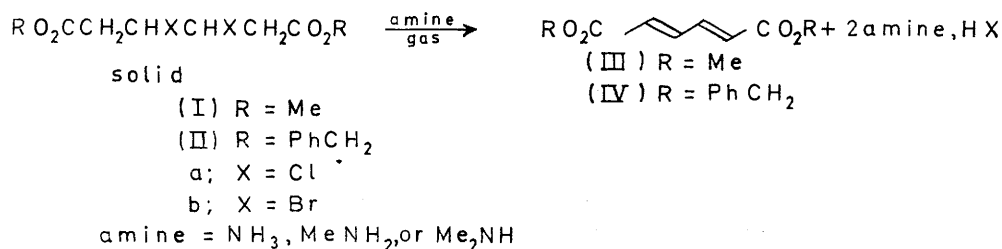# Heterogeneous Reactions with Organic Solids. Part I.[1] The Stereo-specific Dehydrohalogenation of Solid β,β'-Dihalogenoadipates by Gaseous Amines

By **Gad Friedman,** * **Meir Lahav,** and (the late) **Gerhard M. J. Schmidt,** Department of Structural Chemistry, Weizmann Institute of Science, Rehovot, Israel

Solid dimethyl and dibenzyl esters of meso-β,β'-dichloro- and meso-β,β'-dibromo-adipates react quantitatively with gaseous dry ammonia, methylamine, and dimethylamine, yielding stereospecifically the corresponding diesters of trans,trans-hexa-2,4-dienedioic acid. When the same reactants were combined in ethanol or dimethylformamide solutions, a mixture of 2,4-trans,cis- and trans,trans-diesters and -diamides was obtained. Possible routes for the reaction are discussed.

In a previous series of papers we analysed reactions between gaseous halogens and crystalline materials.[2] We there discussed the addition of bromine from the vapour, a two-phase reaction known for over a century,[3] and the isomerisation of crystalline olefins with iodine (for reviews see refs. 4 and 5). Recently, the selective

oxidation of crystalline 11-hydroxy-steroids to the corresponding ketones by atmospheric oxygen,[6] and the interaction of solid carboxylic acids with gaseous amines[7] have been reported.

The present paper is concerned with the elimination of hydrogen halide from solid diesters of meso-β,β'-di-

$$R O_2C\,CH_2CHXCHXCH_2C O_2R \xrightarrow[\text{gas}]{\text{amine}} R O_2C \diagup\diagdown\diagup\diagdown C O_2R + 2\,\text{amine,}HX$$

solid

(I) R = Me   (III) R = Me

(II) R = PhCH$_2$ (IV) R = PhCH$_2$

a; X = Cl

b; X = Br

amine = NH$_3$, MeNH$_2$, or Me$_2$NH

SCHEME 1

[1] Presented in part in, *Israel J. Chem.*, 1969, **7**, 18.

[2] (a) E. K. Hadjoudis, E. Kariv, and G. M. J. Schmidt, *J.C.S. Perkin II*, 1972, 1056; (b) E. K. Hadjoudis and G. M. J. Schmidt, *ibid.*, p. 1060.

[3] R. E. Buckles, E. A. Hausman, and N. G. Wheeler, *J. Amer. Chem. Soc.*, 1950, **72**, 2494 and references cited therein.

[4] H. Morawetz, ' Physics and Chemistry of the Organic Solid State,' eds. D. Fox, M. M. Labes, and E. Weissberger, Interscience, New York, vol. 1, 1963.

[5] G. Adler, ' Organic Solid State Chemistry,' Gordon and Breach, London and Paris, 1969.

[6] (a) M. L. Lewbart, *Nature*, 1969, **222**, 663; (b) G. Brenner, F. E. Roberts, A. Hainows, A. Hainowski, J. Budavori, B. Powell, D. Hinkley, and E. Schoenewaldt, *Angew. Chem. Internat. Edn.*, 1969, **8**, 957.

[7] R. S. Miller, D. Y. Curtin, and I. C. Paul, *J. Amer. Chem. Soc.*, 1971, **93**, 2784.

chloro- and dibromo-adipic acid by ammonia or gaseous amines at ambient temperature and atmospheric (or lower) pressure. The reactions are summarised in Scheme 1. Reactions proceeded to completion. The elimination was stereospecific within the accuracy ($\pm 3\%$) of our method of analysis, and yielded practically pure diesters of *trans,trans*-hexa-2,4-dienedioic acid (after washing away the aminium halide). Side reactions, like amidation and amine addition to the double bonds, were essentially excluded by using this method.

