Methanolysis (Solvolysis) and Synthesis of 4'-Substituted 4-Benzyloxybenzyl Chlorides and Some Related Compounds: Comparisons with the Corresponding Benzoyl Compounds

By **Jorge Armando Luis Jorge, Nilo Zengo Kiyan,** and **Yukino Miyata,** Instituto de Química, Universidade de São Paulo, Caixa Postal 20.780, 01.000 São Paulo SP, Brasil
Joseph Miller,* Instituto de Química, Universidade Estadual de Campinas, Caixa Postal 1170, 13.100 Campinas SP, Brasil

The kinetics of methanolysis (solvolysis) in 97.4% MeOH–dioxan of a series of 4'-substituted 4-benzyloxybenzyl chlorides, and of 4-anisyl, 4-phenoxybenzyl, and benzyl chlorides have been studied and discussed, including comparisons with the data for the corresponding series of benzoyl chlorides, previously reported by us. The 4'-substituted precursor alcohols, chlorides, and product methyl ethers are all new compounds. 4-Anisyl chloride and the series of benzyloxybenzyl chlorides react by the S_N1 mechanism, whereas benzyl chloride reacts by the S_N2 mechanism. 4-Phenoxybenzyl chloride shows intermediate behaviour. A similar pattern was observed with the corresponding benzoyl compounds. In both series the reactivity order is CH_3O > 4'-$CH_3C_6H_4CH_2O$ (−0.76) >$C_6H_5CH_2O$ (−0.74) > 4'-$ClC_6H_4CH_2O$ (−0.69) > 4'-$NO_2C_6H_4CH_2O$ (−0.60) > C_6H_5O > H (values in parentheses are new σ^+ values). At 25° the overall range of rates is 4 290 in the benzyl series, compared with only 2.42 in the benzyl series. The Arrhenius parameters in the two series demonstrate, however, an underlying similarity with obvious differences superimposed. In *both* series, the introduction of 4-OR groups leads to a $\Delta S^\ddagger$ increase of *ca.* 40 J mol^{-1} K^{-1}. In the benzyl series this is accompanied by $\Delta E^\ddagger$ *decreases* of *ca.* 6—10 kJ mol^{-1}, whereas in the benzoyl series $\Delta E^\ddagger$ values *increase* by *ca.* 10—15 kJ mol^{-1}. The equation $\log k = \log k_0 + n[\text{MeOH}]$ in mixtures with increasing content of dioxan, was used to study the rate dependence on MeOH concentration. Values of *n* are *ca.* 5 between 97.4 and 8.3.% MeOH, and *ca.* 3 between 83.3 and 50.0% MeOH.

FOLLOWING studies [1] of the methanolysis (solvolysis) in 97.4% MeOH–dioxan of 4'-substituted 4-benzyloxybenzoyl chlorides and some related compounds, we have studied the same reaction with the corresponding benzyl chlorides, to demonstrate the shift from S_N2 to S_N1 mechanism and the similarities and differences in the kinetic data.

All the 4'-substituted chlorides, their precursor alcohols, and product methyl ethers are new compounds.

EXPERIMENTAL

Materials.—The 4'-substituted-4-benzyloxybenzyl alcohols, from which we prepared the chlorides, were synthesized by two methods. Method A involved the condensation of 4-hydroxybenzyl alcohol [2] with various benzyl chlorides or bromides in alkaline medium.[3] Method B involved the reduction of the corresponding methoxycarbonyl compound [1] with lithium aluminium hydride.[4]

4-Hydroxybenzyl alcohol was obtained by reduction of 4-hydroxybenzaldehyde with sodium borohydride in aqueous 1.1N-NaOH.[2] 4-Chlorobenzyl bromide was prepared by the side-chain bromination (Br_2; reflux) of purified 4-chlorotoluene irradiated with light.[5] 4-Nitrobenzyl chloride was prepared by the nitration of purified benzyl chloride, using concentrated HNO_3 and H_2SO_4 under reflux.[6] 4-Anisyl chloride was prepared by treating 4-anisyl alcohol with $SOCl_2$ in light petroleum (b.p. 65—110 °C), followed by fractional distillation at reduced pressure; as well as by treating 4-anisyl alcohol with concentrated HCl, followed by fractional distillation in a Kugelrohr apparatus at reduced pressure.[7] 4-Methylbenzyl chloride was prepared by the chloromethylation of toluene with paraformaldehyde, $ZnCl_2$, and HCl (gas).[8]

