a transition state has also been proposed.[19]

Here we have taken several approaches, including chemical reactivity, kinetic calculations, molecular mechanics and semiempirical (PM3) methods, to verify the possibility of a π–π interaction being involved in the transition phase during the benzylation of 1,3-diphenylpropanone.

Results and Discussion

Benzylations of acetophenone were performed by stirring a mixture of **1**, benzyl bromide **5a**, finely ground potassium hydroxide and Aliquat 336[20] as catalyst, at room temperature for 20 hours in the absence of solvent. Table 1 summarizes the obtained results. Excellent transformations were obtained using a 1:2:1 (**1** : base : benzyl bromide) molar ratio. Minor amounts of 1,3-diphenyl-1-propanone **2a** were formed when a large excess of **1** was used and small amounts of the tribenzylated derivative **4a** could be detected with a large excess of halide.



compound	a	b	c	d	e	f	g
R	C_6H_5	H	$CH_3CH_2CH_2$	*p*-$CF_3C_6H_4$	*p*-$CH_3OC_6H_4$	$H_2C{=}CHCH_2$	$HC{\equiv}CCH_2$

for **5b** and **5c**, iodides are used

Table 1. Benzylation of **1**. Solvent-free PTC conditions.

entry	molar ratio [a]	**2a**	**3a**	**4a**
1	1 : 1 : 1	0	59	0
2	1 : 2 : 1	0	97	0
3	2 : 1 : 1	0	27	0
4	4 : 4 : 1	6	32	0
5	1 : 4 : 4	0	38	5

[a] **1** : base: benzyl bromide **5a** (+10% Aliquat 336)

Table 2 summarizes the influence of the presence or absence of solvent. Dibenzylation is always favoured, but yield and selectivity are far better in the absence of solvent under PTC than in solution.

Table 2. Influence of reaction conditions (reaction time: 20h; molar ratio 1:1:1)

Experimental conditions	**2a** / **3a** ratio	yield (%)
NaOH aq. (50%) : dichloromethane : RT	0 : 0	0
NaOH aq. (50%) : toluene : reflux	43 : 57	23
KOH (s): DMSO : RT	10 : 90	58
KOH (s) : toluene : RT	11 : 89	69
KOH (s) : no solvent : RT	0 : 100	97

Electrophiles not bearing π-moieties, such as methyl and butyl iodide, afforded important amounts of monoalkylated derivatives and substituted benzyl bromides yielded mainly dialkylation products. A predominance of dialkylation was also obtained with allyl and propargyl bromides (Table 3). Thus, it was confirmed that the use of electrophiles bearing a π-moiety undeniably favours the formation of dialkylated products.

Table 3. Reactions of **1** with electrophiles. Solvent-free PTC conditions.

electrophile	**5a**	**5b**	**5c**	**5d**	**5e**	**5f**	**5g**
2/3 ratio	0/100	55/45	67/33	13/87	20/80	20/80	21/79

In order to evaluate the influence of acidity, some competitive alkylations were performed. Thus, **1** and **2a**, which have different acidities, were reacted with benzyl and butyl bromide; **2a** and **2c**, which posseses similar acidities, were reacted with benzyl bromide (Table 4). After 20 h any unreacted ketone was determined by gas

chromatography. These results showed an important difference with respect to benzyl and butyl bromides (entries 1 and 2). In the reaction with butyl bromide the higher conversion of **2a** over **1** simply reflected the higher acidity of **2a**. For benzyl bromide however, an additional specific effect (no conversion of **1**) must be taken into account. In the competitive benzylation of **2a** and **2c**, in which the acidities were similar, the greater conversion of **2a** must be related to the existence of an additional π moiety in **2a**. This selectivity could also be observed by determining the reaction rates using the initial rate method.[21] Benzylation of **1** ($k= 5.2 \times 10^{-3}$ min^{-1}) and butylation of **2a** ($k= 5.5 \times 10^{-3}$ min^{-1}) are slower than benzylation of **2a** ($k= 18.1 \times 10^{-3}$ min^{-1}).

Table 4. Competitive alkylations. Solvent-free PTC conditions.

ketones	electrophile	ketone conversion
1 / 2a	benzyl bromide, **5a**	0 / 66
1 / 2a	butyl bromide, **5c**	27 / 52
2c / 2a	benzyl bromide, **5a**	21 / 60

Consequently, according to chemical and kinetic studies, it can be assumed that the exclusive dibenzylation of **1** is controlled not only by acidity but by an additional factor, namely a stabilizing π–π interaction in the transition state between the aromatic systems of the benzyl halide and at least one of the aromatic groups of the ketone.

