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Investigation into the Acidification Process of Zafirluskast Nitroacid Leads to a Surprising Improvement in Product Quality

Claire L. Ancell, Ian Derrick, Jonathan D. Moseley,* and Jeffery A. Stott

AstraZeneca, Process Research and Development, Avlon Works, Severn Road, Hallen, Bristol BS10 7ZE, UK

Abstract:

An investigation into the acidification step of the zafirlukast nitroacid process was conducted by varying a range of parameters, including acid molarity, addition time, final pH, and temperature. A significant and unexpected improvement in product quality was achieved by using dilute rather than concentrated acid, independent of the final pH, and without a reduction in yield. The change to the dilute-acid process could be accommodated within the constraints of the existing registered process.

Introduction

Zafirlukast[1] is AstraZeneca's LTD_4 receptor antagonist for the oral treatment of asthma.[2] Commercial manufacture of the bulk drug is achieved in four isolated steps (Scheme 1), similar to those used for the first laboratory-scale synthesis.[3] The synthesis starts with a moderately selective silver carbonate-mediated alkylation of 5-nitroindole with bromobenzoate to give the desired nitroester alkylated at C-3. A number of other mono-, di-, and tri-alkylated products also result, of which the C2C3-diester is the most problematic component (Scheme 2). The C2C3-related impurity provides a good marker for all the other related impurities which can be tracked through the subsequent stages.

Fortunately, the crystallisation of nitroester reduces all of these impurities to low levels, such that a specification can be set for the C2C3-diester impurity of 1.0% which is met in routine manufacture. The specification for C2C3-diacid in nitroacid is 0.5%, which is comfortably achieved, and 0.3% for the C2C3-diadduct in DMAP salt. However, subsequent impurity-tracking analysis showed that levels of the C2C3-diester above ∼0.7% at the nitroester stage (i.e. well within specification) produced material that had the potential to fail specification at the DMAP salt stage. This had not occurred during early manufacture because 1.6 batches of nitroester were required for every batch of DMAP salt made, so that acceptable variations in nitroester quality had ameliorated the issue. Given the high cost of DMAP salt batches, there was a strong desire to resolve this potential issue before a batch failed to meet its quality criteria.

(1) Formerly ICI 204219; AstraZeneca trade name Accolate.

(2) Krell, R. D.; Aharony, D.; Buckner, C. K.; Keith, R. A.; Kusner, E. J.; Snyder, D. W.; Bernstein, P. R.; Matassa, V. G.; Yee, Y. K.; Brown, F. J., Hesp, B.; Giles, R. E. *Am. Rev. Respir. Dis.* **1990**, *141*, 978−987. Smith, L. J.; Geller, S.; Ebright, L.; Glass, M.; Thyrum, P. T. *Am. Rev. Respir. Dis.* **1990**, *141*, 988−992.

(3) Matassa, V. G.; Maduskuie, T. P.; Shapiro, H. S.; Hesp, B.; Snyder, D. W.; Aharony, D.; Krell, R. D.; Keith, R. A. *J. Med. Chem.* **1990**, *33*, 1781−1790.

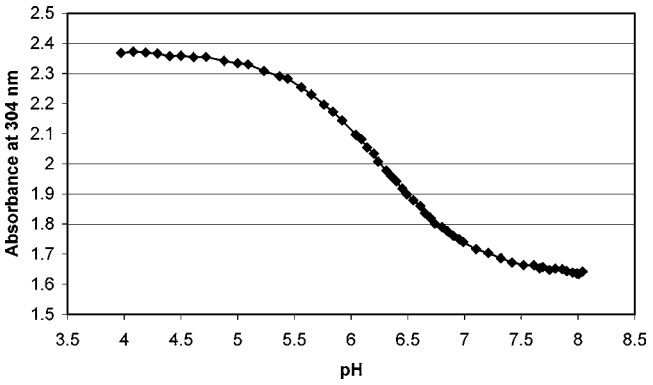

Figure 1.

