Solvent Effects on Isomer Distributions and Relative Rates in Friedel–Crafts Benzylation and Benzoylation of Dibenzofuran Derivatives

Takashi Keumi,* Masatoshi Nakamura, Masao Kitamura, Naoto Tomioka, and Hidehiko Kitajima
Department of Applied Chemistry, Faculty of Engineering, Fukui University, Bunkyo, Fukui 910, Japan

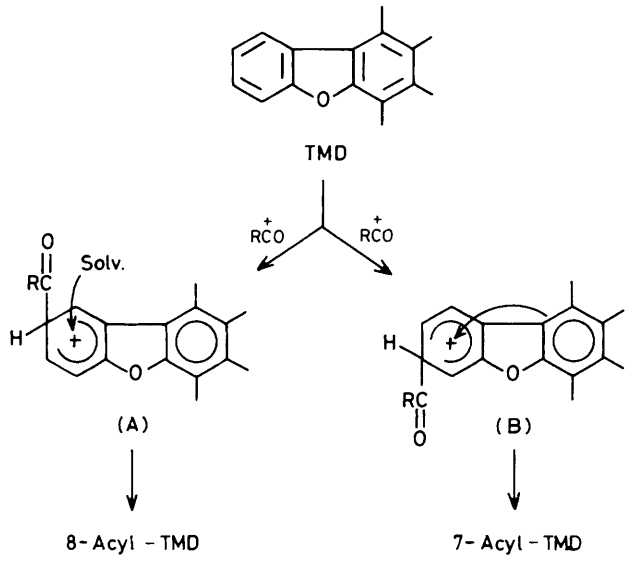
The positional reactivity order in Friedel–Crafts benzoylation and benzylation of dibenzofuran (DBF) is found to be 2 > 3 > 1 ⩾ 4. Both the partial rate factors and the positional selectivity for the benzylation of DBF are very low compared with those of benzoylation. In competitive benzoylation of 1,2,3,4-tetramethyldibenzofuran (TMD) *versus* DBF, a large solvent effect has been observed on the relative rate (TMD *versus* DBF) as well as on the isomer ratio of 8- to 7-benzoyl-TMD, which appears to be due to the difference in solvation of the intermediate σ-complex leading to each of the products. In contrast, in the case of competitive benzylation of TMD *versus* DBF, neither solvent effect on the relative rate nor any isomer ratio was observed. The nature of the transition state determining the relative rate and the positional reactivity for benzylation has been deduced from these results.

Considerable controversy still exists concerning substrate and positional selectivities in electrophilic aromatic substitution (EAS) reactions. Brown showed that there exists a simple linear relationship between relative rates of EAS reactions and relative stabilities of the related σ-complexes and, moreover, that the increase in reactivity of an electrophile results in a decrease in both the positional and substrate selectivities. Brown and Stock summarized this relationship by the well known selectivity rule (SR).[1]

On the other hand, Olah has shown that nitronium salt nitration and Friedel–Crafts benzylation show low substrate but at the same time high positional selectivity. To explain this apparent discrepancy from Brown's SR, Olah proposed a mechanism which involved a π-complex prior to formation of a σ-complex: Formation of a π-complex ('early' transition state on the reaction co-ordinate) would be rate determining, thereby specifying substrate selectivity, whereas rearrangement to the σ-complex ('late' transition state) would determine positional selectivity.[2]

We have previously reported that distribution of the 7- and 8-isomers in Friedel–Crafts acylation of 1,2,3,4-tetramethyldibenzofuran (TMD) changes dramatically with the change in the nature of the reaction solvent.[3] The solvent effects on the product distributions have enabled us to deduce that a σ-complex-like transition state is the key in determining the positional selectivity and moreover, that the transition state for the reaction in nitrohydrocarbon media is stabilized intermolecularly by the outer solvent molecule (A) while in chlorohydrocarbon media the transition state is stabilized intramolecularly by the inner π-conjugation (B) as shown in Scheme 1.