The 4'-substituted 4-benzyloxybenzyl alcohols produced by Method A were converted into the corresponding chlorides by reaction with $SOCl_2$ in light petroleum (b.p. 65—110 °C). The methoxycarbonyl compounds required for Method B were prepared as previously described by us.[1] The reduction to the corresponding alcohols was effected by lithium aluminium hydride in anhydrous tetrahydrofuran.[4]

p-Phenoxybenzyl chloride was prepared by the chloromethylation of diphenyl ether, using formaldehyde (30% aqueous) and HCl (concentrated and gas) in a modification of literature procedures.[9-11] An alternative preparation *via* the reduction of *p*-phenoxybenzoyl chloride [12] involved the sequence: diphenyl ether ⟶ 4-bromodiphenyl ether, conversion of Br into COCl *via* the MgBr compound, and its reaction with CO_2 to give the acid, which was treated with $SOCl_2$.

TABLE 1

4'-Substituted 4-benzyloxybenzyl alcohols,* chlorides,* and methyl ethers *

	Alcohol [a]			Chloride [a]		Methyl ethers
4'-Substituent	Preparation	Yield (%)	M.p. (°C)	Yield (%)	M.p. (°C)	M.p. (°C)
H	Methods A,B	70, 76	87—88	70	78,5—80	
NO_2	Method A	50 [b]	126—128	51	86—87	67—69 [c]
Cl	Method B	59	105—106,5	64	74—75	59,5—61 [d]
CH_3	Method B	72	103—104,5	60	99—101	51—53
OCH_3	Method B	61	115—117	†		

* All are new compounds except the parent (unsubstituted) alcohol, chloride, and methyl ether. † Not obtained at purity (>99% suitable for kinetic studies.

[a] From light petroleum (b.p. 65—110 °C). [b] From MeOH–H_2O then light petroleum. [c] From MeOH–H_2O. [d] From EtOH–H_2O

TABLE 2

Experimental rate constants * for methanolysis (solvolysis) of p-$XC_6H_4CH_2Cl$ in 97.4% MeOH–dioxan (except as shown). Solutions 2.35×10^{-3} M

X	$10^4k/s^{-1}$ (t/°C) (temp. in parentheses)		X	$10^4\ k/s^{-1}$ (t/°C) (temp. in parentheses)	
PhO	0.321, 0.323	(41.0)	p-$NO_2C_6H_4CH_2O$	1.04, 1.04	(33.0)
	0.700, 0.713, 0.713	(49.0)		2.49, 2.50, 2.56, 2.56	(41.0)
	1.49, 1.52, 1.52	(57.0)		5.69, 5.72, 5.80	(49.0)
	2.95	(65.0)		12.9, 12.9	(57.0)
MeO	1.05, 1.06, 1.07, 1.07	(17.0)	p-$ClC_6H_4CH_2O$	1.02, 1.02	(25.0)
	2.76, 2.81	(25.0)		2.66, 2.66, 2.66, 2.67	(33.0)
	6.52, 6.57	(33.0)		6.28, 6.28, 6.33, 6.43	(41.0)
	15.5, 15.8, 16.0	(41.0)		14.6, 14.7, 14.7, 14.8	(49.0)
	34.3, 35.2	(49.0)			
			p-$CH_3C_6H_4CH_2O$	2.20, 2.23	(25.0)
$PhCH_2O$	0.713	(17.0)		5.64, 5. 65,5.67, 5.68	(33.0)
	1.80, 1.83	(25.0)		13.4, 13.4, 13.4	(41.0)
	4.33, 4.35, 4.38	(33.0)		28.8, 28.9, 29.0, 29.0	(49.0)
	10.1, 10.1, 10.1, 10.2	(41.0)			
	5.78 (83.3% MeOH)	(41.0)			
	3.30 (70.0% MeOH)	(41.0)			
	1.52 (50.0% MeOH)	(41.0)			

* In accordance with the high level of reproducibility, the percentage errors are almost all $< \pm 1\%$, and correlation coefficients almost all in the range 0.9990—1.0000.

The structures and purity of all the compounds and the product methyl ethers (see Table 1) were confirmed by elemental analysis, i.r., n.m.r., and mass spectra) as well as by titrimetric or gravimetric estimation of the chlorine after displacement to form chloride ion. No compound was <99% pure by chloride analysis. For this reason we do not yet report kinetic results for the 4'-methoxy-compound which we have so far been unable to purify to this level.