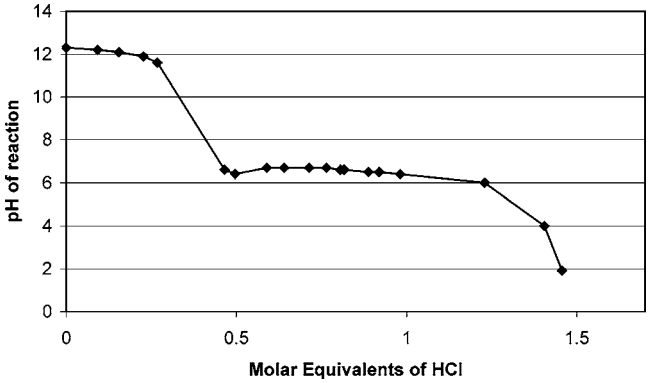

Figure 2.

Results and Discussion

The crystallisations of both nitroester and DMAP salt were felt to be fully developed with little scope for further improvement. Nitroacid, however, was isolated by crystallisation from aqueous acid at pHs in the range 1−2. It was recognized that this might be a lower pH than was actually required and that over acidification might be increasing crystallisation of the di- and tri-acid impurities. Isolation at a higher pH might improve the impurity profile, and if the pH still exceeded the pK_a by 2 log units, then less than a 1% drop in yield could be expected.

A critical piece of information was the pK_a of nitroacid, which was determined to be 6.2 by the change in the UV absorbance between the protonated and disassociated forms, as shown in Figure 1 (see also Experimental Section). This indicated that it should be possible to isolate nitroacid at pH 4 with no loss in yield. The pH profile of the crystallisation process during the HCl addition confirmed that it would be difficult to stop at pH 4 using concentrated HCl (Figure 2). Therefore, we used 2 M HCl and adjusted the pre-addition water charge to compensate for the use of dilute acid so that

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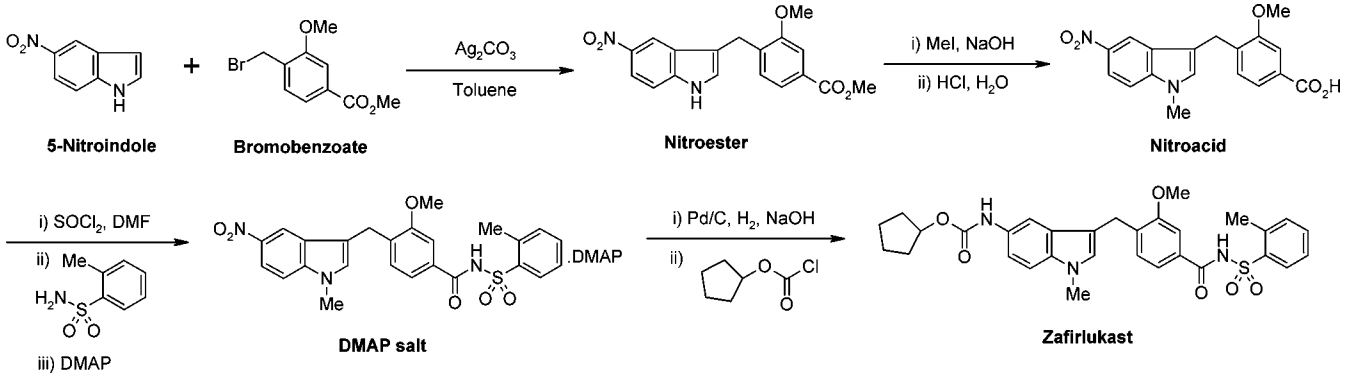
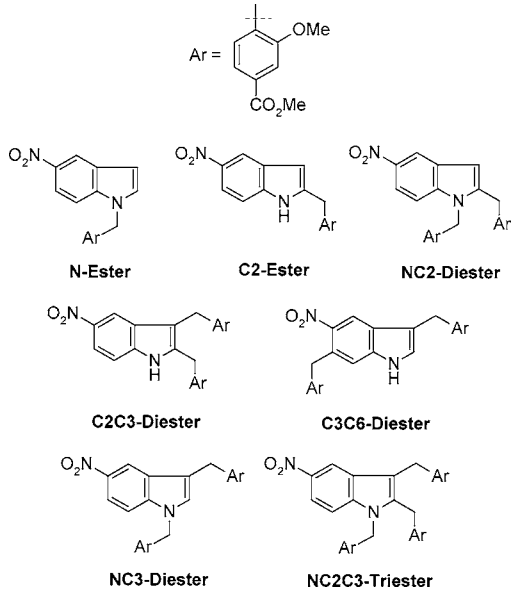
Scheme 1



