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Benzylamine-Free, Heavy-Metal-Free Synthesis of CL-20 via Hexa(1-propenyl)hexaazaisowurtzitane

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Base-catalyzed isomerization of recently reported hexaallylhexaazaisowurtzitane produced a new derivative, hexa(1-propenyl)hexaazaisowurtzitane (HPIW). Photooxygenation of this intermediate by singlet oxygen oxidized most of the 1-propenyl substituents to formyl substituents. The course of this reaction of singlet oxygen with HPIW involves peroxide intermediates, which may include relatively stable macrocyclic (tetroxocane) derivatives. The resulting nitrolyzable polyformylhexaazaisowurtzitane was found to be a promisingly efficient new precursor to CL-20 (in a single preliminary experiment without any process development). The new intermediate HPIW also underwent direct nitrolysis to form CL-20, though not as efficiently as its photooxygenation product did.

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Keywords: CL-20, hexa-allylhexaazaisowurtzitane, hexa-(1-propenyl)hexa-azaisowurtzitane, hexa-nitro-hexa-azaisowurtzitane, polyformylhexa-azaiso-wurtzitane

Introduction

One of the most important new ingredients for munitions applications is hexanitrohexaazaisowurtzitane (CL-20) [1], but its production process suffers from several economic and environmental disadvantages, mostly related to requirements for benzylamine starting material and for heavy metal (typically, palladium) catalysts used in debenzylation steps. Besides its high material cost, benzylamine is an environmentally undesirable starting material because it is produced from benzyl chloride (plus ammonia), which in turn is produced by α-chlorination of toluene. CL-20 production therefore entails all of the problems inherent in the chlorine manufacturing industry [2], such as the long-term toxicity of environmental organochlorine by-products [3] and, potentially, mercury involved in the industrial chlor-alkali process to produce chlorine [4].

All synthetic routes used to prepare the hexaazaisowurtzitane cage for large-scale production of CL-20 depend on the condensation of benzylamine with glyoxal, originally developed by Nielsen [5]. CL-20 has remained expensive, however (as a potential large-scale replacement for HMX), mainly due to the high cost of benzylamine starting material and of hydrogenolysis steps involving palladium catalyst used in the debenzylation of hexabenzylhexaazaisowurtzitane (HBIW) intermediate in the course of preparing acylhexaazaisowurtzitane intermediates, such as tetraacetyldiformylhexaazaisowurtzitane (TADF), tetraacetylhexaazaisowurtzitane, or hexaacetylhexaazaisowurtzitane. The by-product of hydrogenolytic debenzylation of HBIW, toluene, is not economically or cleanly reconverted to benzylamine (only via chlorination followed by amination), so benzyl is not a clean, recoverable protecting group in that system. Various R&D

projects, including Navy ManTech programs [6], have addressed process development for reducing the cost of CL-20 production, but most have not approached potential cost reduction by developing a fundamentally different synthetic approach to the hexaazaisowurtzitane cage. Thiokol (now ATK Launch Systems) researchers have devoted significant effort to developing process improvements in CL-20 production [7]. Most of these improvements have involved parameterizations of hydrogenolytic debenzylation of HBIW followed by nitrolysis.

An alternative, benzylamine-free route to a polyacylhexaazaisowurtzitane precursor to CL-20 was envisioned by us following the recent report by Hervé et al. (SNPE France) of a preparation of hexaallylhexaazaisowurtzitane (HAllylIW) from a condensation of allylamine and glyoxal [8] (mechanistically the same as that described by Nielsen et al. to prepare HBIW [5]) and its use as a new precursor to CL-20 [9]. Their treatment of 1 g of HAllylIW with mixed acid produced a yellow solid (CL-20 is colorless) that had a detectable content of CL-20, according to HPLC and NMR analysis, but no yield was specified. (Nitrolysis of hexafurfurylhexaazaisowurtzitane produced CL-20 in a specified yield of 12%.)

The new route we envisioned was to utilize HAllylIW in a well-known isomerization reaction of allylamines into 1-propenylamines. The resulting hexa(1-propenyl)hexaazaisowurtzitane could then be oxidized by singlet oxygen (generated, for example, by dye-sensitized photolysis of oxygen gas) via another well-known transformation: cleavage of the C=C bond of propenylamines to produce formamides [10]. The resulting poly- or hexaformylhexaazaisowurtzitane would be another example of the class of polyacylhexaazaisowurtzitanes that should be susceptible to direct nitrolysis to CL-20.

Results and Discussion

Our preparation of hexaallylhexaazaisowurtzitane (HAllylIW) used reaction conditions similar to those of Hervé et al., but

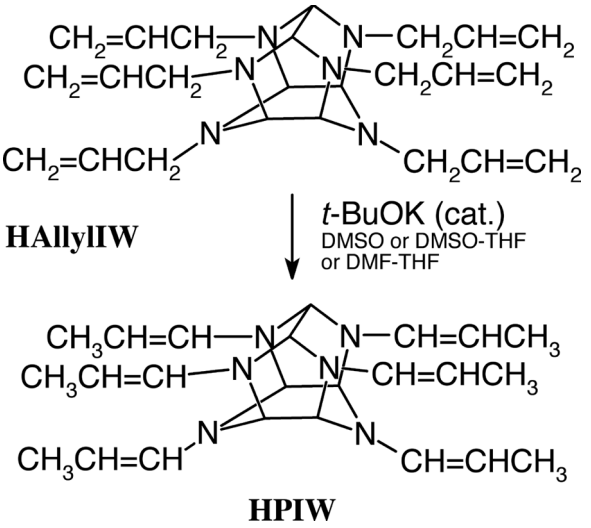

Figure 1. Base-catalyzed formation of hexa(1-propenyl)-hexaazaisowurtzitane.

with a modified workup procedure, gave isolated, purified yields of HAllylIW around 26%, close to the 20–25% previously reported [8,9].