Kinetic Studies.—With a Metrohm conductance bridge E382 we used a conductimetric method to obtain rate constants, *viz.* by Guggenheim plot analysis of the conductance increases resulting from the methanolysis of *ca.* 2.3×10^{-3}M solutions of the various chlorides in 97.4% MeOH–2.6% dioxan: the small amount of dioxan, which has little effect on rates, was added to increase the solvent power of the medium. Some measurements were also made in mixtures containing 83.3, 70.0, and 50.0% MeOH with dioxan.

Rate constants and derived parameters evaluated by a PDP 10 computer are given in Tables 2 and 3.

DISCUSSION

The phenyl group facilitates the S_N2 as well as the S_N1 mechanism.[13] The level of the former is diminished and of the latter augmented by electron-donating groups (*e.g.* 4-OMe) in the ring. Thus benzyl chloride reacts in most conditions by the S_N2 and p-anisyl chloride by the S_N1 mechanism.[14]

Table 3, which includes some literature data, demonstrates the marked differences in the patterns of rates and Arrhenius parameters of benzyl chloride when compared with 4-anisyl and the various 4'-substituted 4-benzyloxybenzyl chlorides. The intermediate character of kinetic data for 4-phenoxybenzyl chloride is also clear.

Our results demonstrate that the 4-OR groups cause a 2 800—4 300-fold increase in solvolysis rates (25 °C), a change in the order of dependence on methanol concentration in mixtures with dioxan, and marked changes in the pattern of Arrhenius parameters.

Analysis of the latter shows that the rate increases relate mainly to substantial increases (less negative) of the entropy of activation ($\Delta S^‡$) of *ca.* 40 J mol^{-1} K^{-1}, which is equivalent to a $\log_{10}A$ increase from *ca.* 9 to 11. We relate these increases to the looser transition-state implied by the shift from the S_N2 to the S_N1 mechanism. It is noteworthy that the $\Delta S^‡$ (and $\log_{10}A$) values for benzyl chloride are themselves quite high, which we regard as implying an S_N1-like reaction even in that case.

Activation energy decreases of the order of 6—10 kJ

TABLE 3

Rate constants and derived kinetic data for methanolysis of 4-substituted benzyl chlorides in MeOH–dioxan 97.4% (w/w), except as shown

Substituent	Rate constant $10^5\ k/s^{-1}$ 25.0 °C	Rate constant $10^5\ k/s^{-1}$ 41.0 °C	Relative rates 25.0 °C	Relative rates 41.0 °C	Activation energy $\Delta E^‡$/kJmol^{-1}	Frequency factor $\log_{10}$ (A/s^{-1})	Activation entropy $\Delta S^‡$/J mol^{-1} K^{-1}
H *	0.006 36		1.00		94.1	9.3	−75.1
PhO	0.597	3.22	93.9	0.032	82.2	9.2	−77.0
MeO	27.3	158	4 290	1.56	84.8	11.3	−36.4
$PhCH_2O$	18.1	101	2 850	1.00	84.2	11.2	−38.3
In 83.3% MeOH		57.9		0.572			
In 70% MeOH		33.0		0.327			
In 50% MeOH		15.2		0.150			
p-$NO_2C_6H_4CH_2O$	4.13	25.3	649	0.251	87.9	11.0	−42.6
p-$ClC_6H_4CH_2O$	10.4		1 640	0.627	88.1	11.5	−33.0
p-$MeC_6H_4CH_2O$	22.8		3 590	1.33	85.1	11.3	−36.4

* See D. L. Dalrymple *et. al.*, *J. Org. Chem.*, 1964, **29**, 2647; R. A. Clement *et al.*, *J. Amer. Chem. Soc.*, 1960, **82**, 2449.

mol^{-1} are ascribed to enhanced conjugation in and solvation of the forming $4\text{-ROC}_6H_4CH_2^+$ intermediates.

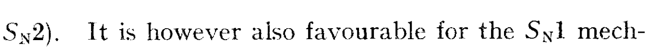
The relationship $\log k = \log k_0 + n[\text{MeOH}]$ was used to evaluate the dependence on methanol concentration, in the case of methanolysis of the parent benzyloxybenzyl chloride. The n value was *ca.* 5 between 97.4 and 83.3% methanol, and *ca.* 3 between 83.3 and 50.0% methanol. These values are consistent with the operation of the S_N1 mechanism, suffering some inhibition as the proportion of methanol decreases.