Unlike for other reported π–π interactions, no spectroscopic and crystallographic methods could be used to prove the interaction and so we turned our attention to theoretical approaches.

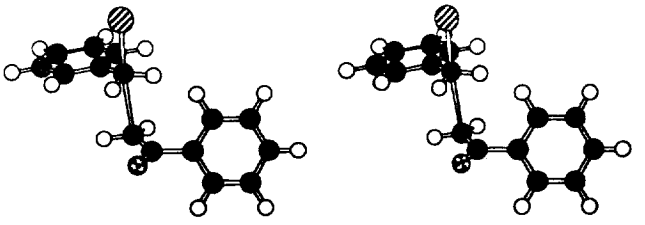
Molecular mechanics calculations were performed using MAD.[22] The model we considered admits the approach of the enolate and the alkyl halide leading to a supermolecule with a geometry which approximates the reaction transition state. Four supermolecules from benzylation and butylation of **2a** and **2c**, were considered (Table 5). Differences in energy are not significant, but the geometry of the supermolecule in the dibenzylation process (**2a+5a**) clearly pointed to an influence of π-stacking: this is the only case where the supermolecule geometry approximates a transition state.

Table 5. Molecular Mechanics (MAD 2.0)[22]

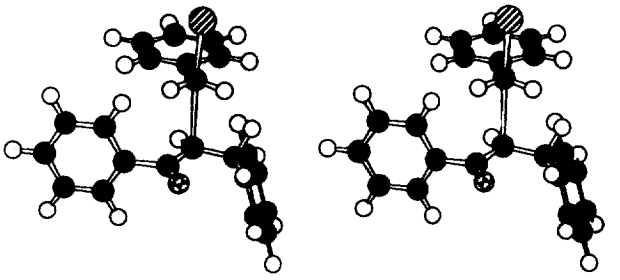
reaction	E (kcal/mol)	ΔE(kcal/mol)	θ (°)	d (Å)
1 + 5a	23.93	-3.90	-127	5.5
2a + 5a	33.51	-5.09	92	3.8
1 + 5c	17.05	-4.15	157	5.1
2a + 5c	19.84	-5.07	60	5.6

E= supermolecule energy. ΔE= difference between supermolecule and reactants energy. θ(°)= enolate - CBr bond, dihedral angle. d= distance between reactive centres.

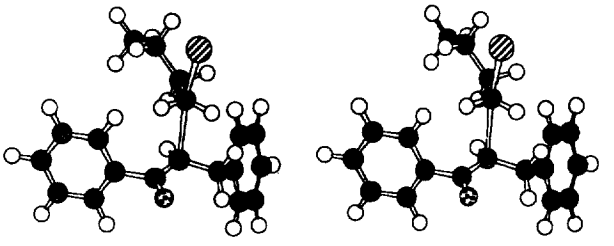
Stereoview of transition state of the reaction **1a** + **5a**



Stereoview of transition state of the reaction **2a** + **5a**



Stereoview of transition state of the reaction **2a** + **5c**



Figure

A more accurate approach to the transition state geometries was performed by semiempirical calculations (PM3).[23] Taking into account the experimental conditions, absence of solvent and a large ammonium cation, and the fact that we compared two transition states for two reactions performed under identical conditions a simplified model for the transition state has been considered.

The figure shows the calculated geometries for the transition state during the benzylation of **1** and **2a** and the butylation of **2a**. According to Hunter[24] the SICD (Shortest Inter-residue Carbon-carbon Distance), the Rxy (the projection of the position vector of the centre of the observed phenyl from the centre of the reference phenyl on the xy plane which includes the reference phenyl group) and α (dihedral angle between phenyl groups) values (Table 6) indicate the existence of three stabilizing π-interactions in the transition state during the benzylation of **2a**, while only one interaction is present in the benzylation of **1** and butylation of **2a**. Examination of these transition states shows a new interaction (enolate-electrophile) to be present. This new interaction takes place with the phenyl moiety of the benzyl group, not with the benzoyl group.