The required rearrangement of HAllylIW was successfully achieved (Fig. 1) by base catalysis [11]: clean, efficient isomerization of HAllylIW to hexa(1-propenyl)hexaazaisowurtzitane (HPIW) [12] was effected—essentially quantitatively—by potassium *t*-butoxide base in dimethyl sulfoxide at room temperature in $\sim$6 h (also at 80°C in $\sim$1/4 h). The isomerization is also efficiently achieved by introducing potassium *t*-butoxide as its commercially available tetrahydrofuran solution into a solution of HAllylIW in DMSO or in dimethylformamide. Reactions in such $\sim$1:1 solvent mixtures typically proceeded to completion in an overnight run. (However, THF as the sole solvent did not allow isomerization at room temperature, even on prolonged reaction.) As in previous similar transformations of this type [13], the allylamine-to-propenylamine isomerizations require only catalytic *t*-butoxide; some of our successful

runs employed 1/3 equivalent of potassium *t*-butoxide per allyl substituent.

HPIW was most easily purified (sufficiently for subsequent reactions) by removing solvent(s) under high vacuum and redissolving the HPIW in a suitable solvent in which residual potassium *t*-butoxide is insoluble. We initially chose benzene-d_6 for the sake of characterizing the dissolved HPIW and subsequent reaction products by NMR. Potassium *t*-butoxide has sufficiently low solubility in benzene that this is an effective purification method; however, other hydrocarbon solvents in which potassium *t*-butoxide has low solubility, such as toluene or xylene or even some aliphatics, should be suitable for this process.

We tested other methods of ''neutralizing'' potassium *t*-butoxide in situ so that the processed solution might be used directly without workup of the HPIW. In one case, methylation of contained potassium *t*-butoxide was attempted by reaction with stoichiometric dimethyl sulfate injected into the crude HPIW product solution, with the intention of producing *t*-butyl methyl ether and potassium sulfate by-product. This approach was partially successful in a single attempt, but it was fraught with complications. Actual *t*-butoxide content must be determined in order to distinguish it from *t*-butanol formed from adventitious hydrolysis of *t*-butoxide during handling of the hygroscopic solutions. Otherwise, excess toxic dimethyl sulfate—beyond that required to methylate *t*-butoxide—might alkylate HPIW intermediate or interfere in other ways. In the course of this approach, we developed a potentially useful diagnostic measure of potassium *t*-butoxide–*t*-butanol mixture compositions in DMSO-d_6 solvent using ^{13}C NMR spectrometry. In ^{13}C NMR spectra of mixtures of *t*-butanol and potassium *t*-butoxide, the quaternary carbon resonance occurs at an average chemical shift (δ) of the two species, weighted by the mole fraction (X) of each:

$$\delta_{\text{obsd}} = X_{t\text{-BuOK}}\delta_{t\text{-BuOK}} + X_{t\text{-BuOH}}\delta_{t\text{-BuOH}} \quad (1)$$

From analyses of four solutions of *t*-butanol–potassium *t*-butoxide mixtures in DMSO-d_6—quantified by integration of

the quaternary carbon absorptions vs. those of DMSO-d_6 (i.e., all non-protiated carbons)—linear regression of a plot of mole fraction of *t*-butoxide vs. quaternary carbon chemical shift produced the following relationship, useful for determining potassium *t*-butoxide content in DMSO-d_6 solutions by ^{13}C NMR:

$$X_{t\text{-BuO}^-} = 49.17 - \delta_{^{13}\text{C}}^{\text{quat}}/1.36 \tag{2}$$

This regression estimates a chemical shift of δ 66.87 for pure *t*-butanol in DMSO-d_6 , comparing very favorably with a literature value of δ 66.88 [14].

The ^{1}H and ^{13}C NMR spectra of HPIW in various solvents indicate that it exists in a few (two to four) rotational isomers (rotamers) due to cis-trans isomerism of the propenyl substituents and restricted rotation about the *N*-propenyl bonds. Other examples of exo-heterocyclic enamines, *N*,*N*-dimethylaminomethylene-substituted pyrazoles, exhibit complex NMR spectra due to rotamers as well [15].

The recovered yield of HPIW via base-catalyzed isomerization of HAllylIW was somewhat dependent on workup conditions. Conversions of HAllylIW to HPIW by potassium *t*-butoxide in DMSO–tetrahydrofuran solutions appear to be essentially quantitative by NMR analyses. Efficiency of separation of HPIW from by-products of this isomerization (especially potassium salts) appears to be more condition dependent. One experiment in which the crude product solution was heated (40–60°C) during rotary evaporation—in order to remove DMSO solvent prior to redissolution in benzene—gave a relatively low isolated yield of 70% HPIW. Additional treatment of the benzene extract solution with *n*-pentane showed some precipitation of material consistent with polymeric degradation product(s) of HPIW. The benzene–pentane solution contained purer HPIW, but its yield was lower presumably due to degradation at elevated temperature.

In a second preparation of HPIW, the reaction product solution was split into two portions for separate workups. One half was initially treated similarly to previous

preparations: THF under house vacuum and then DMSO under high vacuum were pumped off at ambient temperature. HPIW was dissolved from the residue by 1:1 benzene–pentane; the suspension was filtered; and the filtrate was concentrated by rotary evaporation. The yield of HPIW by this treatment was 93%; some residual solvents (benzene, DMSO) were still present (not included in this yield) but would not interfere with subsequent photooxygenation reactions.

The other half of product solution was extracted with hexanes, which removed most of the HPIW from the DMSO solution and gave a 69% yield (in the presence of some residual DMSO). The hexane–unextractable portion of the solution was treated ''conventionally'': solvents were removed under high vacuum at ambient temperature; HPIW was then extracted with benzene–pentane. This treatment produced an additional 15% HPIW (total yield: 84%). Thus, extraction by hexanes could alleviate most of the DMSO removal, which could be unwieldy in a larger-scale production process, though there is some loss in yield this way. An alternative workup using longer-term liquid-liquid extraction at low temperature, such as with pentane, might improve this efficiency.

HPIW was next subjected to oxidation by singlet oxygen, generated by halogen-lamp photolysis of oxygen gas, sensitized by catalytic amounts of zinc tetraphenylporphine. The transformation of enamines to formamides via photooxygenation has been reported to occur in a variety of different solvents [16]. We conducted this reaction several times in a variety of solvents under various conditions because all runs produced preliminary evidence that polymerization of one or more enamine intermediate(s) may have been occurring: precipitation of an organic solid that was soluble in DMSO-d_6 but otherwise poorly soluble in most other solvents, including acetone.