EXPERIMENTAL

I.r. spectra were taken in KBr pellets on a Perkin-Elmer model 137 spectrometer and n.m.r. spectra on a Varian A60 instrument (CDCl₃ solution with tetramethylsilane as internal reference). G.l.c. analyses were performed on a Varian Aerograph 1200 instrument (flame ionisation detector) with columns of 5% BDS on Chromosorb P, acid washed, DMCS, 16 ft × 1/8 in, 180°, flow rate 15 ml min⁻¹.

Dimethyl meso-β,β'-*Dichloroadipate* (Ia).—This had m.p. (from methanol) 77—79° (lit.,[8] 78—79°). Only one crystal modification has been observed so far.

Dimethyl meso-β,β'-*Dibromoadipate* (Ib).—(i) Hex-3-ene-dioic acid (0·1 mol) exposed to bromine vapour (16 g, 0·1 mol) in a desiccator yielded 3,4-dibromoadipic acid (30·4 g), m.p. 194—196° (lit.,[9] m.p. 185—207° depending on rate of heating). The acid was esterified [10] to the ester (Ib), m.p. 91—93° (lit.,[10] m.p. 93°).

(ii) Absolute methanol (500 ml) containing *meso*-2,3-dibromo-1,4-dicyanobutane (50 g) [11] was saturated with dry hydrogen chloride and left for 24 h. Filtration and treatment of the precipitate with hot water gave material which after crystallisation from propan-2-ol (35 g) had m.p. 91—93°. Only one crystal modification has been observed.

Dibenzyl meso-β,β'-*Dibromoadipate* (IIb).—meso-β,β'-Dibromoadipic acid (15 g), benzyl alcohol (30 ml), benzene (450 ml), and a little toluene-*p*-sulphonic acid were boiled under reflux for 12 h in an azeotropic distillation apparatus. Unchanged acid was filtered off and the solution was washed with 2% sodium hydrogen carbonate solution and water, dried, and concentrated. After recrystallisation (ethyl acetate and light petroleum) the pure *ester* (8·1 g) had m.p. 90—91° (Found: C, 49·9; H, 4·1; Br, 33·3. C₂₀H₂₀Br₂O₄ requires C, 49·6; H, 4·2; Br, 33·0%), τ 2·6 (10H, s, aromatic), 4·8 (4H, m, 2 × C*H*₂Ph), 5·38 (2H, m, 2 × C*H*Br), 6·50 (2H, dd, *J* 3·5, 16 Hz, 2 × C*H*CHO), and 7·01 (2H, dd, *J* 9, 16·5 Hz, 2 × C*H*HCO₂).

Elimination Experiments with Gaseous Amines.—These experiments were carried out in desiccators which were evacuated and then charged with gas dried by passage over pellets of potassium hydroxide. For sampling, the amine was removed by application of a vacuum, the desiccator filled with dry air and opened, an aliquot portion withdrawn, the remaining material ground rapidly, and the desiccator recharged with the amine. For large-scale preparations a vessel equipped with inlet and exit tubes was

employed and ammonia gas purged through the vessel for several minutes to displace the air.

The percentage of conversion was calculated from halide ion content of the samples determined by potentiomeric titration.

Dimethyl meso-β,β'-*Dichloroadipate and Dimethylamine Gas.*—Compound (Ia) (5 g) was exposed to dry dimethylamine gas at an (initial) pressure of *ca.* 150 mmHg. After 5 h excess of amine was removed and a sample (3·33 g) was treated with water, filtered, and dried to yield dimethyl *trans,trans*-hexa-2,4-dienedioate (1·5 g, 89%), m.p. 155—158° (lit.,[12,13a] 158°).

Dimethyl meso-β,β'-*Dibromoadipate and Ammonia Gas.*—Compound (Ib) (5 g) reacted with dry ammonia gas (atmospheric pressure). Samples were taken and the solid material was ground after each sampling. Excess of ammonia was removed after 60—200 h, when reaction was complete. The residue (3·60 g) was washed with water (6 ml), filtered, and dried to give the product (1·65 g, 97%), m.p. 153—158°. According to i.r., g.l.c., and mixed m.p. comparison with an authentic sample the product was the pure diester (III).