In light of these results, we have investigated the benzylation of TMD and dibenzofuran (DBF), together with the benzoylation in various nitro- and chloro-hydrocarbon media. Careful examination of solvent effects on the substrate and positional selectivities for the reactions would provide further insight into the structure of the transition state.



Scheme 1.

Results and Discussion

Competitive Friedel–Crafts benzoylation and benzylation of DBF and benzene were carried out to obtain the partial rate factors. The reactions were performed with excess of substrates at 20 °C. The crude products were analysed by g.l.c. In the case of benzylation, dibenzyl-DBFs were also produced but in negligible amounts.

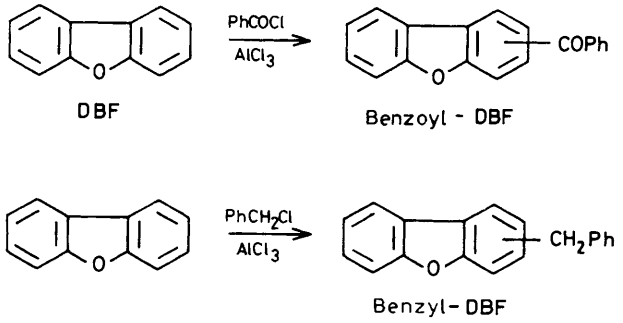
The partial rate factors calculated from the relative rates of DBF to benzene and the isomer distributions are summarized in Table 1 together with previously reported data for the proton-exchange reactions of DBF.

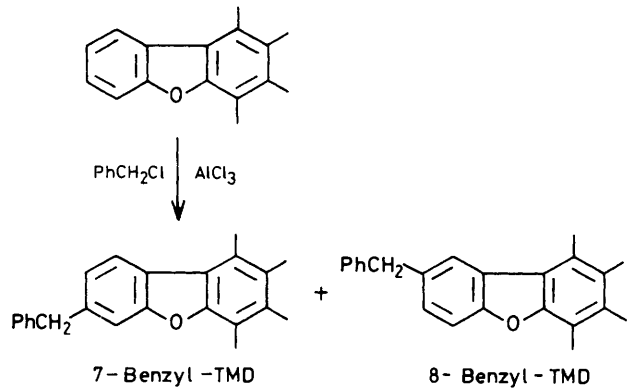
Friedel–Crafts benzylation is not subject to the sort of criticism raised concerning the validity of data for fast competitive reactions like nitronium-salt nitration, where mixing rates may be slow compared with the rate of reaction.[4] It has been shown that relative rates and isomer distributions obtained by the competitive benzylation of toluene and benzene can be used in satisfactory agreement with those derived by the non-competitive method.[5]

The positional reactivity order of DBF for both Friedel–Crafts benzoylation and benzylation has been found to be 2 > 3 > 1 ⩾ 4, which is in good agreement with those observed for proton-exchange reactions and also the relative stability of the protonated dibenzofuranonium ions estimated by CNDO/2 calculations.[6] The partial rate factors for the 2- and

Table 1. Partial rate factors for Friedel–Crafts reactions and a few other substitutions in DBF

Reaction	Reagent	Reaction conditions		Partial rate factor				Ref.
		Solvent	Temp.(°C)	f_1	f_2	f_3	f_4	
Benzoylation	$PhCOCl-AlCl_3$	o-$Cl_2C_6H_4$	20	51	6 414	777	22	
Benzoylation	$PhCOCl-AlCl_3$	$CHCl_2CHCl_2$	20	54	5 495	688	25	
Benzoylation	$PhCOCl-AlCl_3$	CH_2Cl_2	20	35	5 246	543	12	
Benzoylation	$PhCOCl-AlCl_3$	CH_2ClCH_2Cl	20	43	4 745	612	16	
Benzoylation	$PhCOCl-AlCl_3$	$PhNO_2$	20	35	4 520	371	20	6
Protiodetritiation	CF_3COOH	CF_3COOH	70	135	3 670	313	160	7*a*
Protiodesilylation	$HClO_4$	CH_3OH	50	0.65	19.2	2.4	0.92	7*b*
Benzylation	$PhCH_2Cl-AlCl_3$	$CHCl_3$	20	2.29	9.58	6.25	1.12	
Benzylation	$PhCH_2Cl-AlCl_3$	$PhNO_2$	20	1.69	9.74	6.75	1.22	
Benzylation	$PhCH_2Cl-AlCl_3$	CH_3NO_2	20	1.55	10.5	7.61	1.18	
Benzylation	$PhCH_2Cl-AlCl_3$	$CH_3CH_2NO_2$	20	1.48	10.2	7.25	1.06	