Also, the ^{1}H NMR spectra of the reaction products showed quite broad absorptions of all signals attributable to hexaazaisowurtzitane species. However, a mixture of several different compounds containing various numbers of 1-propenyl and formyl substituents might be expected to exhibit unusually complex ^{1}H NMR spectra due to potentially even more rotamers

than in HPIW. (TADF [7a] and triacetyltribenzylhexaazaisowurtzitane [17] exhibit complex ^{1}H NMR spectra due to rotamers of these polyacylhexaazaisowurtzitanes.) Other preliminary evidence that initially suggested that the product(s) formed in these reactions might include polymeric species rather than ''simple'' polyformylpoly(1-propenyl)hexaazaisowurtzitane intermediates (i.e., a mixture of cages with various multiple numbers of both substituents, rather than polymeric species) included the chemical shift of the methyl protons in the ^{1}H NMR spectra in DMSO-d_6: $\delta \sim 1.14$ (rather than $\delta \sim 1.60$ seen in the HPIW reactant), which is tentatively more consistent with methyl groups on a saturated chain rather than on a 1-propenyl substituent.

Integration of the various broad absorptions of the crude products' ^{1}H NMR spectra suggested that the average formyl content was typically between three and four substituents per hexaazaisowurtzitane cage before significant precipitation may have prevented completion of oxidation (which would require heterogeneous gas–solid reactions for further progress). In order to minimize such possible polymerization that may have been occurring, one run was conducted at a much lower concentration than others (1–10% of the HPIW concentration of any other run) and at low temperature (cooled in a dry ice–ethanol bath). Even at 0.8-h reaction time, a sample withdrawn for analysis yielded an ^{1}H NMR spectrum that exhibited (in addition to expected acetaldehyde, which was always apparent in spectra of the crude reaction mixtures) broad resonances at chemical shifts consistent with polyformylpoly(1-propenyl)-hexaazaisowurtzitane intermediates (but with a formyl content of significantly less than three substituents per cage); broad methyl absorptions were apparent over a range of δ 0.9–1.6. Table 1 lists the variety of conditions that were attempted to effect photooxygenation of HPIW to polyformylhexaazaisowurtzitane derivatives.

In a preliminary test of nitrolyzability, the products of some photooxygenation reactions were subjected to nitrolysis after isolation from reaction suspensions by removal of all volatiles (solvent and acetaldehyde by-product). An initial

Table 1
Conditions of photooxygenation of HPIW

Solvent system	Temperature	Reaction time (h)
C_6D_6	R.T.	3
2:1 C_6D_6–acetone-d_6	0°C	8
3:5 $CDCl_3$–CD_2Cl_2	0°C	3
1:1 C_6H_6–DMSO-d_6	0°C	3
Acetone-d_6	Dry ice–EtOH bath	4–6
1:5 CD_2Cl_2–$CDCl_3$	Dry ice–EtOH bath	0.8
1:1 Acetone–DMSO	Dry ice–EtOH bath	5.6

run utilizing a mixture of 98–100% nitric acid and acetonitrile-d_3 produced a minor amount of CL-20 (<10%)—confirmed by HPLC analysis as well as ^{1}H and ^{13}C NMR spectrometry—in a complex mixture after 6 days of reaction at ambient temperature. (Such prolonged reaction conditions significantly hydrolyzed acetonitrile ultimately to acetic acid.) In another run, the residue from a photooxygenation reaction was subjected to nitrolysis conditions using 98–100% nitric acid in the presence of Nafion® NR50 beads as a strong Brønsted acid catalyst. Reflux of the reaction solution for a total of 30-1/2 h resulted in a surprisingly clean conversion of the crude polyformyl intermediate to CL-20, which was the predominant constituent in the NMR spectral region attributable to hexaazaisowurtzitane species.

The cleanliness of the nitrolysis of the oxidation product called into question the assignment of the broad NMR absorptions as being due to polymeric species containing saturated alkyl substituents on hexaazaisowurtzitane cages. Such saturated substituents would not be expected to be as easily nitrolyzed as formyl or 1-propenyl's substitution products (vide infra). That the photooxygenation reactions yielded products with NMR characteristics reminiscent of polymers regardless of the temperature (dry ice–ethanol, 0°C, or room temperature) or reaction time (0.8–8 h) also left in question the actual

presence of significant polymeric substitution in the reaction product.

Literature on oxidations of enamines by singlet oxygen [18,19] suggests that the typical mechanism of oxidation followed in this transformation could proceed via a specific unusual regiochemical course in the case of conformationally restricted enamines presented by the structure of hexa(1-propenyl)hexaazaisowurtzitane (HPIW). Specifically, the 1-propenyl substituents at N^2 and N^{12} (according to isowurtzitane nomenclature for hexaazaisowurtzitanes [20,21]) could be proximately oriented such that peroxide-substituted ionic intermediates (**1** in Fig. 2) formed from addition of singlet oxygen to the propenyl double bonds (following formation of a transient charge-transfer complex [22]) could reasonably link the N^2 and N^{12} substituents intermolecularly (i.e., between the two substituents within one hexaazaisowurtzitane molecule) via path b rather than intramolecularly—which typically leads to 1,2-dioxetane intermediates that rapidly cleave to an amide

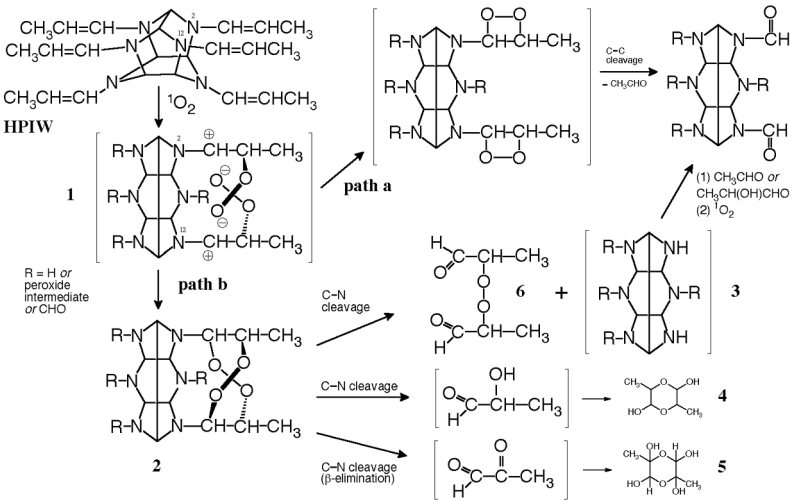

Figure 2. Apparent mechanisms of singlet oxygen reaction with HPIW.

product plus a cleaved carbonyl product—via path a. Both pathways may be feasible for hexaazaisowurtzitane structures.