The high precision of the kinetic data is indicated by the satisfying relationship of rates within the series of 4′-substituted 4-benzyloxybenzyl chlorides including 4′-H and in comparing them all with values for 4-anisyl chloride.

Comparing CH_3O and $ArCH_2O$ groups as 4-substituents, the donating power of oxygen should be less in the latter, since a C_6H_5 group is electron-withdrawing compared to H when joined to saturated carbon; and its effect should be modified by 4′-substituents in a readily understandable way. Thus we found the reactivity order of methanolysis (solvolysis) of $4\text{-XC}_6H_4CH_2Cl$ to be: X = $CH_3O > 4'\text{-}CH_3C_6H_4CH_2O > C_6H_5CH_2O > 4'\text{-}ClC_6H_4CH_2O > 4'\text{-}NO_2C_6H_4CH_2O$. The range of rates is only *ca.* 6-fold and the Arrhenius parameters are similar for all the compounds.

Applying the Hammett equation, and using the widely accepted value for $\sigma^+_{p\text{-OMe}}$ of -0.78 our reaction series has a minimum * ρ value of -4.7 (25 °C). We thus estimate new σ_p^+ values ($4'\text{-XC}_6H_4CH_2O$): 4′-CH_3 -0.76, 4′-H -0.74, 4′-Cl -0.69, 4′-NO_2 -0.60.

Data for the 4′-substituted 4-benzyloxybenzyl chloride solvolyses permit the evaluation of a subsidiary ρ' constant using ordinary σ values for the 4′-substituents. The ρ' value obtained is -0.82; and the ratio $\rho' : \rho$ is equivalent to a transmission coefficient, which has the value 0.18. There are no literature values for transmission across a benzene ring and attached methylene to an oxygen atom, itself exercising a substituent effect across a benzene ring to an attached methylene reaction centre. Comparison with the results given in our earlier paper on methanolysis (solvolysis) of the corresponding benzoyl chlorides demonstrates a number of interesting features. However, we first emphasize some differences between the functional groups involved. A COCl group has a structure very favourable for the non-synchronous addition–elimination S_N2 mechanism (AE



S_N2). It is however also favourable for the S_N1 mechanism, due to the internal stabilisation of the acylium ion.

The additional conjugation with the phenyl group in benzoylium ion further favours the S_N1 and impedes the AE S_N2 mechanism. Nevertheless in most conditions (including neutral methanolysis) benzoyl chloride reacts by the latter mechanism but the methanolysis of 4-anisoyl and 4-benzyloxybenzoyl chlorides has marked S_N1 character.

Comparisons of kinetic data for the two series demonstrate obvious substantial differences superimposed on a certain similarity in pattern. The principle difference is that the range of substituents studied by us corresponds to a large range of rates in the benzyl series, but a very much smaller range of rates in the benzoyl series. Nevertheless the substituent order of rates is the same for both 4-XC_6H_4COCl and $4\text{-XC}_6H_4CH_2Cl$ series, *viz.* 4-X = $CH_3O > 4'\text{-}CH_3C_6H_4CH_2O > C_6H_5CH_2O > 4'\text{-}ClC_6H_4CH_2O > 4'\text{-}NO_2C_6H_4CH_2O$.

We explain the large differences in relative rates as follows. In the COCl reactions the CO group itself markedly favours the S_N1 (as well as the AE S_N2) mechanism, so that substituents in the benzene ring joined to the COCl group simply modify it. In contrast, in the CH_2Cl reactions, the CH_2 group contains no element favouring S_N1 reactions. It is the benzene ring joined to it (especially when containing electron-donating substituents) which makes the S_N1 reactions possible, so that substituent effects are much larger.

Table 4 illustrates very clearly the difference between the two series.

