Electronic Supplementary Material (ESI) for Green Chemistry.

Electronic Supplementary Material

Documentation of Data collated from the Excel spreadsheets obtained following input of experimental data into the iSUSTAIN Green Chemistry Index Version 2.0 web-based program

This document includes a Reaction Scheme showing the steps in the alternate routes for the synthesis of tacn (**1**) and bis(tacn) (**2**). The pages following the Scheme include all the inputs required to analyse each step against the 12 Principles of Green Chemistry using the iSUSTAIN program. There are 11 sections, one for each reaction step annotated in the Scheme as "iSUSTAIN 1", 'iSUSTAIN 2", etc. Each section reports the score as a Metric against each Green Chemistry Principle, with the data illustrated as a spider graph.

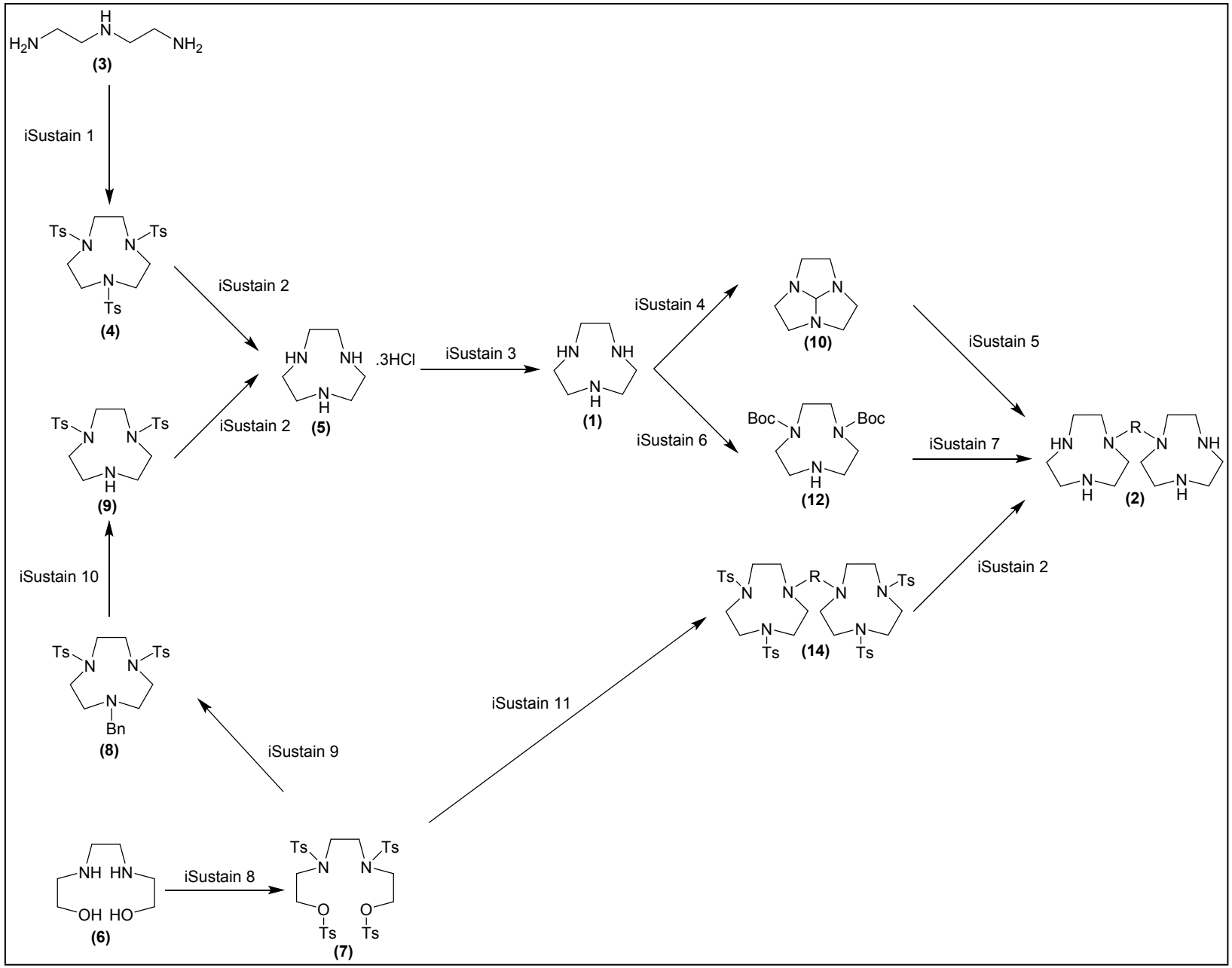
Input data includes a "Bill of materials in" which includes information as to type and amount of material used in the process, and whether it is a catalyst and whether it is recycled and/or renewable. Scores are then calculated by the software in the program and values for the various Metrics (based on the Green Chemistry Principles 2, 3, 5, 7 and 9) are allocated.