Scheme 2



the overall aqueous volume was unchanged. A double-sized batch was prepared according to the procedure in the Experimental Section and split in half prior to the acidification process, one-half being acidified as normal using concentrated HCl, the other half using 2 M HCl with the modified water charge. In both cases, the yellow nitroacid product precipitated after about one-third of the acid had been added. All other aspects of the workup and the washing and drying procedures were the same for both batches.

Analysis of the dried product showed the C2C3-diacid level was 0.41% (w/w) for isolation at pH 1.8 compared to 0.23% for isolation at pH 4.1 (the input C2C3-diester level was 0.82%). Other impurities were generally lower in the batch isolated at pH 4, but since the actual values were smaller, they were statistically less reliable. The yields were comparable at 84 and 82% respectively, indicating that as hoped, the yield had not been affected (within experimental error). A second split-batch experiment was run to confirm the results, which were similar within experimental error. Overall, this seemed to confirm our hypothesis that isolation at a higher pH could be achieved with improved product quality regarding the key C2C3-diacid without loss in yield.

We decided to investigate further the ideal pH at which to isolate nitroacid. Another batch was run from which 10-mL aliquots of slurry were individually worked up at pHs

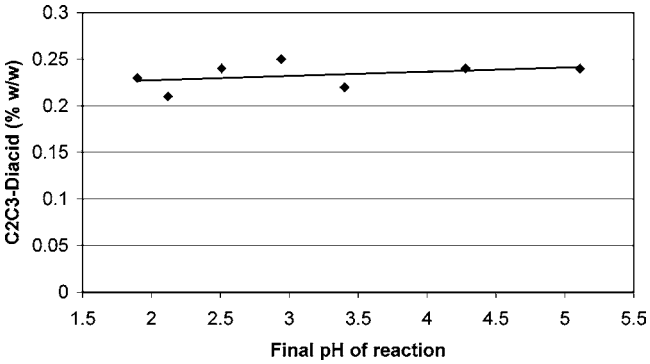


Figure 3.

varying from 5.1 down to 2.1, with solvent washes adjusted for scale accordingly. The remainder of the batch was isolated at pH 1.9 and isolated with appropriately adjusted solvent washes. The unexpected results revealed that there was no effect due to pH across the range examined, as shown in Figure 3. In fact, the isolation at pH 1.9 using 2 M HCl was identical to that for isolation at pH 4.1.[4] The other impurities were also all in good agreement across this range, most varying by only ±0.01% in actual figures. These results clearly indicated that there was no correlation between the final isolation pH and product quality. Instead, quality seemed to be dependent on the concentration of the HCl used for the acidification, and in all subsequent lab work nitroacid was isolated at pH 2 or below.

We then prepared several batches of nitroacid isolated by acidification with HCl of differing concentrations, again adjusting the separate pre-addition volume of water in each case to keep the final aqueous content of the batch unchanged. The results for all batches are collected in Figure 4 which shows a clear trend of reduced C2C3-diacid levels for lower-molarity HCl used, about 0.12% w/w between most- and least-concentrated HCl solutions. Before further work, we decided to check the effect over a range of input C2C3-diester levels, since thus far all the work had been performed on a single batch of nitroester.[5] Five batches with

(4) No effect on the yield could usefully be discerned for these samples due to the small size of the aliquots, but we were confident that the isolation procedure was reliable for quality on this scale; wash sizes were between 5 and 8 mL for 10-mL aliquots isolated on a small sinter.