TABLE 4

Substituent rate ratios at 25° of methanolysis (solvolysis in 97.4% MeOH–dioxan) of some benzoyl and benzyl chlorides ($ArCOCl$ and $ArCH_2Cl$)

Ar group, showing 4-X of 4-XC_6H_4	Reaction centre	
	COCl	CH_2Cl
H	1	1
C_6H_5O	0.895	23.9
$4'\text{-}NO_2C_6H_4CH_2O$	1.29	649
$C_6H_5CH_2O$	2.01	2 850
$4'\text{-}CH_3C_6H_4CH_2O$	2.15	3 590
CH_3O	2.42	4 290

As interesting as the large differences in substituent effects is a certain similarity in Arrhenius parameter patterns. In both series, 4-OR groups cause $\Delta S^\ddagger$ increases of the order of 40 J mol^{-1} K^{-1} which we have related (see above) to the marked loosening of the transition state in the shift from S_N2 to S_N1 reactions. It is therefore the $\Delta E^\ddagger$ values which discriminate the two series. In the benzyl series, as we mentioned, $\Delta E^\ddagger$ values for the 4-ROC_6H_4 compounds are *ca.* 6—10 kJ mol^{-1} lower than that of the C_6H_5 compound. In the benzoyl series the $\Delta E^\ddagger$ values are *ca.* 10—15 kJ mol^{-1} higher than the value of the C_6H_5 compound.

We comment that the rate-limiting transition states of S_N2 reactions (benzoyl series) have a much greater degree of bond formation (nucleophile to electrophilic carbon) than in the transition-states of synchronous S_N2 reactions (benzyl series). This implies a considerably greater loss of bonding energy in the change to an S_N1 mechanism. The $\Delta\Delta E^\ddagger$ values mentioned above are

---

* Minimum value because the S_N1 rate for benzyl chloride methanolysis must be less than the S_N2 experimental value used to obtain ρ.

consistent with these comments, as well as the effect of ' built-in ' conjugation in the benzoyl series.

It is satisfying that in both series the values of the Arrhenius parameters of the 4-phenoxy-compounds have intermediate values. As pointed out by Kohnstam[13] the conjugation of the ether oxygen with two benzene rings must considerably reduce its ability to facilitate S_N1 reactions, whereas its effect on S_N2 reactions should be much less.

Our final comments are on the absolute values of the rates in the benzyl and benzoyl series. The very large difference in S_N2 rates is shown by the rate ratio PhCOCl : $PhCH_2Cl$ for methanolysis in 97.4% MeOH–dioxan, which equals 6.75×10^4. The large difference in the change from S_N2 to S_N1 reactions is shown by the rate ratios for the methanolysis (same solvent) of $4\text{-}MeOC_6H_4COCl$: $4\text{-}MeOC_6H_4CH_2Cl$ and 4 $BzOC_6H_4COCl$: 4 $BzOC_6H_4CH_2Cl$, equal to only 38.1 and 47.7, respectively.

[9/1572 *Received, 3rd October, 1979*]

REFERENCES

[1] P. C. Ferreira, N. Z. Kiyan, Y. Miyata, and J. Miller, *J.C.S. Perkin II*, 1976, 1648.

[2] M. Brink, *Acta Univ. Lund, Sect. II*, 1965, **16**, 1 (*Chem. Abs.*, 1966, **64**, 9620 e).

[3] R. S. Shelton and M. G. Van Campen, (*Chem. Abs.*, 1952, **46**, 8678 d).

[4] R. B. Moffett, *Org. Synth.*, 1963, Coll. Vol. 4, 834.

[5] M. Weissman and S. Patai, *J. Amer. Chem. Soc.*, 1946, **68**, 150.

[6] F. Giral and C. A. Rojahn, ' Produtos Químicos y Farmaceuticos,' Editorial Atlante S.A. Mexico, 1946, p. 765.

[7] K. Rorig, J. D. Johnston, R. W. Hamilton, and T. Telinski, *Org. Synth.*, Coll. Vol. 4, 1963, 576.

[8] P. P. Shorigin and A. V. Bogdanova, *J. Appl. Chem. (U.S.S.R.)*, 1938, **11**, 1217 (*Chem. Abs.*, 1939, **33**, 4216 8).

[9] A. Brunner, Ger. P. 569,570/1933 (*Chem. Z.* 1933, *II*, 609).

[10] C. S. Marvel and H. O. Calvery, ' Sínteses Orgânicas ' Editorial Gustavo Gili S.A., 1950, Vol. I, p. 519.

[11] T. Ojima, *Nippon Kagaku Zasshi*, 1967, **88**, 1231.

[12] H. C. Brown and B. C. Subba Rao, *J. Amer. Chem. Soc.*, 1956, **78**, 2582.

[13] G. Kohnstam, A. Queen, and T. Ribar, *Adv. Phys. Org. Chem.*, 1967, **5**, 121.

[14] C. K. Ingold, ' Structure and Mechanism in Organic Chemistry ', Bell, London, 1969, 2nd edn., pp. 444—445.