Input data also includes a "Bill of materials out" which includes information as to type and amount of material resulting from the process, i.e. product and waste. The human and aquatic toxicity and biodegradability is calculated. Scores for the various Metrics (based on the Green Chemistry Principles 1, 4 and 10) are allocated by the program software.

Input data is also required for the process steps (heating, cooling, stirring, pressure, work-up, extraction, distillation, chromatography etc) to enable calculation of the energy efficiency and process complexity of the entire process. The program software then gives a score for the 2 relevant Metrics (based on the Green Chemistry Principles 6 and 8).

Finally two sets of criteria assess safety and risks of the process and points are awarded depending on Yes/No answer. One set gives a Metric based on Green Chemistry Principles 11 (real-time analysis, monitoring and control) and the other gives a Metric based on Green Chemistry Principles 12 (safe chemistry/process)

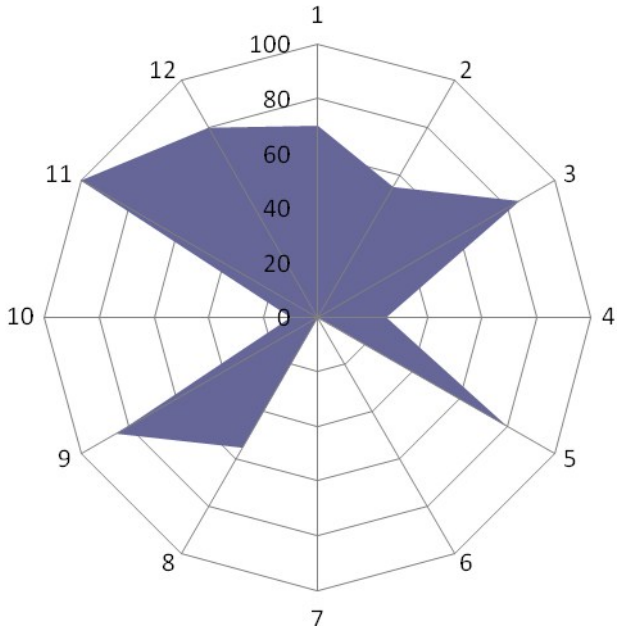
Reaction Scheme



Scenario: **Synthesis of Ts_3Tacn (4)**
Description:

iSUSTAIN 1

1. Waste Prevention	70
2. Atom Economy	55
3. Safe Raw Materials	85
4. Safe Product	25
5. Safe Solvents	80
6. Energy Efficiency	0
7. Renewables	0
8. Process Complexity	55
9. Catalysis	85
10. Biodegradability	10
11. Process Control	100
12. Safe Process	80