Path a leads initially to 1,2-dioxetane intermediates and ultimately to the originally desired *N*-formyl derivatives of hexaazaisowurtzitane. However, path b appears to be able to form 1,2,5,6-tetroxocane derivatives (**2**), which may be expected to be much more stable than alternative 1,2-dioxetane intermediates. Several other 1,2,5,6-tetroxocane derivatives have been isolated [23,24] and may have quite high stabilities. (For example, one member of this class, 5,8*a*,13,16*a*-tetramethyldinaphtho[2,1-*c*,2′,1′-*g*][1,2,5,6]tetroxocane, has a melting point of 230°C [25].) The saturated nature of the bonding in tetroxocane intermediates such as **2** is more consistent with ^{1}H NMR chemical shifts that were actually observed for the photooxygenation product than the bonding in polyformylpoly(1-propenyl)hexaazaisowurtzitane species would be: $\delta \sim 1.14$ vs. $\delta \sim 1.60$ seen in the HPIW reactant.

Peroxide (tetroxocane) intermediates such as **2**, being hemiaminals (α-oxygen-substituted alkylamines), would also be expected to be nitrolyzable to the corresponding nitramines (as other α-substituted alkylamines are known to be, such as 1-(alkoxymethyl)hexahydro-3,5-dinitro-1,3,5-triazines [26] and hexahydro-1-nitratomethyl-3,5-dinitro-1,3,5-triazine [27], which have been nitrolyzed to RDX), more so than would be saturated polymeric substituents that might be consistent with the ^{1}H NMR chemical shifts.

Finally, proof of the hypothesized peroxide-intermediate mechanism was obtained from fresh samples of the products of photooxygenation reactions. A solid sample of product prepared in acetone solvent, when redissolved in dimethyl sulfoxide, produced a dramatic positive peroxide test result with acidified starch-iodide solution. A sample of crude reaction solution in 1:1 DMSO-acetone from another run similarly gave a positive qualitative peroxide test result. A quantitative titration for peroxide content in the latter reaction solution suggests that peroxide intermediates, such as **2**, have finite stability, as would also be reasonable. Besides C−C bond

cleavage that would lead to *N*-formyl products—as undergone by 1,2-dioxetanes in some structural systems and reaction conditions—peroxide intermediates may also undergo C−N bond cleavage to produce aldehydes plus (at least transient) free amines [28]. Often, such free amines, including **3** in the present system (Fig. 2), may react with aldehyde (e.g., acetaldehyde) molecules generated from C−C bond cleavage at other enamine sites to form new enamines that are themselves susceptible to continued reaction with singlet oxygen.

Further direct evidence of C−N bond cleavage as an alternative mode of peroxide intermediate degradation was seen in our recent experiments. Expected by-products of such cleavage from *N*-propenyl photooxygenation intermediates would be 2-hydroxypropionaldehyde (lactaldehyde) and methylglyoxal [28]. Both of these compounds are fairly reactive species and tend to hydrate and/or dimerize in various ways. Lactaldehyde forms an equilibrium mixture of three different conformations of 3,6-dimethyl-1,4-dioxane-2,5-diol (**4**) [29]. Methylglyoxal may also form similar hydrated forms and/or cyclic dimers or trimers, such as 2,5-dimethyl-1,4-dioxane-2,3,5,6-tetraol (**5**), depending on conditions [30]. It is revealing that ^{1}H NMR spectra of reaction solution aliquots from photooxygenations of HPIW (Fig. 3) show very complex absorptions in aliphatic proton regions that appear consistent with containing the complex patterns that are apparent in spectra of lactaldehyde dimer [29] as well as methylglyoxal [30].

Finally, one species that forms in HPIW photooxygenation reaction solutions under some conditions (Fig. 3) exhibits a relatively simple ^{1}H NMR pattern (δ 1.196 [d, 7.0 Hz], 4.028 [q of d, 7.0 Hz, 0.97 Hz], 9.626 [d, 0.97 Hz]) that is qualitatively very similar to—but not identical to—known [31] 2-hydroxypropionaldehyde monomer (δ 1.14 [d, 7.25 Hz], 4.01 [CH], 5.55 [OH, $J_{\mathrm{H-OH}} = 5.5$ Hz], 9.80 [CHO, $J_{\mathrm{H-CHO}} = 1.0$ Hz]). Since the reaction product species lacks vicinal HC^{2}–OH coupling, it may be assigned as a chemically similar peroxide derivative (dimer **6** in Fig. 2) that could reasonably result from degradation of tetroxocane intermediate **2**.

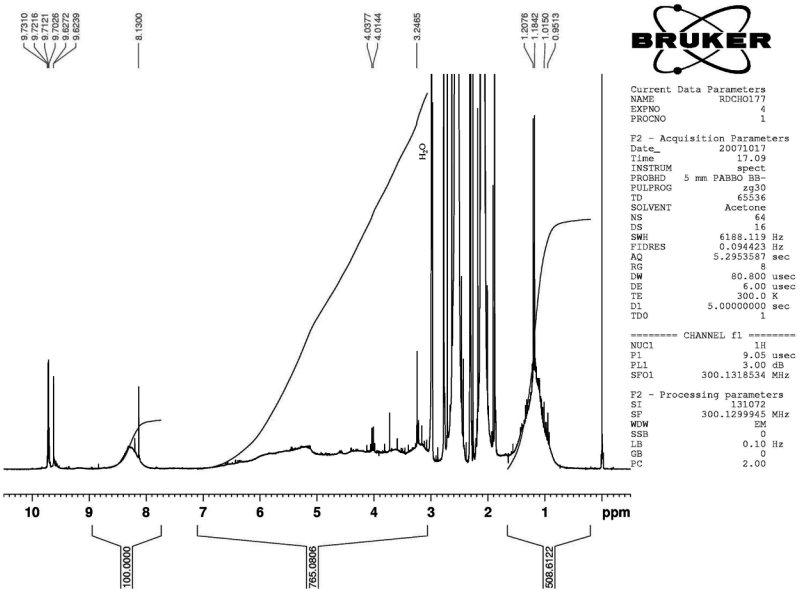

Figure 3. ^{1}H NMR spectrum of a crude reaction sample of HPIW photooxygenation (1:1 DMSO–acetone signals are vertically offscale).