Table 6. Transition state (TS) geometries from PM3[23]

TS	ΔH (kcal.mol^{-1})	SICD (Å)	R_{xy} (Å)	α	π-moieties	π-interaction
1+5a	-3.72	4.7	6.6	63	$PhCO/BrCH_2Ph$	yes
2a+5a	12.89	4.7	5.9	98	$PhCO/CHCH_2Ph$	yes
		3.6	4.8	95	$PhCO/BrCH_2Ph$	yes
		3.6	5.4	71	$BrCH_2Ph/CHCH_2Ph$	yes
2a+5c	-28.71	4.8	5.6	81	$PhCO/CHCH_2Ph$	yes

This result is in agreement with all the experimental results reported above and could be used as a predictive tool. Hence, pinacolone, which has no π-moieties, should react like acetophenone, because its π-system is not involved in the new interaction. Indeed, using standard reaction conditions, pinacolone affords the dibenzylated derivative as does acetophenone.

In conclusion, theoretical approaches and chemical evidence indicate that the unexpected dibenzylation of acetophenone cannot be explained solely by the higher acidity of the alkylated acetophenones but by considering the existence of stabilizing π–π interactions during the transition state of the second benzylation. Under similar reaction conditions with reactants of comparable acidities, the number of π–π interactions in the transition state is a reliable predictive tool. In this regard PM3 calculations for the transition state geometries prove to be very useful.

Experimental Section

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. IR spectra were recorded on a Philips PW9500. ^{1}H-NMR spectra were recorded at 300 MHz (Varian Unity 300) in $CDCl_3$; chemical shifts are reported in δ units (ppm) relative to tetramethylsilane and coupling constants are expressed in Hz. Elemental analyses were performed on a Perkin Elmer PE2400 CHN elemental analyser. GC analyses were performed on a Konik 3000 and Carlo Erba GC 6000 apparatus using hydrogen and helium respectively as the carrier.

All solvents used for extractions or reactions in solid-liquid or liquid-liquid PTC were dried according to standard procedures and kept over molecular sieves. All chemicals used were commercially available. Compounds **2a, 2d** and **2e** were prepared by hydrogenation of the appropriate chalcones following literature procedures.[25]

PM3 calculations were run on a Silicon Graphics 4D35 workstation using a MOPAC 6.0 program.[26] Used keywords were PM3, XYZ, NLLSQ, PRECISE, GNORM=0.01, FORCE.

1,3-Diphenyl-1-propanone (2a): mp 71-3°C (ethanol). IR (KBr) 1685 cm^{-1}. ^{1}H NMR 3.06 (2H, t, J=7), 3.29 (2H, t, J=7), 7.19-7.97 (10H, m). Anal. Calcd for $C_{15}H_{14}O$: C, 85.68; H, 6.71%. Found: C, 85.77; H, 6.65%.

1-Phenyl-3-(p-trifluorophenyl)-1-propanone (2d): mp 48.5-50°C (ethanol/water). IR (KBr) 1672 cm^{-1}. ^{1}H NMR 3.13 (2H, t, J=7), 3.33 (2H, t, J=7), 7.35-7.98 (9H, m). Anal. Calcd for $C_{16}H_{13}F_3O$: C, 69.06; H, 4.71%. Found: C, 69.20; H, 4.79%.

1-Phenyl-3-(p-methoxyphenyl)-1-propanone (2e): mp 57.5-58.5°C (light petroleum). IR (KBr) 1677 cm^{-1}. ^{1}H NMR 3.00 (2H, t, J=7), 3.27 (2H, t, J=7), 3,78 (3H, s), 6.82-7.98 (9H, m). Anal. Calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71%. Found: C, 80.12; H, 6.90%.

General procedure for alkylations of acetophenone (table 2). Acetophenone (10 mmol), finely ground potassium hydroxide (10 mmol) and Aliquat 336 (1 mmol) were stirred at room temperature for 5 min. The appropriate alkyl halide (10 mmol) was then added and the reaction was stirred for 20 h. The crude product was extracted with dichloromethane and analysed by GC or ^{1}H-NMR.

2-Benzyl-1,3-diphenyl-1-propanone (3a): mp 74-75°C (ethanol). IR (KBr) 1678 cm^{-1}. ^{1}H NMR 2.79 (2H, dd, J=6.3 and 14.0), 3.13 (2H, dd, J=7.7 and 14.0), 4.02 (1H, quint, J=7), 7.12-7.34 (15H, m). MS (ammonia chemical ionization) m/z(%) 318 (M+18, 33), 301 (M+1, 100), 300 (M, 1), 209 (40), 105 (22). Anal. Calcd for $C_{22}H_{20}O$: C, 87.96; H, 6.71%. Found: C, 87.78; H, 6.78%.