3-position and their ratios observed in benzylation are, however, significantly lower than those for benzoylation and proton-exchange reactions, *i.e.*, relatively low positional and substrate selectivities in benzylation.

The benzylation of TMD with benzyl chloride in the presence of aluminium chloride was also carried out in various solvents under the usual preparative conditions. Crude products were analysed by g.l.c. Although two peaks showing a formation of other products, probably 6- or 9-benzyl-TMD, were detected in the vicinity of the retention times for the 7- and 8-benzyl-TMD, the intensities for the two were less than 7% of total peak areas for the products. The isomer ratios are collected in Table 2, along with the previously reported results for Friedel–Crafts acetylation and benzoylation.

As shown in Table 2, the isomer ratios in Friedel–Crafts acetylation and benzoylation of TMD are very sensitive to the reaction media. On the other hand, the isomer distribution in benzylation is not dependent on the nature of the solvent. The observed ratios of 8- to 7-benzoyl-TMD, *ca.* 0.77, are almost solvent-independent.

Next, competitive Friedel–Crafts benzoylation and benzylation between DBF and TMD were carried out in a variety of solvents to explore their influence upon the relative rate and isomer distribution. The observed results are summarized in Tables 3 and 4.

In the case of benzoylation, both the relative rate of TMD *versus* DBF and the isomer distribution of benzoylated products were found to vary significantly with the nature of solvent. For example, in chlorohydrocarbons such as 1,2-dichloroethane, high relative rates and low isomer ratios of 8- to 7-benzoyl-TMD were observed. Benzoylation in the presence of varying amounts of nitroethane in 1,2-dichloroethane solution, revealed that with the increase in concentration of nitroethane the relative rate decreased and in direct contrast the isomer ratio increased. The lowest relative rate and the highest 8- to 7-isomer ratio were observed in the reaction in nitroethane (Table 3). The isomer ratios of benzoyl-TMDs in chlorohydrocarbons under competitive conditions are slightly larger than those from reactions under non-competitive conditions (Table 2). This is probably due to the use of excess of DBF and TMD which serve as weak nucleophiles in the transition state.

The observed results can be satisfactorily explained by the hypothesis that the transition state of Friedel–Crafts benzoylation of TMD is a 'late' one which has a strongly charge-developed structure resembling a σ-complex.

As previously reported,[3] a large change in the isomer ratio observed between nitrohydrocarbons and chlorohydrocarbons can be explained by a marked difference in the mode of stabilization of the σ-complex leading to each of the product. The positive charge in the σ-complex (A) (Scheme 1) formed by benzoylation at the 8-position of TMD is localized within the benzoyl-substituted ring system involving the oxygen atom. A polar solvent such as nitroethane, while it reduces the reactivity of acylating agents by solvation, at the same time can approach efficiently to stabilize the σ-complex (A) intermolecularly, whereas the positive charge in the σ-complex (B) formed by benzoylation at the 7-position can be delocalized in both the ring systems. In fact, the positive charge is more stabilized in the ring substituted with four methyl groups, and the polar solvent has difficulty in approaching the cationic centre due to the steric bulk of methyl groups.

