Tetrahedron Letters,Vol.25,No.2,pp 135-138,1984
Printed in Great Britain

0040-4039/84 $3.00 + .00

# MECHANISMS AND INTERMEDIATES FOR SQUARIC ACID SYNTHESIS FROM HEXACHLOROBUTADIENE AND MORPHOLINE

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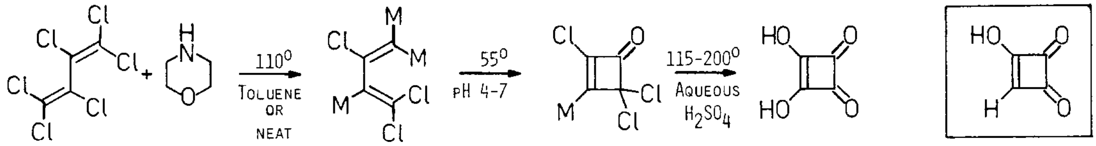
Summary: *The mechanistic course of the 3-stage synthesis of squaric acid from hexachlorobutadiene and morpholine has been elucidated, and 5 novel intermediates isolated and characterized.*

Squaric acid (SA) and semisquaric acid (SSA) are of interest for their unusual physical properties and for their use as precursors for the synthesis of antioxidants, bacteriocides, fungicides, insecticides and squaraines[1-3]. Fourteen synthetic routes to SA have been published,[2,4-13] including two patented processes[9,12,13]. One of the proprietary routes is the morpholine/hexachlorobutadiene (MH/HCB) route shown in Equation 1, claimed by both Chemische-Werke Huls AG[7,12] and International Business Machines Corp.[13] HCB reacts with 6 equivalents of morpholine to form 1,1,3-trichloro-2,4,4-trimorpholinobutadiene (TMBD) plus 3 equivalents of morpholine hydrochloride. TMBD is cyclized with an aqueous buffer of pH 4-7 to form 2,4,4-trichloro-3-morpholinocyclobutenone (MCB), which, in turn is hydrolysed to SA in aqueous $H_2SO_4$.

[1]



HCB MH TMBD MCB SA SSA

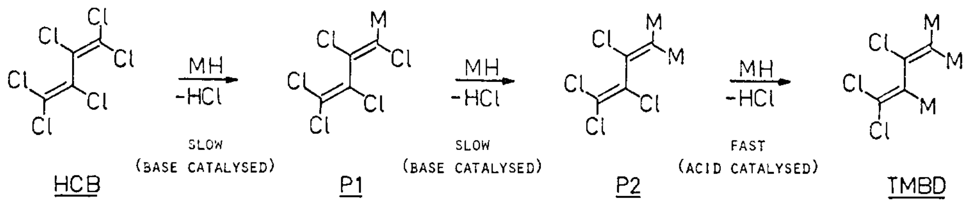
The reported yields of this process are low (< 50%) and the course of the reaction has not been corroborated with any structural proof for the putative intermediates. The present investigation sought to develop a comprehensive mechanistic picture of this remarkable transformation, and to characterize as many intermediates as possible. Of particular interest was the course of the morpholine addition to HCB, and the response of MCB hydrolysis to acid composition in aqueous $H_2SO_4$.

Reaction of HCB with MH (1-18 eq) was monitored by high performance liquid chromatography (hplc) and carbon-13 nmr spectroscopy. Hplc reaction profiles revealed the slow conversion (20-300 min) of HCB to a new product, P1, which was slowly converted (2-24 hours) to the final product, TMBD.

Cmr analysis of reaction aliquots demonstrated a two phase kinetic sequence: HCB → P1 → TMBD, where P1 was clearly monomorpholino substituted and TMBD contained 3 morpholines. There was no cmr evidence for any (> 1-2%) disubstituted intermediate (P2), implying that the final substitution (P2 → TMBD) was much faster than the first two processes. The rate equation ($v = (d[P1]/dt)_0 = k_1[HCB]_0[MH]_0^2$) and the accelerating effect of insoluble bases ($K_2CO_3$ or polyvinylpyridine) on the first substitution both indicate general base catalysis of the initial displacement, so possibly there is a change in mechanism to acid catalysis for the third reaction (Equation 2). (A referee has suggested that all three reactions may be base catalysed, but the third may be faster because of superior HOMO-LUMO matching.)