(5) Nitroester batch 103, which had a C2C3-diester level of 0.82% w/w, was used for much of the initial work. Later, batch 108 was used, which had a C2C3-diester level right on the specification limit at 1.04% w/w, which provided the most exacting test for the new methodology.

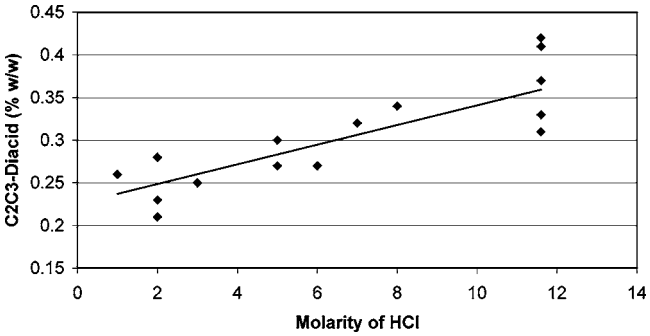


Figure 4.

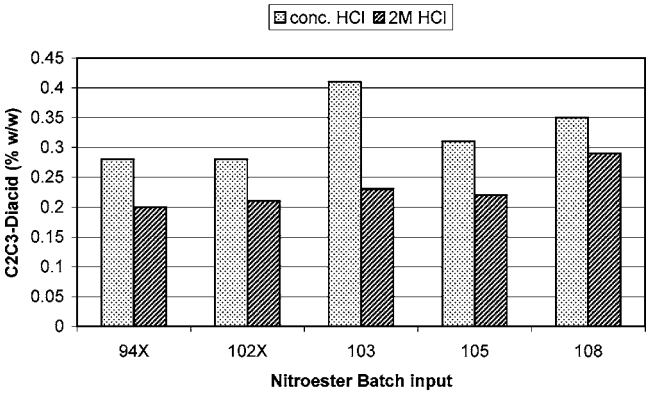


Figure 5.

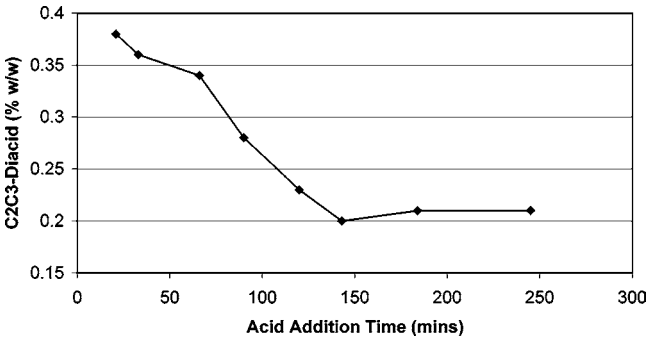


Figure 6.

average-to-high C2C3-diester levels were assayed using the 2 M HCl method. The results are collected in Figure 5, and although the results are variable between batches, there is a significant improvement in every case, indicating a clear benefit in using 2 M HCl.

All of these results taken in combination indicated to us that there was a local over-concentration effect occurring, which was preferentially crystallising the di- and tri-acid impurities compared to the desired mono-acidic nitroacid. Other parameters that might further support this hypothesis were acid addition time and agitation rate. All acidifications thus far had been made over a constant 60-min period. Several batches were prepared using 2 M HCl added over between 21 and 245 min, keeping all other factors constant with the original process. The results are collected in Figure 6 and show a steady and linear improvement in product quality up to about 2.5 h, after which no additional benefit is seen. The agitation rate was investigated at three levels, 200 rpm being the standard laboratory rate. The three results are shown in Figure 7 which indicated a considerable

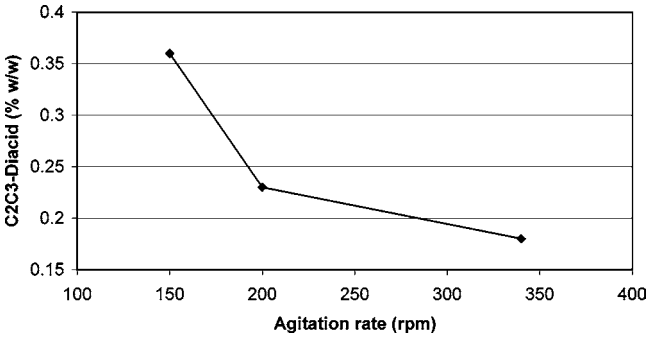


Figure 7.