In solvents which are not capable of such intermolecular stabilization (*e.g.*, *o*-dichlorobenzene), intramolecular stabilization by conjugation is preferred, resulting in substitution at the 7-position. As the activation effect of the four methyl groups in TMD contributes more strongly to the σ-complex (B) rather than to (A), the difference in rates of benzoylation between TMD and DBF would be large in chlorohydrocarbons lacking

Table 2. Solvent effects on the isomer distributions in Friedel–Crafts reactions of TMD

Reaction solvent	Benzylation: Conversion (%)	Benzylation: Isomer distribution % 7-	8-	6- or 9-	Benzylation: 8-isomer / 7-isomer	Benzoylation[3] 8-isomer / 7-isomer	Acetylation[3] 8-isomer / 7-isomer
CH_3NO_2	12	53	42	5	0.79	5.4	5.7
$CH_3CH_2NO_2$	24	53	43	4	0.81	4.9	5.3
$PhNO_2$	32	51	42	7	0.82	3.0	3.2
CCl_3CHCl_2	29	54	41	5	0.76	0.81	1.9
PhCl	40	53	40	7	0.75	0.43	1.2
$CHCl_2CHCl_2$	41	54	39	7	0.72	0.69	0.85
CH_2Cl_2	40	54	40	6	0.74	0.62	0.69
o-$Cl_2C_6H_4$	41	54	40	6	0.74	0.39	0.72
CH_2ClCH_2Cl	48	54	40	6	0.74	0.67	0.72
$CHCl_3$	30	54	40	6	0.74		

Table 3. Solvent effects on the relative rate and the isomer distributions for competitive benzoylation of TMD with DBF

Reaction solvent	Relative rate k_{TMD}/k_{DBF}	Isomer distribution (%): in benzoyl-DBFs 1-	2-	3-	4-	in benzoyl-TMDs 7-	8-	8-benzoyl-TMD / 7-benzoyl-TMD
o-$Cl_2C_6H_4$	43.2	0.7	88	11	0.3	60	40	0.67
CH_2Cl_2	39.9	0.6	90	9	0.4	55	45	0.82
CH_2ClCH_2Cl (DCE)	36.4	0.7	88	11	0.3	52	48	0.92
$CHCl_2CHCl_2$	34.0	0.7	88	11	0.3	52	48	0.92
1M-$EtNO_2$ in DCE	24.0	0.6	92	7	0.4	37	63	1.70
2M-$EtNO_2$ in DCE	16.2	0.5	93	6	0.5	23	77	3.35
$PhNO_2$	16.1	0.6	94	5	0.4	22	78	3.55
4M-$EtNO_2$ in DCE	12.0	0.6	93	6	0.4	20	80	4.00
6M-$EtNO_2$ in DCE	11.9	0.6	94	5	0.4	19	81	4.26
$EtNO_2$	10.0	0.6	95	4	0.4	18	82	4.56

Table 4. Solvent effects on the relative rate and the isomer distributions for competitive benzylation of TMD with DBF

Reaction solvent	Relative rate k_{TMD}/k_{DBF}	Isomer distribution (%): in benzyl-DBFs 1-	2-	3-	4-	in benzyl-TMDs 7-	8-	6- or 9-	8-benzyl-TMD / 7-benzyl-TMD
CH_2Cl_2	2.33	8	50	36	6	54	40	6	0.74
$CHCl_3$	1.91	11	50	33	6	54	40	6	0.74
CH_2ClCH_2Cl (DCE)	1.87	9	52	34	5	54	40	6	0.74
$CHCl_2CHCl_2$	1.74	12	50	31	7	53	39	8	0.74
4M-$EtNO_2$ in DCE	1.80	7	51	36	6	54	42	4	0.78
4M-$MeNO_2$ in DCE	1.69	9	50	33	8	52	41	7	0.79
$EtNO_2$	1.34	8	51	35	6	53	43	4	0.81
$PhNO_2$	1.31	9	50	35	6	50	42	8	0.84

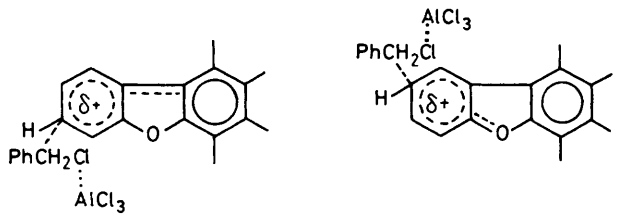
such specific solvation ability, compared with those in nitrohydrocarbons. In addition, the low relative rate in nitrohydrocarbons may also be ascribed to the lowering of the difference in the activation energy by solvation of the cationic intermediates in both cases.