TMBD was isolated by extraction into a minimum of $CH_2Cl_2$ (leaving the morpholine hydrochloride salt behind). Crude yields were 80-90% when mole ratios MH/HCB of 9 or higher were used. White crystals from $CH_3CN$ or $CH_2Cl_2$ or $CH_2Cl_2$/hexane turn yellow ($\lambda_{max}$ 380 nm) very rapidly upon filtration. Cmr and spectroscopic data are reported for TMBD and P1 in the Table.

[2]

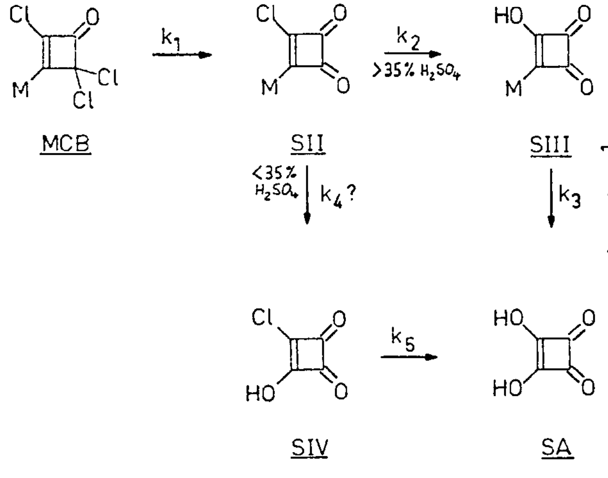


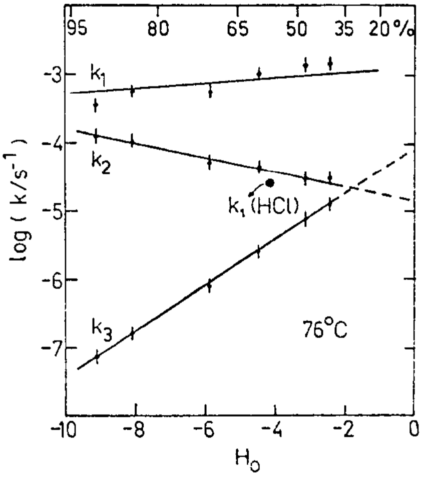
The yellowing reaction of TMBD in air or water prevented meaningful investigation of the cyclization step (pH 4−7) in homogeneous solution by either uv or cmr spectroscopy. Excellent preparative yields of MCB (up to 85%; based on HCB) may be obtained by stirring a toluene solution of crude TMBD with the buffer for a few hours at ~ 60°C. The MCB product is preferentially extracted into the toluene layer ($K_{dist}$ ~ 30−120) and is stable for at least 10−20 cyclization half-lives. A vinylogous amide, MCB is non-basic, apparently unprotonated even in 85% $H_2SO_4$. Spectroscopic data are found in the Table.

Hydrolysis of MCB to squaric acid is achieved with aqueous $H_2SO_4$. Of interest are: (a) the yield of hydrolysis *vs* ring opening; and (b) whether any intermediates could be isolated from the reaction. In aqueous $H_2SO_4$ of $\geq$ 40% acid, the hydrolysis of MCB was found to involve three discernable stages, through intermediates SII and SIII in Equation 3. Rate constants (see Figure) were determined from iterative Runge-Kutta integration fitting of the concentration *vs* time profiles obtained from multicomponent analysis of reaction aliquot uv spectra, using pure MCB, SII, SIII, and SA as standards[14]. Cmr analyses confirmed that these were the only species present. The yield of SA after cooling and filtration was 90−92%. SII and SIII were isolated by quenching the reaction into ice at an appropriate time and working up into $CH_2Cl_2$. Spectroscopic data and mps are reported in the Table.