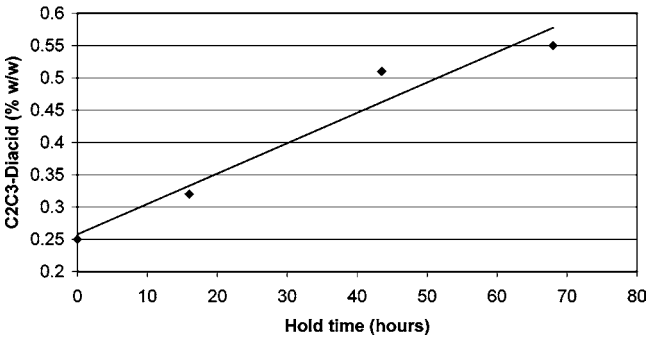


Figure 8.

detrimental effect on product quality on reducing the agitation rate, and a moderate improvement on increasing it.[6] The agitation rate could not be easily modified on the plant vessels, but we now knew this was a potential issue.[7]

The recommendation for modifying the plant process would be to use 2 M HCl added over 2.5 h.[8] These changes could be made within the registered process and easily accommodated. For completeness, we now investigated some further parameters at the edges of their proven acceptable ranges as stated in the registered process. Both the acid addition and isolation temperatures were investigated at the upper and lower proven acceptable values of the current process using 2 M HCl with all other factors kept constant. There was effectively no difference between these values or with the standard preparations. The pre- and post-acidification hold points at 50 and 35 °C respectively were also investigated. A triple-sized batch was prepared and split into thirds; individual batches were held at 50 °C for 0, 24, and 96 h before the acidification step. There was no difference in C2C3-diacid level between these three batches, which identified a long and robust potential hold point. However, the post-acidification hold 35 °C showed a considerable detrimental effect as shown in Figure 8 with the level of the C2C3-diacid impurity increasing linearly, such that there is

(6) It is not known to what the lab rpm rates are equivalent on the plant, and no further work was conducted in this area, mainly because there was little scope to change the plant agitation.

(7) The effect of the shape of the plant vessel and the use of a modified spray ring was considered in this work, but not further investigated.

(8) For an initial trial, the use of 2 M HCl was considered on plant scale since this could be purchased diluted. The most dilute acid that could have been used without increasing the overall water charge was 1.3 M HCl. This would have required dilution from concentrated HCl in a suitable make-up vessel, which was not readily available in the manufacturing facility.

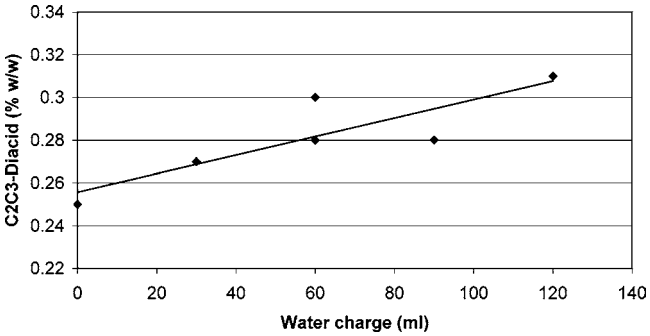


Figure 9.