Alternatively, the low relative rate but the high positional selectivity in nitroethane might be in agreement with Olah's hypothesis. This hypothesis is, however, clearly inconsistent with the experimental observation that nitrohydrocarbons reduce the reactivity of acylium cations.[3] The high substrate but low positional selectivities obtained in chlorohydrocarbons are also inconsistent with this hypothesis.

Mondro and his co-workers observed that the relative rate of bromine addition to alkenes compared with ethylene is high in nonpolar solvents but low in hydroxylic solvents. They also stated that there is no need to invoke different rate-determining transition state structures for addition in polar and nonpolar media, and the solvent effect is due to the difference in mode of the solvation of the cyclic bromonium ion-like transition state.[8]

On the other hand, the nature of Friedel–Crafts benzylation of TMD is clearly different from the benzoylation. As shown in Table 1, both the substrate and the positional selectivities for the benzylation of DBF are lower than those for benzoylation or proton-exchange reactions. A similar trend is observed for the reactions of TMD in Tables 3 and 4. It seems as if these results are consistent with Brown's SR which is based on a σ-complex mechanism.

However, competitive Friedel–Crafts benzylation of TMD



Scheme 2.

versus DBF does not show significant solvent effects on either the relative rate or the isomer distribution. The variation of the relative rates for benzylation is only 1.02 in contrast with 33.2 for benzoylation. This implies that the step determining the intermolecular reactivity of benzylation is different from benzoylation, *i.e.*, for the benzylation an 'early' transition state is important in determining the substrate selectivity.

If the isomer distributions are controlled at the σ-complex formation step as Olah suggests, then the isomer distribution of benzyl-TMDs should be strongly influenced by the nature of reaction solvents. In practice, solvent effects on the ratio of 8- to 7-benzyl-TMD observed in benzylation is significantly smaller than those observed in benzoylation. These facts lead us to deduce that both substrate and positional selectivities are determined at the same transition state which lies early on the reaction co-ordinate.

The structure of the transition state is of an orientated π-complex[9] nature as shown in Scheme 2, in which the polarized benzyl chloride–aluminium chloride complex is loosely bound to the carbon atom of TMD.

This would suggest that the positive charge of the reagent is slightly brought into the aromatic ring. For benzylation in nitrohydrocarbons the relative rate for TMD *versus* DBF decreases as the ratio of the 8- to 7-isomer increases as observed for benzoylation. The existence of such an orientated π-complex had been indicated by Nakane and his co-workers in Friedel–Crafts ethylation of toluene with the ethyl fluoride–boron trifluoride system.[10] Recently, Santiago and his co-wokers have attempted to interpret the SR for EAS reactions in terms of a single transition state, whose character varies from an orientated π-complex to a σ-complex-like species. Using protonation of benzene and toluene as a model, they performed STO-3G calculations. Their calculations indicate that the positional and substrate selectivities diminish as the transition state becomes earlier.[11]

As for Friedel–Crafts benzylation of DBF and TMD, there seems to be no need for two different transition states, the first being rate determining and the second product determining. Both substrate and positional selectivities for the reaction are controlled at an early point on the reaction co-ordinate.

Experimental

1,2,3,4-Tetramethyldibenzofuran (TMD), m.p. 111 °C, was prepared according to the procedure described previously.[12] Benzoyldibenzofurans[6] and benzoyl-TMDs[3] were also prepared according to previously reported procedures. All solvents used for reactions were of spectroscopic grade. I.r. spectra were recorded on a Hitachi EPI-S2 spectrophotometer with KBr pellets. ^{1}H N.m.r. spectra were recorded on a JEOL-4H 100 spectrometer in tetrachloromethane solution with $SiMe_4$ as internal standard. G.l.c. analyses were carried out on a Hitachi GC 163 gas chromatograph equipped with a hydrogen flame ionization detector and a stainless steel column (3 m × 3 mm) packed with 3% Dexil 300 GC on Chromosorb W. Isomer distributions were calculated from peak areas obtained by a Takeda TR-2220A integrator after calibrating for each authentic compound.