Dimethyl meso-β,β'-*Dibromoadipate and Dimethylamine Gas.*—Compound (Ib) (5 g) was exposed to dry dimethylamine gas for 24 h at an (initial) pressure of *ca.* 150 mmHg. After removal of excess of amine, the product (4·22 g) was washed with dilute nitric acid and yielded the pure diester (III) (96%, 1·62 g).

Dimethyl meso-β,β'-*Dibromoadipate and Methylamine Gas.* —Compound (Ib) (5 g) exposed to dry methylamine gas (initially at *ca.* 150 mmHg) had reacted to completion, according to bromide analysis, after 4—11 h. The product (3·45 g) was washed with dilute nitric acid (5 ml), filtered, dried, and purified by column chromatography (eluant ethyl acetate) to give the pure diester (1·44 g).

Samples which were left in contact with the amine for 4 days were converted to *trans,trans*-*NN'*-dimethylhexa-2,4-dienediamide, m.p. 290—295° (after washing with dilute hydrochloric acid) and mixed m.p. 293—297°. The authentic amide was prepared from compound (III) and methylamine in methanol and had m.p. 297—300°.

Dibenzyl meso-β,β'-*Dibromoadipate and Dimethylamine Gas.*—Compound (IIb) (4·8 g) reacted with dimethylamine and after 30—60 h the organic product (3 g, 93%) had m.p. 97—103°, and was t.l.c.-homogeneous [silica gel, benzene–light petroleum (7 : 3), ethyl acetate–light petroleum (1 : 4)]; after recrystallisation it had m.p. 107—108° (from benzene–light petroleum).

Dibenzyl trans,trans-*hexa-2,4-dienedioate* (IV).—This was prepared by transesterification of compound (III) with excess of benzyl alcohol with the aid of toluene-*p*-sulphonic acid. Compound (IV) was purified by column chromatography [silica gel, ethyl acetate–light petroleum (1 : 9)], m.p. 107—108°, ν_max. 1720, 1620, and 970 cm⁻¹; τ 2·63 (12H, m, aromatic and vinylic), 3·77 (2H, dd, vinylic), and 4·85 (4H, benzylic) (Found: C, 74·3; H, 5·7. C₂₀H₁₈O₄ requires C, 74·5; H, 5·6%). A sample was hydrolysed in boiling 10% KOH to the corresponding acid, m.p. 292—296° (decomp.), which after treatment with diazomethane, gave pure (III).

Attempted Synthesis of Dimethyl 4-*Bromohex-2-enedioate.*—

[8] H. Walther and G. Zimmermann, *Chem. Ber.*, 1958, **91**, 630.
[9] S. Ruhemann and F. F. Bluckman, *J. Chem. Soc.*, 1890, **57**, 370.
[10] E. H. Farmer, *J. Chem. Soc.*, 1923, **123**, 253.
[11] G. Friemdan, M. Lahav, and G. M. J. Schmidt, to be published.

[12] J. A. Elvidge and P. D. Ralph, *J. Chem. Soc.* (C), 1966, 387.
[13] (a) M. Lahav and G. M. J. Schmidt, *J. Chem. Soc.* (B), 1967, 312. (b) B. S. Green, M. Lahav, and G. M. J. Schmidt, *ibid.*, 1971, 1552.

A mixture of dimethyl hex-2-enedioate (86 mg), carbon tetrachloride (15 ml), N-bromosuccinimide (98 mg), and a few grains of dibenzoyl peroxide was boiled for 2 h under reflux. After cooling, filtration, and removal of excess of solvent, the residue was chromatographed on silica gel. Ether–light petroleum (1 : 7) eluted a mixture, the n.m.r. spectrum of which showed the patterns typical of (III) and of the starting material. G.l.c. shows a peak corresponding to (III).

Dimethyl meso-β,β'-*Dibromoadipate with Dimethylamine in Solution.*—To a stirred solution of (Ib) (0·25 g) in ethanol (4·5 ml) was added an aqueous saturated solution of dimethylamine (0·5 ml). G.l.c. analysis of the mixture after 2 h revealed dimethyl *trans,trans*- and *trans,cis*-hexa-2,4-dienedioate in a 2 : 1 ratio. A similar reaction with dimethylformamide as solvent resulted in a 1 : 1 ratio of the two isomers.