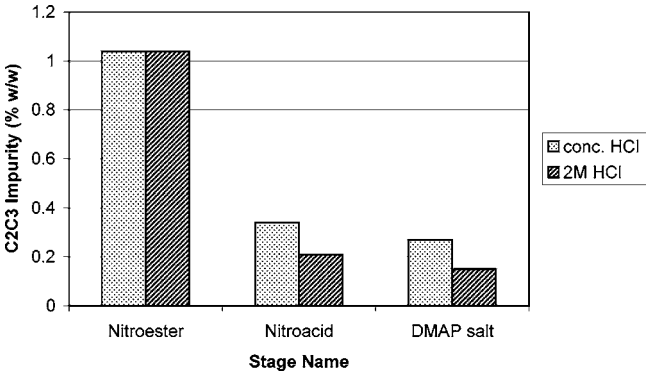


Figure 10.

clearly a dynamic aspect to this crystallisation. Therefore, the isolation should be made as soon as possible.

Last, the effect of the pre-addition water charge was also investigated using the 2 M HCl process. The normal charge on a standard 2 M HCl laboratory preparation was 60 mL to compensate for the change from concentrated HCl with 147 mL of water. The water charge was varied from 0 to 120 mL at several values. The results shown in Figure 9 showed a slight improvement in product quality for the reduced water charge, but the batch became less mobile, and the yield may have reduced slightly. Since the effect was very small, especially when compared to the standard charge of 60 mL, no recommendation to change this volume was made, especially as a thicker slurry might have been more problematic on plant scale.

As a final check, several typical batches of nitroacid (prepared using the improved 2 M HCl process) were user trialled in the following DMAP salt stage. The expected improvement in product quality was demonstrated in this stage also, as shown in Figure 10 for a split-batch preparation using the concentrated and 2 M HCl processes.[9] Significantly, no new impurities were detected using nitroacid from the modified process, and the yields were unaffected.

Conclusions

We have demonstrated that the quality of the nitroacid product can be significantly improved (up to 50% for worst case batches) by the use of dilute (2 M) rather than concentrated HCl in the acidification process. We believe this to be due to a local concentration effect, since we have clearly shown that the effect is dependent on acid molarity, addition time, and agitation rate, and independent of the final pH. We have shown that dilute acid, longer addition times and better agitation, all of which would result in smaller localised concentrations, each independently improve product quality. The temperatures (within the acceptable ranges) of the hold times before, during, and after the crystallisation do not affect the quality, nor does the length of the hold time before crystallisation. However, there is a dynamic aspect to the crystallisation of the C2C3-diacid impurity since a long hold time after crystallisation is detrimental to product quality. Using 2 M HCl requires a small corrective water charge, and reducing this is also moderately beneficial to product quality.

Overall, a change to dilute acid with other process changes would result in typically a 20−40% improvement in product quality at nitroacid, thus reducing the troublesome impurities to well inside the specification at both the nitroacid and DMAP salt stages. There is no detrimental effect on yield, and the improvement has been proved in the DMAP salt stage by appropriate user trials. All other processing changes, including the use of dilute acid,[10] are within the scope of the currently registered processes and proven acceptable ranges and could thus be implemented on the plant with minimum effort.

Experimental Section

All laboratory preparations of nitroacid initially followed the standard procedure described below using concentrated HCl and nitroester batch 103 (C2C3-diester level 0.82%). Variations in these parameters are noted below. All raw materials were chosen to be consistent with those used in plant manufacture wherever possible, and the same batch of reagent was used for all experiments. All other parameters not specifically mentioned were kept constant throughout the project.

HPLC Method for Nitroacid. Nitroacid quality was analysed by reverse phase HPLC on a Hewlett-Packard 1050 according to the following conditions: column, Spherisorb S5ODS-2, 250 mm × 4.6 mm i.d.; eluent A, acetonitrile (150 mL), water (850 mL), and glacial acetic acid (2 mL); eluent B, acetonitrile (600 mL), water (400 mL) and glacial acetic acid (2 mL); gradient, eluent B, 30% at 0 min to 100% at 40 min, 100% at 50 min, then eluent A 70% at 51 min, 70% at 60 min; flow rate 2.0 mL/min; wavelength 254 nm; injection volume 10 μL; temperature, ambient. Typical retention times were: *N*-methyl-5-nitroindole, 18.2 min; nitroacid, 25.9 min; C2C3-diacid, 29.5 min; nitroester, 30.9 min. Sample preparation: accurately weigh ∼10 mg of nitroacid into a 10-mL volumetric flask and dissolve in THF (1 mL) and dilute to volume with acetonitrile. Chromatograph against a standard solution of nitroacid or related impurity made up as follows: accurately weigh ∼5 mg of nitroacid/impurity into a 100-mL volumetric flask, dissolve in THF (10 mL) and dilute to volume with acetonitrile; pipet 20.0 mL of this solution into a 100-mL volumetric flask and dilute