Another observation that is consistent with long-term degradation (via C–N bond cleavage to produce aldehyde by-products) of initially isolated peroxide intermediates is that the storage of solid oxidation products produced a noticeable odor (which involatile hexaazaisowurtzitanes would not have), and storage under vacuum over phosphorus pentoxide allowed apparent absorption of organic material by the phosphorus pentoxide, which darkened somewhat during desiccation of the oxidation products.

Elemental analysis of one crop obtained from workup of the product of one photooxygenation reaction was consistent with a composition containing several of the components referred to above. It was not consistent with a single specific hexaazaisowurtzitane derivative. It is surmised, therefore, that the product material contains a mixture of

hexaazaisowurtzitanes with various substituents as suggested in Fig. 2: initially isolable peroxide intermediates leading, on storage, to ultimate products that should contain N-unsubstituted (NH) sites, *N*-formyl sites, and C−N cleavage products such as methylglyoxal. Following such cleavage, smaller by-products might be separable from hexaazaisowurtzitanes, though they might not interfere with subsequent nitrolysis reactions.

With a better understanding of the structural nature of products formed in photooxygenation reactions (Fig. 2), it is recognized that the oxidation reactions that lead to nitrolyzable intermediates appear to be essentially quantitative, according to NMR characterizations of these reactions, since there are no residual propenyl groups apparent. Although the compositions of such reaction products may be very complex—due to the parallel pathways available for degradation of initial intermediates formed during singlet oxygen reaction—the hexaazaisowurtzitane products formed from these pathways tentatively appear to be nitrolyzable. However, nitrolysis of theoretically nitrolyzable precursors is not necessarily quantitative. Thus, nitrolytic cleavage of hemiaminal substituents (as in **2**) may be more or less efficient than nitrolytic replacement of *N*-formyl groups, and both of these electrophilic substitutions should be less efficient—or least kinetically slower—than simple nitration of N-unsubstituted intermediates present from C−N bond cleavage of peroxide intermediates. Such N-unsubstituted intermediates may be indefinitely stable if proximate nitrogens are protected, as the structures would be chemically similar to tetraacetylhexaazaisowurtzitane, the preferred precursor in the current production process for CL-20.

The answer to the question of relative nitrolyzability of the various substituents appears available in one nitrolysis experiment conducted on a sample of photooxygenation product. One nitrolysis was performed using a solid sample of a product precipitated from photooxygenation in acetone solvent. A solution of the solid product dissolved in nitric acid, in the presence of Nafion® NR50 acid catalyst, was heated at reflux for 26-1/2 h. After neutralization and extraction with dichloromethane, the

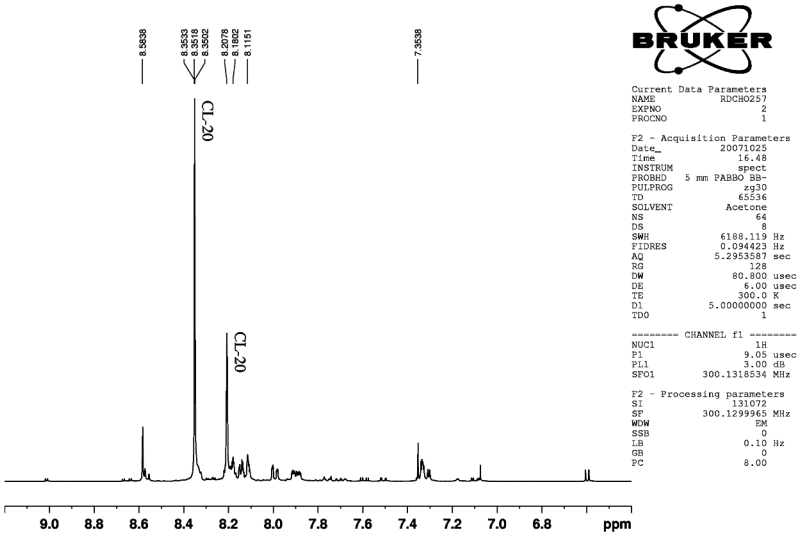

Figure 4. ^{1}H NMR spectrum of products of incomplete nitrolysis of photooxygenation product.

solute's hexaazaisowurtzitane composition appeared to be only ~52 mol% CL-20. The balance of absorptions in the hexaazaisowurtzitane cage proton region of the ^{1}H NMR spectrum (Fig. 4) looked remarkably like a mixture of predominantly 4-formylpentanitrohexaazaisowurtzitane (WFN_5) and a lesser amount of 4,10-diformyltetranitrohexaazaisowurtzitane (*sym*-WF_2N_4), by comparison to their published spectra [21]. This result may be consistent with easier susceptibility to nitrolysis of the hexaazaisowurtzitane cages' imidazolidine nitrogens than of the piperazine ring nitrogens. This result has been similarly observed in past nitrolyses of tetraacetyldiformylhexaazaisowurtzitane (TADF).