Preparation of Benzyldibenzofurans. 1-*Benzyl-DBF.*—To a mixture of lithium aluminium hydride (0.20 g, 5.3 mmol) and aluminium chloride (0.50 g, 3.8 mmol) in anhydrous ether (55 cm^3) was added dropwise a solution of 1-benzoyl-DBF (0.80 g, 2.9 mmol) and aluminium chloride (0.50 g, 3.8 mmol) in ether (25 cm^3), with stirring under nitrogen. After the mixture was heated under reflux for 1 h, the reaction was quenched by addition of 3M-sulphuric acid (25 cm^3) and the product was extracted with ether. The organic layer was washed with water, dried (Na_2SO_4) and evaporated under reduced pressure to obtain an oil (0.61 g). After vacuum distillation of the product, the fraction of b.p. 170 °C at 2 mmHg was recrystallized from methanol to give 1-benzyl-DBF (0.24 g, 19.4%), m.p. 75—76 °C (Found: C, 88.3; H, 5.4. $C_{19}H_{14}O$ requires C, 88.3; H, 5.5%); $\nu_{max.}$(KBr) 2 880, 1 458, 1 202, and 752 cm^{-1}; δ (CCl_4) 4.47 (2 H, s), 7.65—7.90 (1 H, m), and 6.85—7.55 (11 H, m).

The following compounds were prepared by heating a mixture of benzoyl compounds, potassium hydroxide, and hydrazine hydrate in diethylene glycol under reflux: 2-*benzyl-DBF*, m.p. 92—93 °C (from EtOH); 41.1% yield (Found: C, 88.2; H, 5.5%); $\nu_{max.}$(KBr) 3 000, 1 451, 1 197, and 753 cm^{-1}; δ (CCl_4) 4.06 (2 H, s) and 7.60—7.85 (12 H, m); 3-*benzyl-DBF*, m.p. 104—105 °C (from EtOH); 41% yield (Found: C, 88.2; H, 5.6%); $\nu_{max.}$(KBr) 2 900, 1 452, 1 204, and 741 cm^{-1}; δ (CCl_4) 4.06 (2 H, s), 7.60—7.85 (2 H, m), and 7.00—7.50 (10 H, m); 4-*benzyl-DBF*, m.p. 54—56 °C (from MeOH); 30% yield (Found: C, 88.2; H, 5.5%); $\nu_{max.}$(KBr) 3 060, 1 452, 1 190, and 747 cm^{-1}; δ (CCl_4) 4.23 (2 H, s), 7.55—7.90 (2 H, m), and 7.00—7.55 (10 H, m); 2,8-*dibenzyl-DBF*, m.p. 89—90 °C (from EtOH); 40% yield (Found: C, 89.6; H, 5.8. $C_{26}H_{20}O$ requires C, 89.6; H, 5.8%); $\nu_{max.}$(KBr) 2 930, 1 455, 1 196, and 740 cm^{-1}; δ (CCl_4) 4.04 (4 H, s), 7.58—7.85 (2 H, m), and 6.93—7.50 (14 H, m); 7-*benzyl-TMD*, m.p. 94—95 °C (from EtOH); 25% yield (Found: C, 87.85; H, 7.1. $C_{23}H_{22}O$ requires C, 87.85; H, 7.05%); $\nu_{max.}$(KBr) 3 000, 1 500, 1 230, and 740 cm^{-1}; δ (CCl_4) 2.62 (3 H, s), 2.27 (3 H, s), 2.25 (3 H, s), 2.43 (3 H, s), 4.07 (2 H, s), 7.00—7.20 (6 H, m), 7.25 (1 H, s), and 7.80 (1 H, d, *J* 8 Hz); 8-*benzyl-TMD*, m.p. 114—115 °C (from EtOH); 25% yield (Found: C, 87.7; H, 7.1%); $\nu_{max.}$(KBr) 3 000, 1 490, 1 225, and 730 cm^{-1}; δ (CCl_4) 2.58 (3 H, s), 2.25 (3 H, s), 2.22 (3 H, s), 2.43 (3 H, s), 4.07 (2 H, s), 7.73 (1 H, s), and 7.10—7.40 (7 H, m).