(9) Other batches are not shown because more than one parameter had been changed, but the improvements were significant in each case.

(10) We observed no change in the polymorph of nitroacid throughout these investigations.

to volume with acetonitrile. Nitroacid and impurity peaks are reported by reference to the corresponding nitroacid and impurity standards. The in-process test to check for complete reaction was similar but used an isocratic method run over 25 min with eluent composed of acetonitrile (500 mL), water (500 mL), and glacial acetic acid (2 mL), all other parameters being the same as those described above.

Determination of Nitroacid pK_a. A pure sample of nitroacid was prepared using the standard procedure below from doubly recrystallised nitroester, so that the UV absorbance of the residual trace impurities present was minimal (the maximum residual impurity was ~0.05% w/w). A number of wavelengths were assessed on a dilute solution (0.1 mg/mL) of nitroacid in 50/50 THF/water. A maximum difference of 0.6 absorbance units was found at 304 nm between the spectra for the protonated (pH 1.6) and dissociated (pH 8.4) forms. A very dilute solution of nitroacid (100 mg) in 50/50 THF/water (1000 mL) was then acidified from pH 8.0 to pH 4.0 by the addition of 0.1 M HCl, and UV spectra were taken at ~0.05 pH units intervals. The change in absorption between the dissociated and protonated forms of nitroacid could be determined from the UV spectra as shown in Figure 1, from which an approximate figure for the pK_a of nitroacid could be determined as ~6.2. Within ±0.6 pH units of the approximate pK_a value, the following equation can be used:

$$pK_a = pH + \log \frac{(A - A_I)}{(A_M - A)}$$

where A_I = absorbance of the fully dissociated (i.e. ionized) species, A_M = absorbance of the fully protonated (i.e. molecular) species, A = absorbance at a given pH.

Using the equation the calculated value of the pK_a was determined as 6.24, from which a working value of 6.2 was taken.

Standard Preparation of Nitroacid using Concentrated HCl Process. Nitroester (38.7 g at assumed 100% strength, 114 mmol) was dissolved in THF (120 mL) by heating to 35 °C with stirring for 30 min to ensure complete solution, before cooling back to 20−25 °C. Water (39 mL) was added, followed by NaOH (27.0 g, 18.0 mL at 47% strength w/w (100° T_w)) in one portion which resulted in an 8 K exotherm on this scale. The reaction mixture was cooled back to 20−25 °C, and methyl iodide (19.6 g, 8.6 mL, 138 mmol) was added in one portion, followed by a line wash of THF (2 mL). The reaction mixture was stirred at 20−25 °C for 2 h, after which time the methylation reaction is ~70% complete. Additional THF (14 mL) and water (19 mL) are added, and the reaction mixture is heated to reflux at 65 °C over ~1 h (NB: The additional THF and water charges are to mimic vessel/lines washes that occur in the plant when the batch is transferred to a second plant vessel at this point). The methylation reaction is completed during the heat up. The mixture is held at reflux for 3 h, then cooled back to 50 °C. Water (147 mL) is added, keeping the temperature in the range 50−55 °C. Concentrated HCl (up to 21.7 g, 18. 4 mL of 36% strength w/w (36° T_w)) is added smoothly over 1 h until pH 1−2 is achieved. A yellow precipitate forms after about one-third has been added, which results in a thick slurry initially. The reaction mixture is cooled to 35 °C over ~40 min and the product isolated by filtration immediately. The reactor is rinsed with water (186 mL) and used to slurry wash the product. The product cake is then sequentially washed by displacement with water (116 mL) and acetone (136 mL), slurry is washed with acetone (157 mL), displacement is washed with acetone twice (116 mL and 128 mL) and dried in vacuo at 60 °C (in the lab; in the plant, the product is dried by hot nitrogen at 80 °C on a pressure filter). The product nitroacid is a bright-yellow solid obtained in typically 81−85% yield (uncorrected for nitroester input) with strength close to 100%.