Another nitrolysis experiment under similar conditions—with a different sample of photooxygenation product—was allowed to run for 44-1/2 h to ensure complete nitrolysis. This experiment utilized a workup of quenching into ice-water, neutralization with solid sodium bicarbonate, and filtering off precipitated CL-20. A yield could be calculated for this

nitrolysis even without knowing the exact composition of the photooxygenation product, since elemental analysis of the material is available and an assumption is made that all of the nitrogen in the reactant sample is present in the form of hexaazaisowurtzitane derivatives, since no nitrogen is introduced by any other treatment of the material. The observed yield for this run under these conditions was 47%. Conditions for nitrolysis of this intermediate were not optimized in any way. Optimal nitrolysis times may be dependent on the chemical composition of the intermediate mixture, and they may occur in between the times of 26-1/2 and 44-1/2 h used in these two experiments. Alternative nitrolysis reagents and acid catalysts might prove to be superior following adequate process development.

In parallel with the success of the nitrolysis of a crude product of photooxygenation of HPIW, an experiment to directly nitrolyze HPIW itself was carried out. It may be expected that HPIW could be a feasible intermediate for nitrolysis. Enamines are known to undergo electrophilic attack at the β carbon, such as by acylating reagents and halogens, preferentially over the complete displacement of an *N*-alkenyl substituent [32]. A similar initial nitration of the 1-propenyl substituent(s) by a nitrating reagent such as nitric acid could produce an α-(nitratoalkyl)amine, a class of tertiary amine—along with various other electronegatively α-substituted alkylamines—that is known to be nitrolyzable to the corresponding nitramine (vide supra).

This mechanistic route to displacement of substituents on the hexaazaisowurtzitane cage makes it superior to nitrolysis of α-unsubstituted alkyl derivatives, such as would be formed by initial nitration of allyl substituents in hexaallylhexaazaisowurtzitane (HAllylIW) [9]. In contrast, the isomerization performed here on HAllylIW produces more easily removed substituents—tentatively following their initial nitration in HPIW. It is postulated that transient intermediates of β-nitration of HPIW could be mixed polynitropoly(α-substituted β-nitropropyl)hexaazaisowurtzitanes (Fig. 5, wherein X = NO_2, Ac, etc.). (X = H, such as with simple nitric acid, would leave

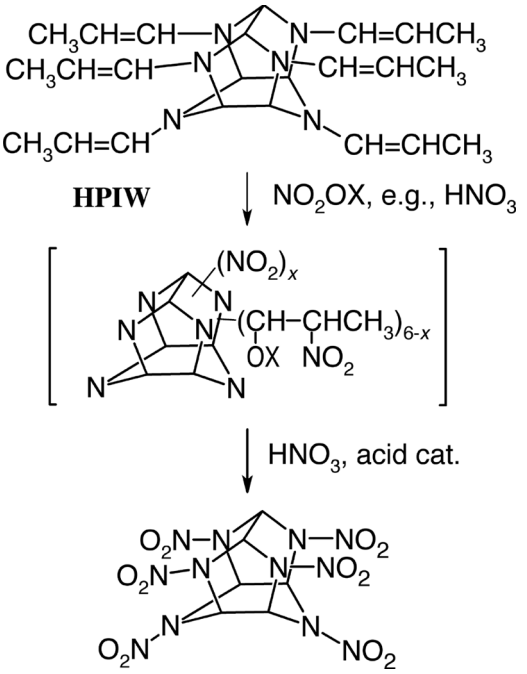

Figure 5. Direct nitrolysis of HPIW to CL-20.

α-hydroxy sites susceptible to further nitration by the nitrating reagent, still forming nitrolyzable intermediates with X = NO_2.)

One direct nitrolysis of HPIW—using conditions similar to those for nitrolysis of the photooxygenation product, but with a reaction time of 94 h to ensure complete nitrolysis—provided an isolated yield of CL-20 of only 11.6%. Again, reaction conditions were in no way optimized, and shorter nitrolysis times might provide higher yields. From these preliminary results, however, it appears worthwhile to carry out oxidation of HPIW to stable, nitrolyzable intermediates, which seem to survive nitrolysis conditions better (as intact hexaazaisowurtzitane cages) than HPIW itself.

A sample of HAllylIW subjected to similar nitrolysis conditions for 46 h showed no or negligible evidence of the formation of CL-20, according to ^{1}H NMR analysis.

Conclusions

By improving the efficiency of converting HAllylIW to CL-20 with two additional steps, a potentially practical benzylamine-free, heavy-metal-free synthesis of CL-20 has been successfully achieved. The overall process now avoids the preparation of benzyl chloride, which uses elemental chlorine, and catalytic hydrogenolysis steps—requiring palladium metal/compounds—are avoided. A heavy-metal-free sequence leading to CL-20 can now be envisioned: glycerol (available from biodiesel) is dehydrated in formic acid to make allyl alcohol [33]; the alcohol is efficiently converted to allyl bromide [34] or chloride [35] by treatment with the corresponding hydrohalic acid; and the allyl halide is aminated to make allylamine [36]. This commercially available reagent condenses with glyoxal to make HAllylIW [8], and the subsequent steps have been developed in the current work, leading to CL-20 with potentially high efficiency.

The following recommendations derive from the results of this work, which was only a small-scale feasibility demonstration:

- Process development is needed to improve efficiency of certain steps. Hervé et al. reported 20–25% yields of HAllylIW [8,9]; our slight modification of their published procedures yielded 26% HAllylIW; and Li et al. recently reported a yield of 37.1% from modified conditions for the condensation [37]. Further process development may make the allylamine–glyoxal condensation similar in efficiency to that which has been achieved with benzylamine–glyoxal, since the chemistry and conditions are fundamentally similar. In fact, the development of HAllylIW is approximately paralleling that of HBIW: the first yield of HBIW was 12.7%, reported in March 1986 [38]; by October 1986, it had improved to 30–40% [39]; and upon an August 1989 manuscript submission, process development had brought it to ∼80% [5].
- The HAllylIW-to-HPIW isomerization has proven to be very efficient, but more economical alternative solvents

might be found for this transformation and may improve the efficiency of isolation.

- The limits of catalysis by *t*-butoxide in effecting this isomerization have not been determined. Still lower quantities of potassium *t*-butoxide could improve the economics of the process.
- If the photooxygenation product remains desirable, its composition should be better characterized, and process development in conducting the photooxygenation most efficiently should be carried out. Known alternative methods of generation of singlet oxygen—e.g., solid metal peroxide–gaseous hydrogen halide reactions [40]—should also be considered.