Solvent Effects on Isomer Distributions in the Benzylation of TMD.—To a solution of TMD (0.500 g, 2.2 mmol) and benzyl chloride (0.280 g, 2.2 mmol) in a given solvent (5 cm^3) was added a suspension of anhydrous aluminium chloride (0.150 g, 1.1 mmol) in the same solvent (15 cm^3) at 20 °C, and the mixture was then stirred at the same temperature for 2 h. After addition of 0.1M-hydrochloric acid (10 cm^3), the solvent was distilled off with steam. The resulting crude product was dissolved in benzene (10 cm^3) containing DBF (0.100 g) as the internal standard and analysed by g.l.c. to determine the isomer distribution.

Competitive Benzoylation of TMD versus *DBF.*—To a solution of DBF (0.375 g, 2.2 mmol) and TMD (0.100 g, 0.4 mmol) in dichloroethane (2 cm^3) was added a solution of benzoyl chloride (0.067 g, 0.5 mmol) and aluminium chloride (0.064 g, 0.5 mmol) in the same solvent (2 cm^3) over 10 min at 20 °C. The mixture was stirred for 3 h at the same temperature and then was hydrolysed with 1M-hydrochloric acid. After steam distillation the resulting residue was extracted with ether and analysed by g.l.c.

Acknowledgements

We thank Dr. G. K. Surya Prakash, University of Southern California, and Dr. M. Nojima, Osaka University, for help with the manuscript.

References

1 L. M. Stock and H. C. Brown, *Adv. Phys. Org. Chem.*, 1963, **1**, 35.
2 G. A. Olah, *Acc. Chem. Res.*, 1971, **4**, 240.
3 T. Keumi, Y. Yagi, Y. Kato, R. Taniguchi, M. Temporin, and H. Kitajima, *J. Chem. Soc., Perkin Trans. 2*, 1984, 799.
4 J. H. Ridd, *Acc. Chem. Res.*, 1971, **4**, 248.
5 F. P. DeHaan, W. D. Covey, M. S. Anisman, R. L. Ezelle, J. E. Margetan, K. D. Miller, S. A. Pace, S. L. Pilmer, M. J. Sollenberger, and D. S. Wolf, *J. Am. Chem. Soc.*, 1978, **100**, 5944.
6 T. Keumi, S. Shimakawa, and Y. Oshima, *Nippon Kagaku Kaishi*, 1977, 1518.
7 (*a*) R. Baker and C. Eaborn, *J. Chem. Soc.*, 1961, 5077; (*b*) C. Eaborn and J. A. Sperry, *ibid.*, 4921.
8 A. Mondro, G. H. Schmid, and K. Yates, *J. Org. Chem.*, 1977, **42**, 3673.
9 M. Christen, W. Koch, W. Simon, and H. Zollinger, *Helv. Chim. Acta*, 1962, **45**, 2077.
10 R. Nakane, A. Natzubori, and O. Kurihara, *J. Am. Chem. Soc.*, 1965, **87**, 3597; 1969, **91**, 4528.
11 C. Santiago, K. N. Houk, and C. L. Perrin, *J. Am. Chem. Soc.*, 1979, **101**, 1337.
12 T. Keumi, Y. Oshima, and N. Tokura, *Bull. Chem. Soc. Jpn.*, 1975, **48**, 1065.

Received 22*nd May* 1984; *Paper* 4/837