1-Phenyl-1-hexanone (2c): (yellow oil) bp 75°/0.2 mmHg. IR (neat) 1684 cm^{-1}. ^{1}H NMR 0.89-1.74 (9H, m), 2.97 (2H, t, J=7.2), 7.46-7.99 (5H, m).

2-Butyl-1-phenyl-1-hexanone (3c): (yellow oil) bp 150°/1.5 mmHg. IR (neat) 1678 cm^{-1}. ^{1}H NMR 0.7-1.85 (18H, m), 3.26-3.50 (1H, m), 7.45-8.00 (5H, m).

1-Phenyl-2-(*p*-trifluoromethylbenzyl)-3-(*p*-trifluoromethylphenyl)-1-propanone (3d): (yellow oil) IR (neat) 1676 cm^{-1}. ^1H NMR 2.85 (2H, dd, J=6.1 and 13.7), 3.20 (2H, dd, J=7.8 and 13.7), 4.04 (1H, quint, J=7), 7.23-7.98 (9H, m).

1-Phenyl-2-(*p*-methoxybenzyl)-3-(*p*-methoxyphenyl)-1-propanone (3e): (yellow oil) IR (neat) 1676 cm^{-1}. ^1H NMR 2.71 (2H, dd, J=6.2 and 13.8), 3.03 (2H, dd, J=7.9 and 13.8), 3.70 (6H, s), 3.89 (1H, quint, J=7), 6.70-7.95 (9H, m).

1-Phenyl-4-penten-1-one (2f): (yellow oil) IR (neat) 1680 cm^{-1}. ^1H NMR 2.49-2.56 (2H, m), 3.09 (2H, t, J=7.3), 4.99-5.14 (2H, m), 5.80-6.00 (1H, m), 7.30-8.00 (5H, m).

1-Phenyl-2-allyl-4-penten-1-one (3f): (yellow oil) IR (neat) 1677 cm^{-1}. ^1H NMR 2.30 (2H, m, J=1.2, 6.1, 7.0 and 14.0), 2.53 (2H, m, J=1.2, 7.0 and 14.0), 3.59 (1H, tt, J=6.1 and 7.0), 4.96-5.09 (4H, m), 5.74 (2H, qt, J=7.0, 10.2 and 17.1), 7.46-7.56 (3H, m), 7.95 (2H, m).

1-Phenyl-4-pentin-1-one (2g): (yellow oil) IR (neat) 1675 cm^{-1}. ^1H NMR 2.10 (1H, t, J=2.6), 2.65 (2H, td, J=2.6 and 7.3), 3.22 (2H, t, J=7.3), 7.30-8.00 (5H, m).

1-Phenyl-2-propargyl-4-pentin-1-one (3g): (yellow oil) IR (neat) 1679 cm^{-1}. ^1H NMR 2.00 (2H, t, J=2.6), 2.62 (2H, dd, J=2.6 and 6.6), 2.63 (2H, dd, J=2.6 and 6.6), 3.80 (2H, t, J=6.6), 7.40-8.00 (5H, m).

Reactions under classical PTC methods (table 3).

Liquid-liquid PTC. A solution of acetophenone (25 mmol), benzyl bromide (25 mmol) and Aliquat 336 (2.5 mmol) was added to aqueous 50% sodium hydroxide (4 ml), and the reaction mixture was stirred at the indicated temperature. Dichloromethane (50 ml) was added and the aqueous phase was extracted twice with dichloromethane (2x25 ml). The combined organic fractions were dried over anhydrous magnesium sulfate and analysed by GC.

Solid-liquid PTC. Acetophenone (10 mmol), KOH (20 mmol), Aliquat 336 (1 mmol) and the corresponding solvent (2 ml) were stirred at room temperature for 5 min, then benzyl bromide (10 mmol) was added and the mixture was stirred at room temperature for 20 h. The organic layer was extracted with dichloromethane, dried over magnesium sulfate and analysed by GC.

Competitive reactions (table 4). An equimolecular amount of the appropriate ketone (1 mmol + 1 mmol), KOH (1 mmol), the catalyst (0.1 mmol) and the corresponding halide (1 mmol) were stirred at room temperature for 20 h. The crude reaction mixture was extracted with dichloromethane and analysed by GC.

Kinetics. Employing the initial rate method, a set of reactions (under the standard conditions) was run and stopped at 5, 10, 15, 30 and 45 min respectively. Three GC analyses for each reaction were performed.

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