Experimental

Hexaallylhexaazaisowurtzitane (HAllylIW)

To 10.6 g of allylamine dissolved in 30 mL of acetonitrile was added 1.2 g of formic acid (99%) plus 0.2 mL of water. After cooling to 0°C, 9.0 g of 40% aqueous glyoxal was added over 1 h with stirring. The solution was then stirred for an additional hour at 0°C; then 24 mL of saturated sodium bicarbonate was added and stirring continued at 0°C for one more hour. After standing in a freezer (–16°C) overnight, the product was filtered, washed with water, and air dried for 2 h, giving 3.46 g of an off-white soft solid. The product was dissolved in 25 mL of dichloromethane, dried over $MgSO_4$, filtered, and evaporated to an off-white crystalline solid. This was pumped under high vacuum for 1 h, giving 3.32 g of product (26% yield).

Hexa(1-propenyl)hexaazaisowurtzitane (HPIW) (Procedure A)

HAllylIW (1.00 g) was dissolved in 4.0 mL anhydrous DMSO plus 1.0 mL DMSO-d_6 plus 3.0 mL of a 20 wt% solution of potassium *t*-butoxide in tetrahydrofuran, and the mixture was magnetically stirred overnight at ambient temperature. After ~18 h, isomerization of HAllylIW to HPIW was

complete by NMR analysis. ^{1}H NMR (DMSO-d_6) of HPIW in the crude reaction mixture: δ 1.52–1.63 (m, CH_3), 4.24–4.33 (m, C*H*CH_3), 4.84 (s, 4 H, cage CH), 4.89 (s, 2 H, cage CH), 5.88–5.96 (NCH); ^{13}C NMR (DMSO-d_6) of the crude reaction mixture: δ 11.78, 11.89, 12.20, 15.08, 74.07, 76.61, 77.14, 81.02, 82.11, 82.60, 92.75, 100.24, 100.96, 101.62, 101.77, 102.51, 134.84, 135.30, 135.46, 135.58. THF was removed at ambient temperature under vacuum, and the temperature was raised (40–60°C) to remove most of the DMSO. Residual DMSO was pumped off under high vacuum and ambient temperature overnight. The residue was shaken with benzene (∼25 mL), and the suspension was filtered. To the filtrate was added an equal volume of *n*-pentane, which precipitated a small amount of amber solid, which was filtered off. The filtrate was concentrated by rotary evaporation at ambient temperature. Pentane was added to the residue, and the suspension was filtered again. The solution was concentrated by rotary evaporation, and the residue was left under high vacuum for 3 days. Yield: 0.7035 g (70%). NMR analysis of the residue showed it to be relatively quite pure HPIW. ^{1}H NMR (CD_2Cl_2): δ 1.59–1.70 (m, CH_3), 4.42–4.76 (m, C*H*CH_3), 4.75 (s, 4 H, cage CH), 4.84 (s, 2 H, cage CH), 5.93–6.02 (NCH). ^{13}C NMR (CD_2Cl_2): δ 12.46, 12.57, 12.82, 15.49, 75.67, 75.81, 77.95, 78.30, 78.71, 78.85, 78.94, 81.92, 82.48, 83.35, 83.89, 95.45, 102.85, 103.78, 104.38, 104.87, 105.90, 135.47, 135.59, 135.76, 135.88, 136.09.

Hexa(1-propenyl)hexaazaisowurtzitane (HPIW) (Procedure B)

To HAllylIW (3.16 g, 7.75 mmol) dissolved in 15 mL anhydrous DMSO was added 7.0 mL (11.6 mmol) of a 20 wt% solution of potassium *t*-butoxide in tetrahydrofuran, and the mixture was magnetically stirred overnight at ambient temperature. The reaction solution was divided into two equal portions for separate workups.

Workup 1: THF was removed at ambient temperature under vacuum, and DMSO was pumped off at high vacuum

and ambient temperature overnight. The residue was shaken with ∼100 mL of 1:1 benzene–pentane, and the suspension was filtered. The filtrate was concentrated by rotary evaporation at ambient temperature; pentane was added to the residue, and the suspension was filtered again. The solution was concentrated by rotary evaporation, and the residue was left under high vacuum for 4 days. The residue was dissolved in CCl_4 to a volume of 9.6 mL. NMR analysis of a sample showed it to contain some residual solvents in addition to usably pure HPIW. Contained yield of HPIW: 1.46_6 g (93%).

Workup 2: The other half of the reaction solution was stirred vigorously overnight with 80 mL of hexanes. The hexanes layer was decanted, and the DMSO layer was rinsed with 5–10 mL hexanes, which was added to the first hexanes solution. The collected hexanes solution was treated with a little $MgSO_4$, filtered, and evaporated to a pinkish oil. NMR analysis (DMSO-d_6) of a sample showed it to contain some residual DMSO in addition to quite pure HPIW. Contained yield of HPIW: 1.09_0 g (69%). The DMSO layer was processed as in Workup 1 above. NMR analysis of a sample showed it to contain some residual solvents in addition to usably pure HPIW. Contained yield of HPIW: 0.24_4 g (15%). Total yield from Workup 2: 84%.

Photooxygenation of HPIW (Procedure A)

The HPIW product from Procedure A above was dissolved in 10 mL of acetone-d_6 in a 10-mL graduated cylinder (with a standard-taper joint) fitted with a Claisen adapter to allow inlet as well as egress of an oxygen purge via a glass capillary; a few milligrams of zinc(II) tetraphenylporphine sensitizer was added to the solution, and the base of the cylinder was submerged in a dry ice–ethanol bath. With a purge of oxygen passing through, the solution was irradiated with a quartz halogen headlamp. After 4 h of treatment, a pale pink flocculent solid was suspended in the solution. The suspension was filtered, and the filtrate was subjected to additional reaction with singlet oxygen for a couple of hours. A small amount of additional solid precipitated, which was filtered off. The filtrate in

acetone-d_6 was reduced in volume by rotary evaporation. An equal volume of chloroform was then added, which precipitated more pale pink solid, which was filtered off. All filtered solids were dried in a vacuum desiccator over P_4O_{10}. Melting-point determination of the first precipitate from the reaction showed it to darken starting at 149°C, melting with decomposition above 180°C with evolution of a clear condensable liquid. Elemental analysis was determined for the final precipitate from chloroform (%, mean of two): C, 47.64_5 ; H, 5.61; N, 18.97_5; O (by difference), 27.77. A qualitative peroxide test was conducted on some of the final precipitate from chloroform: 9.0 mg in ~1/2 mL DMSO-d_6 was added to a solution of ~1/2 g KI plus 1 mL acetic acid in ~10 mL water, producing a yellowish color; addition of starch solution produced a distinct blue color in <1 min. A control test with all components (including DMSO) except the oxidation product showed no color change.