Interestingly, all three processes in MCB hydrolysis respond differently to the solvent composition, as represented by the $H_0$ acidity function[15]. For example, log $k_1$ averages −3.1 ± 0.3 from $H_0$ = −9 to pH 7, independent of both acidity and water concentration over 16 orders of magnitude of proton activity! On the other hand, $k_2$, which also describes chlorine replacement, is slightly faster in acidic media (slope of log $k_2$ *vs* $H_0$ ~ −0.1). The third process, $k_3$, is the most sensitive, and appears approximately first order in water activity.

[3]



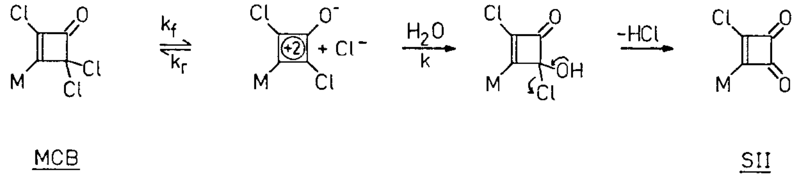


The Figure clearly shows that MCB hydrolysis is not acid catalysed, consistent with the non-basic character of the intermediates involved (uv spectra suggest that MCB, SII, and SIII are not significantly protonated, even in 85–90% $H_2SO_4$). Furthermore, $k_1$ and $k_2$ do not involve water in the rate limiting step either[16], leaving rate determining dissociation *via* a solvolysis mechanism (Equation 4) as the operating hypothesis emerging from our preliminary investigation.

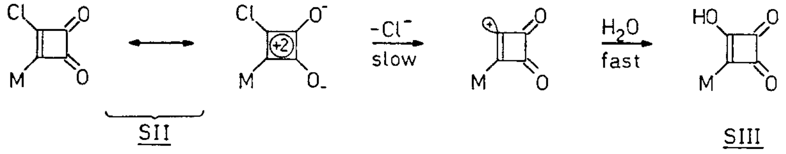
Hydrolysis of MCB to SII is not significantly reversible in aqueous $H_2SO_4$ because the rate is independent of water activity (i.e. $k_1 = k_f\,k[H_2O]/(k_r[Cl] + k[H_2O]) \rightarrow k_f$ for Equation 4), but does appear reversible in conc. HCl ($k_1 \rightarrow k_f\,k[H_2O]/k_r[Cl]$), where the rate is ~ 50X slower (12 M HCl; $H_o$ ~ −4.4 (ref. 15); see Figure).

Hydrolysis of SII, a vinylogous acid chloride, to SIII appears best rationalized by rate limiting formation of a vinyl cation which is rapidly trapped by water (Equation 5). The non-basic nature of vinylogous amide SIII appears to prevent the expected acid catalysed hydrolysis mechanism, with the result that $k_3$ seems to describe a neutral water hydrolysis (also shown in Equation 6). Normally, neutral hydrolyses are bimolecular in water (the second molecule is a general base catalyst), but here, $k_3$ is only first order in water activity over 40–70% $H_2SO_4$. Perhaps the adjacent carbonyl oxygen atom in SIII acts as an intramolecular general base catalyst.

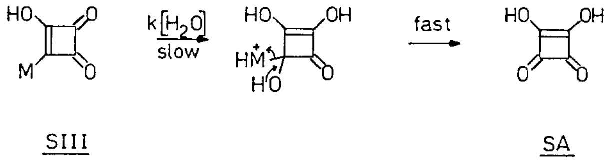
[4]



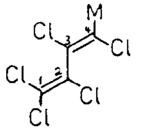
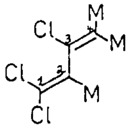
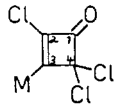
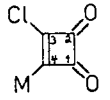
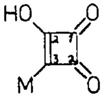
[5]



[6]