RESULTS AND DISCUSSION

Products of the Reaction.—Whereas reaction with ammonia was slow in both the chloro- and bromo-derivatives (Ia), (Ib), and (IIb), the use of organic amines led to rapid and near-quantitative double elimination of HX (*ca.* 95%). G.l.c. analysis of the products from (Ia and b) indicated the presence of only the *trans,trans*-isomer (III); according to blank experiments 3% of the other two isomers are detectable in the presence of (III). T.l.c. analysis and comparison with an authentic sample of the products from (IIb) suggested similar stereospecificity; as a further check the dibenzyl ester was hydrolysed in alkali (where *cis–trans*-isomerisation is known not to take place [14]), the acid re-esterified with diazomethane, and the product shown by g.l.c. to be the all-*trans*-isomer only.

Analyses of reaction mixtures at several stages of conversion by means of n.m.r. and t.l.c. revealed starting material and the hexadiene derivatives only: the possible intermediate, dimethyl 4-bromohex-2-enedioate, arising from a single elimination step, could not be detected. An attempt to prepare the latter by allylic bromination of dimethyl hex-2-enedioate with N-bromosuccinimide yielded the diester (III).

If the organic amines were allowed to condense on the solid phase partial amidation of the esters took place, a process most noticeable with methylamine which tended to condense on the methylammonium halide; reactions with these amines were therefore carried out under reduced pressure, and the reacting gas was immediately removed after completion of the reaction.

Conversion Rates.—The elimination reactions were performed with several batches of crystals and the three amines. Whilst conversion values recorded after equal periods of time in parallel runs show a broad and unpredictable distribution for 'identical' samples of crystals (see Table) general trends can nevertheless be discerned. A feature, common to all reactions in ammonia of properly recrystallised compounds, is a delay or induction period during which no detectable amount of reaction takes place. In reactions of (Ib)

this delay lasts for *ca.* 10 h. Compound (IIb) produced no detectable amount of bromide upon exposure to ammonia for up to 50 h. This stage is followed by a reaction which proceeds to *ca.* 90% conversion within 55—220 h, and then slows down (Table). A switch from ammonia to volatile organic amines such as methyl- and

Typical conversion periods (h) for elimination reactions of dimethyl meso-β,β'-dibromoadipate (Ib)

Batch	Amine	Delay	50% Conversion period	90% Conversion period
a	NH_3 [a]	10	90	180
b	NH_3 [a]	10	35	55
b	Me_2NH [b]		3	9
c	$MeNH_2$ [b]			15

[a] Ammonia at atmospheric pressure. [b] Amine (initial) pressure 150 mmHg.

dimethyl-amine, reduced the initial delay to practically zero and speeded up the reactions so that they were essentially complete within 9—15 h for (Ib), and 30—60 h for (IIb). Compound (Ia) which reacted very sluggishly with ammonia was converted to (III) after short contact (*ca.* 5 h) with dimethylamine.

A qualitative study of the effect of crystal size on reaction time was performed with crystals of (Ib). Material derived from one recrystallisation was divided into two portions which were simultaneously exposed in one desiccator to ammonia gas. One portion was ground prior to reaction and re-ground on each sampling, whereas samples from the other were removed for analysis without crushing. No significant difference in the rate of elimination could be observed between ground and unground material of a common origin. The time scale for completion of the reaction changed, however, sometimes by a factor of 3 for samples of different origin. All the samples were otherwise 'identical' by the criteria of m.p., n.m.r., t.l.c., and elemental analyses, but could have contained trace impurities and have had different textures. These might effect reaction rates much more strongly than alteration of crystal size and surface area.

Topochemical Control of the Reaction.—The very precise stereospecificity of the double elimination reaction of the dihalogenoadipate esters suggests that the crystal lattice has some kind of controlling influence over the course of the reaction, particularly in view of the absence of such specificity in the solution reaction. Compound (Ib) and dimethylamine in ethanol gives a mixture of dimethyl *trans,trans*- and *trans,cis*-hexa-2,4-dienedioate in a ratio of *ca.* 2 : 1; in aqueous dimethylformamide the isomer ratio changes to *ca.* 1 : 1.

In previous publications the crystal lattice ('topochemical') control of homogeneous solid-state reactions was demonstrated.[13] In these reactions the packing arrangement of the molecules, particularly the nearest-neighbour contact, determines the nature of the photoproduct.