Variations to Standard Nitroacid Process. In the variations below where no values are given, assume the standard process parameters have been used.

Acid Molarity. Batch 103 used with pre-acidification water charge adjusted as follows: concentrated (11.6 M), no change (147 mL); 8 M, 139 mL; 6 M, 131 mL; 5 M, 124 mL; 3 M, 96 mL; 2 M, 60 mL; 1 M, 0 mL.

Nitroester Batch. Nitroester batches used with C2C3-diester levels as follows: 94×, 0.99; 102×, 0.49; 103, 0.82; 105, 0.58; 108, 1.04% w/w. Concentrated and 2 M HCl used with appropriate water charges, isolated at pH 2.

Acid Addition Time. Batch 108 used with 60 mL water charge and 2 M HCl; acid addition times as shown in Figure 6.

Agitation Rate. Batch 108 used with 60 mL water charge and 2 M HCl added over 120 min; agitation rates at 150, 200, and 340 rpm in standard laboratory equipment (Figure 7).

Hold at 50 °C before Acidification. Batch 103 used with 60 mL water charge and 2 M HCl added over 50−55 min; hold periods of 0, 24, and 96 h before acidification.

Acid Addition Temperature. Batch 108 used with 60 mL water charge and 2 M HCl added over 180 min; acid addition temperatures of 42, 52, and 60 °C.

Hold at 35 °C before Isolation. Batch 108 used with 60 mL water charge and 2 M HCl added over 75−80 min. A double-sized batch was prepared, acidified, and split in two, and the first half was isolated immediately at 35 °C. The second half was held at 35 °C from which 10-mL aliquots of slurry were taken at 16 and 44 h and individually worked up with solvent washes adjusted for scale accordingly. The remainder of the batch was isolated after 68 h and isolated with appropriately adjusted solvent washes (Figure 8).

Isolation Temperature. Batch 108 used with 60 mL water charge and 2 M HCl; isolation temperatures of 28, 35, and 42 °C.

Pre-acidification Water Charge (separate from acid molarity investigation). Batch 108 used with 2 M HCl; water charges as shown in Figure 9.

Preparation of DMAP Salt. Nitroacid (29.5 g at assumed 100% strength, 86.8 mmol) and DMF (0.75 mL, 9.7 mmol) were stirred in dichloromethane (203 mL) and heated to reflux (41 °C). Thionyl chloride (10.9 g, 6.7 mL, 91.6 mmol) was added over 20 min followed by a line wash of dichloromethane (4 mL) and the heating continued at reflux

for 3 h. A clear, orange solution formed after this time. The volume was reduced by distilling off dichloromethane (30 mL) and the solution cooled to 25 °C. *o*-Toluene sulfonamide (17.8 g, 104.0 mmol) was added in one portion and the reaction mixture returned to reflux. A solution of DMAP (31.8 g, 261.0 mmol) dissolved in dichloromethane (111 mL) was added over 90 min, followed by a line wash of dichloromethane (8 mL). A thick yellow precipitate starts to form after about three-quarters of this solution has been added. Heating at reflux was continued for 1 h, and then the reaction mixture was cooled to 20 °C overnight. The product was isolated by filtration and the reactor rinsed with dichloromethane (8 mL). The product cake was slurry-washed with methanol (147 mL) and then washed by displacement with fresh methanol (74 mL) and dried in vacuo at 60 °C. The product DMAP salt is a bright-yellow solid obtained in typically 90−92% yield uncorrected for input nitroacid, and with strength close to 100%.

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