Although the sequence MCB → SII → SIII → SA describes hydrolysis in ≥ 40% $H_2SO_4$, there were additional cmr signals in 30.5% $H_2SO_4$ ($H_o$ = −1.68), and the multicomponent uv analysis broke down. This suggests a competing course for the hydrolysis in this solvent (not ring opening, because the isolated yield of SA is unchanged, at 91%). The crossover of the $k_2$ and $k_3$ lines in the Figure occurs at ~35% $H_2SO_4$, suggesting that the new course in less acidic media might involve SIV (Equation 3; loss of morpholine becomes faster than loss of chloride ion). Further work will be required to fully understand the more complex situation in the less acidic media, as well as the reversibility, common ion effect, and water activity dependence of all processes in Equation 3.

| Structure[a] |  |  |  |  |  |
|---|---|---|---|---|---|
| Name | **P1** | **TMBD** | **MCB** | **SII** | **SIII** |
| Recryst. Solvent | --b-- | $CH_2Cl_2$/hexane | $PhCH_3$ | 2-PrOH | 2-PrOH |
| mp / °C | | 140.5-1 | 102.5-4 | 127-9 | 245 (dec.) |
| $^{13}C$ NMR Solv.[c] | $CDCl_3$ | $CDCl_3$ | $CDCl_3$ | 30% $D_2SO_4$ | 30% $D_2SO_4$ |
| Morph. $\underline{C}H_2O$ | 65.4 | 66.3, 66.1, 66.0 | 66.3, 66.0[d] | 64.7, 64.4[d] | 64.6 |
| Morph. $\underline{C}H_2N$ | 48.8 | 49.2, 48.6, 47.9 | 48.5, 47.3 | 46.9, 46.2 | 47.5 |
| C1 | 124.9 | 101.0 | 171.8 | 181.6 | 176.7 |
| C2 | 125.9 | 144.2 | 96.5 | 188.7 | 170.1 |
| C3 | 109.3 | 86.0 | 163.7 | 147.6 | 172.9 |
| C4 | 142.1 | 156.8 | 85.1 | 176.6 | --e-- |
| UV $\lambda_{max}$ /nm | 216, 270 | 255, 355 | 275 | 258 | 291[f] |
| (log ε; solv.) | (80% MeCN) | (3.88; MeCN) | (4.43; pH 0-10) | (4.46; pH 0-10) | (4.49; pH 7) |
| IR ($CDCl_3$)/$cm^{-1}$ | ---- | ---- | 1642,1803 | 1632,1750<br>1807 | 1608,1700[g]<br>1820 |

a Consistent combustion analyses and mass spectra were obtained for all intermediates.
b This intermediate was not isolated in this study. See ref. 18.
c Shifts relative to external MeOH (49.0 ppm).
d Hindered rotation of the morpholine ring doubles these carbon-13 resonances.
e Fast proton exchange gives this molecule a two-fold symmetry axis.
f SIII(20% $H_2SO_4$): 278 nm (log ε: 4.40); $pK_a$(SIII) = 1.1±0.3 (pH at half-equivalence).
g Plus a broad OH stretch ~2700 $cm^{-1}$.

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## References and Notes

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14. Aliquots from MCB hydrolysis (0.5 **M**) were diluted in pH 7 buffer for uv analysis using the built-in multicomponent analysis software feature of the Hewlett Packard 8450A diode array spectrometer. Buffer is required because the uv spectra of SIII and SA are pH sensitive. Some data in the Figure was extrapolated from higher temperatures.
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16. The data in the Figure does not fit any well-established mechanism for acid catalysed hydrolysis, including A1 or A2 processes involving 1,2 or 3 water molecules. Even the new X-method of Cox and Yates (ref. 17) cannot explain the data.
17. (a) R. A. Cox and K. Yates. J. Amer. Chem. Soc. 100, 3861-7 (1978). (b) R. A. Cox and K. Yates. Can. J. Chem. 57, 2944-51 (1979).
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(Received in USA 13 June 1983)