In connection with the elimination reactions of solids

[14] J. A. Elvidge and P. Sims, *J. Chem. Soc.* (C), 1966, 385.

the conformation of the starting material in the crystal should be considered. As has been established by X-ray analyses the adipates (Ia and b) in the crystal have a single, defined conformation.[15] We assume that this conformation dictates the steric course of the elimination reaction and hence the configuration of the product. The skeleton of the molecule is fully extended; the carbon atoms and the ether oxygen of the esters are aligned in zig-zag shape almost in one plane. The molecule possesses a crystallographic centre of symmetry. The C_β–C_β' bond is almost antiperiplanar to the C_α–CO_2Me bond. A similar relation exists between each halogen atom and one of the protons of the CH groups.

Transformation of a dihalogenoadipate of this conformation into the planar and elongated diester (III)[16] (and only to this geometrical isomer) involves minimal motion of the carbon and oxygen skeleton.

This description implies that the eliminations of the two molecules of hydrogen halide take place concurrently, or that the elimination of the second molecule occurs while the reacted half still maintains its original conformation. We assume that the elimination takes place in two discrete steps, the first leading to the labile dimethyl 4-bromohex-2-enedioate (which could not be isolated), and the second fast step resulting in the product. This description is based on the geometrical arguments and accounts for the *trans,trans*-diene regardless of the elimination mechanism.

Mechanism of the Reaction.—A Newman projection of the conformation of the isomorphous dimethyl *meso*-β,β'-dichloro- and -dibromo-adipates is shown in the Figure.

The almost antiperiplanar arrangement of the halogen atom to one of the methylene hydrogen atoms (H_a) (the

X = Cl or Br
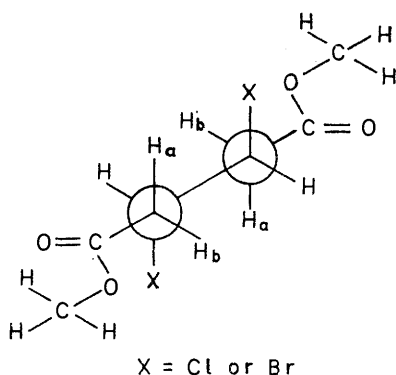
deviation amounting to 10°) suggest that an *anti*-elimination might be operating. Elimination by this route would result in double bonds with a *trans*-configuration.

However, the crystallographic data concerning the spatial arrangement of the halogenoadipates and the

geometry of the eliminated diester (III) also fit a *syn*-mechanism; by this mode of reaction the hydrogen atom H_b is supposed to eliminate with the halogen atom, leading also to a *trans*-double bond. A *syn*-elimination mechanism might be adopted in these solid–gas reactions since it provides an energetically feasible way for the removal and trapping of the halide anion. For an *anti*-elimination mechanism one has to assume formation of an ammonium ion on one side of the molecule and depature of halide ion on the other side of the molecule, which means heterolytic bond breaking and charge separation, without the advantage of solvation this step would receive in solution. Elimination by a *syn*-mechanism does not involve this complication. Thus a *syn*-mechanism seems to be more favourable for these reactions although at first sight the molecular
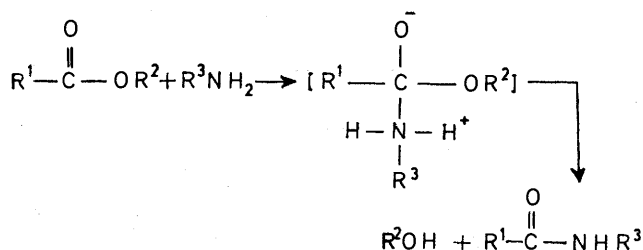
SCHEME 2

conformation looks almost perfectly arranged for an *anti*-elimination. Work is now being carried out in order to try and establish the actual mechanism. As for the timing of the bond breaking and making steps, the present experimental information gives no hint to allow a decision whether the reaction is concerted or stepwise.

Chemical Selectivity of the Process.—The efficient double dehydrohalogenation of the dihalogenoadipates is the sole observable reaction taking place in this process; amidation, which is common in similar solution reactions, is practically excluded. The inertness of the ester function cannot be explained as due to inaccessibility to the gas since chemical and environmental changes take place at the adjacent carbon atom. The reason has to be sought in the nature of the amidation reactions on one hand, and of the solid–gas reaction, on the other.