The final precipitate's main broad ^{1}H NMR absorptions—formyl C*H*O, oxygenated substituent CH_3, and other aliphatic protons including cage C*H*—proposed for the product mixture (Fig. 2) show relative integrations consistent with a formula of

$$(C_6H_6N_6)(CHO)_{3.428}(C_6H_{10}O_4)_{1.286}$$

where $C_6H_{10}O_4$ may be due to residual tetroxocane intermediate (occupying two cage nitrogens as in **2**) or two dissociated propionaldehyde derivatives, such as methylglyoxal, leaving residual unsubstituted free (NH) nitrogens.

Photooxygenation of HPIW (Procedure B)

The HPIW product from Procedure B (hexanes extract of Workup 2) above was dissolved in 25 mL of 1:1 DMSO–acetone in a 25-mL graduated cylinder (with a standard-taper joint) fitted with a Claisen adapter to allow inlet as well as egress of an oxygen purge via a glass capillary; a few milligrams of zinc(II) tetraphenylporphine sensitizer was added to the solution, and the base of the cylinder was submerged in a dry ice–ethanol bath. With a purge of oxygen passing through, the

solution was irradiated with a quartz halogen headlamp. After 5.6 h of treatment, the solution remained homogeneous, but NMR analysis of an aliquot showed no residual propenyl signals, so their oxidation was complete. ^{1}H NMR (∼1:1 acetone-d_6–DMSO-d_6) of the hexaazaisowurtzitane product: δ 1.0–1.4 (bm, CH_3), 3.3–6.9 (bm, all CH), 8.1–8.5 (CHO)]. A positive qualitative peroxide test, as in Procedure A, was obtained from the solution. Attempts to identify components of the product by electrospray ionization mass spectroscopy as well as by atmospheric pressure chemical ionization (APCI) mass spectrometry under a variety of conditions were not conclusive.

Partial Nitrolysis of Oxidation Product to CL-20

Some of the first precipitate (203 mg) from photooxygenation Procedure A (previously vacuum-dried over P_4O_{10}) was wetted with ∼1 mL CCl_4 in a 50-mL round-bottom flask—containing a stir bar and fitted with an addition funnel containing 15 mL of cold 98–100% nitric acid (Fluka ''100%'' nitric acid) and a nitrogen bubbler—and cooled in a dry ice–dichloromethane bath. The nitric acid was added quickly via the addition funnel. When the nitric acid started freezing, the cooling bath was removed, and the organic reactant dissolved in the acid upon warming adventitiously. After the solution reached room temperature, Nafion® NR50 beads (0.77 g) were added, and the solution was heated to reflux—with a nitrogen bubbler atop the reflux condenser—in an oil bath maintained at 88 ± 5°C. After 26-1/2 h reflux, 8.7 mL of the reaction was quenched onto a mixture of ice plus aqueous $NaHCO_3$ to neutralize the solution. The aqueous solution/suspension was extracted with CH_2Cl_2 (4×60 mL), which was removed by rotary evaporation. NMR analysis of the residue (Fig. 4) showed ∼52% conversion to CL-20, the balance being mostly WFN_5.

Nitrolysis of Oxidation Product to CL-20

Some of the final chloroform precipitate (123.3 mg previously vacuum-dried over P_4O_{10}) from photooxygenation Procedure

A in a 25-mL round-bottom flask—containing a stir bar and fitted with an addition funnel containing 15 mL of cold 98–100% nitric acid (Fluka ''100%'' nitric acid) and a nitrogen bubbler—was cooled in a dry ice–dichloromethane bath. The nitric acid was added quickly via the addition funnel. When the nitric acid started freezing, the cooling bath was removed, and the organic reactant dissolved in the acid upon warming adventitiously. After the solution reached room temperature, Nafion® NR50 beads (0.77 g) were added, and the solution was heated to reflux—with a nitrogen bubbler atop the reflux condenser—in an oil bath maintained at 92 ± 4°C. NMR analysis of an aliquot in CD_3CN showed nitrolysis to be incomplete after 29 h, so reflux was continued. After 44-1/2 h reflux, the reaction was quenched onto ice and solid $NaHCO_3$ was added to neutralize the solution (∼60 mL). White solid CL-20 was filtered off and vacuum-dried over P_4O_{10}. Yield: 57.5 mg (47% based on nitrogen analysis of the reactant).

Nitrolysis of HPIW to CL-20

A solution (1.0 mL) containing 170 mg HPIW in CCl_4 (Procedure B, Workup 1) in a 50-mL round-bottom flask—containing a stir bar and fitted with an addition funnel containing 15 mL of cold 98–100% nitric acid (Fluka ''100%'' nitric acid) and a nitrogen bubbler—was cooled in a dry ice–dichloromethane bath. The nitric acid was added quickly via the addition funnel. When the nitric acid started freezing, the cooling bath was removed, and the organic reactant dissolved in the acid upon warming adventitiously. After the solution reached room temperature, Nafion® NR50 beads (0.77 g) were added, and the solution was heated to reflux—with a nitrogen bubbler atop the reflux condenser—in an oil bath maintained at 92 ± 4°C. NMR analysis of an aliquot in CD_3CN showed nitrolysis to be incomplete after 29 h, so reflux was continued. After 94 h reflux, the reaction was quenched onto ice and solid $NaHCO_3$ was added to neutralize the solution. White solid CL-20 was filtered off and vacuum-dried over P_4O_{10}. Yield: 17.5 mg (11.6%).

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