Aminolysis of esters has been extensively studied during recent years.[17] These reactions proceed through a tetrahedral intermediate,[18] and are subject to both general base and general acid catalysis.[19] One of the commonly accepted pathways is represented in Scheme 2 which demonstrates the formation and separation of opposite charges in the intermediate (other mechanisms, with various modes of catalysis, also invoke in this or

[15] B. Kaufman, D. Rabinovich, and G. M. J. Schmidt, following paper.
[16] S. E. Filippakis, L. Leiserowitz, and G. M. J. Schmidt, *J. Chem. Soc. (B)*, 1967, 290.
[17] W. P. Jencks ' Catalysis in Chemistry and Enzymology,' McGraw-Hill, New York, 1969, p. 534.

[18] G. M. Blackburn and W. P. Jencks, *J. Amer. Chem. Soc.*, 1968, **90**, 2638.
[19] (a) J. F. Bunnett and G. T. Davis, *J. Amer. Chem. Soc.*, 1960, **82**, 665; (b) W. P. Jencks and J. Carrioulo, *ibid.*, p. 675; (c) T. C. Bruice and M. F. Mayahi, *ibid.*, p. 3082.

some other way, charge separation during the reaction course).

The chemical change which takes place during aminolysis consists of nitrogen–carbon bond making, carbon–oxygen bond breaking, and proton transfer steps. Solvent participates either by stabilising a negative charge on the carbonyl oxygen atom during base catalysed nitrogen–carbon bond making, or by solvation of the base–proton complex, or by protonating the ether oxygen atom, thus assisting in carbon–oxygen bond rupture. In the absence of ' inert ' solvent molecules the tendency to form a tetrahedral intermediate is decreased, as the charges which are inherent in such an intermediate are not solvated. In addition, proton transfer is rendered inefficient in the absence of an auxiliary transfer agent, and thus the aid to carbon–oxygen bond breaking (which resembles acid catalysis) is lacking. As none of the steps which is needed for aminolysis in solution can occur in the solid, the process is practically ruled out. Solid esters, which are not strongly activated, can thus be regarded as stable to gaseous amines. Amidation in the solid can be achieved only in molecules where the carbonyl is linked to efficient leaving groups, such as chloride in acid chlorides and carboxy in anhydrides, where the bond to the carbonyl is polarised and the attachment of the amine nitrogen atom is facilitated.[20] In these cases amidation probably takes place by the cyclic mechanism suggested for solution reactions.[21]

Locus of the Reaction.—The mechanism by which the reaction consumes the bulk of the crystal is of both theoretical and practical interest. The following three observations that were made give a hint of the location of the actual reaction site and the mode of propagation: (a) the delay prior to the reaction; (b) the deviation in the time scale for different batches; and (c) the independence of the reaction rate on crystal size. These observations are compatible with a mechanism in which the process is initiated at reaction centres which expand into the bulk of the solid. The delay may be due to initial multiplication of these centres which then grow exponentially, eroding their boundary faces. Thus the progress of the reaction is dependent on the number of the reaction centres, which might differ from batch to batch, rather than on crystal size. Such centres are most probably at imperfection zones of the crystal which are known to be more reactive than the perfect lattice.[22] The double dehydrohalogenation results in geometrical change in the organic molecule and formation of two aminium halide molecules. This can induce formation of new reactive sites [23] and explain reaction propagation towards full conversion. An alternative surface mechanism by which the reaction starts on faces of the material and proceeds layer-wise into the crystal (*e.g.* alkali-metal oxidation),[24] seems to be ruled out by observations (a) and (c). For such a process the initial stages, at least would be dependent on surface area and would not be slower than the major part of the reaction.

[20] T. S. Kao, M.Sc. Thesis, The Weizmann Institute of Science, 1969; G. Friedman, T. S. Kao, and G. M. J. Schmidt, to be published; R. S. Miller, D. Y. Curtin, and I. C. Paul, *J. Amer. Chem. Soc.*, 1972, **94**, 5117.
[21] M. Bender, V. L. Chow, and F. Chloupek, *J. Amer. Chem. Soc.*, 1958, **80**, 5380.

[22] J. M. Thomas, *Endeavour*, 1970, **29**, 149 and references cited therein.
[23] J. M. Thomas, *Adv. Catalysis*, 1969, **19**, 293.
[24] A. K. Galwey, ' Chemistry of Solids,' Chapman and Hall, London, 1967, p. 190.