Bill of Materials In	Type of Material	Wt/ Batch	Est. % Recycle	% Renew.	Catalyst Mole %	Usage Wt/Wt	Safety	Health	Envir Impact	Regul Status	MatImp	Contrib to Proc Tot
Water	Solvent	3,000	80	80	0	4.323	100	100	100	100	100	**41%**
Potassium carbonate	Auxiliary	162	0	0	0	1.167	100	65	100	100	88	**11%**
p-Toluenesulfonyl chloride	**Raw**	**209**	**0**	**0**	**0**	**1.507**	**100**	**55**	**100**	**100**	**85**	**14%**
Caustic soda [sodium hydroxide]	Auxiliary	127	0	0	0	0.916	100	35	100	100	78	**9%**
Tetrabutylammonium bromide	Auxiliary	10	0	0	9	0.075	100	65	100	100	88	**1%**
Toluene	Solvent	1,600	80	80	0	2.305	55	55	100	50	35	**22%**
Diethylentriamine	**Raw**	**36**	**0**	**0**	**0**	**0.262**	**100**	**55**	**100**	**100**	**85**	**2%**

Metric 2) Atom Economy: Reaction Mass Efficiency = ... 55
Metric 3) Safe Raw Materials: Total Process Material Impact = ... 85
Metric 5) Safe Solvents: Total Process Auxiliary Material Impact = ... 80
Metric 7) Renewables: Total % Process Renewable Feedstock (as-sold basis) = ... 0
Metric 7) Renewables: Total % Process Renewable Feedstock (neat basis) = 0
Metric 9) Minimum Catalyst Mole % = ... 9
Metric 9) Normalized Catalyst Score % = ... 85

Bill of Materials Out	Type of Material	Wt/ Batch	% Diluents	Severity Multiplier	Wt times Severity	Human Tox. Concern	Aq. Tox. Concern	Ultimate Biodeg.
Ts_3Tacn	**Product**	139	0			Moderate	High	1.5
1,2-Dibromoethane	Waste Class 2	80		4	320			
KCl	Waste Class 4	80		0.5	40			
NaBr	Waste Class 4	100		0.5	50			

Metric 1) Environmental factor (E+-factor) = ... 2.97
Metric 1) Waste Prevention: Normalized E+-Factor = ... 70
Metric 4) Safe Product: DSfC = ... 25
Metric 10) Biodegradability: Normalized Biodegradation = ... 10

Process Steps		Reactors, etc.	Asset Count	In-Process Add/Remove
Stirring	Stirring		1	3
Heating	Heating & Addition		2	8
Step 3			0	0
Step 4			0	0

Temp. (º C.)	Time (Hrs)	Pressure (Atm)	Total Weight	Ave. Heat Capacity	Step EE
90	96	1	4,000	4.2	**13943.5**
	0	1	4,000	4.2	**0.0**
	0	1	0	0.0	**0.0**
	0	1	0	0.0	**0.0**

Metric 6) Total Energy Efficiency = ... 13944
Metric 6) Energy Efficency: Normalized EE = ... 0
Metric 8) Process Complexity (PComplex) = ...
. 3 + 11 = 14
Metric 8) Process Complexity: Nomalized PComplex = ...
. 55

Question			Answer	Points
1)	Does the potential exist in this process for the formation of hazardous side-products? (30 pts)		No	30
2)	Are adequate monitoring and control apparatus in place to quickly detect excursions in reactors and storage vessels? (0-50 pts)		Yes	50
3)	Is the process common practice and/or in the scale-up or commercialization stages of production? (20 pts)		Yes	**0**
	a)	Is there a regularly scheduled audit or check of this equipment? (10 pts)	Yes	10
	b)	Do formal (written) catastrophe plans and emergency measures exist? (10 pts)	Yes	10

Metric 11) Real-Time Analysis: Total RTA = ... 100

Question		Risk	Answer	Points
1)	Are any extreme conditions (pressure ≥ 10 atm., temperature ≥ 200º C. or ≤ -78º C.) used in the process? (20 pts)	High	No	0
2)	Does the potential exist for a runaway exotherm under the process or upset conditions (including violent polymerization)? (20 pts)	High	No	0
3)	Do any of the process materials or mixtures present an explosion hazard (contact, dust and/or peroxide-forming)? (20 pts)	High	No	0
4)	Are there any process materials present initially or formed during this process that might restrict or exclude its use in the intended production facility (other high hazards than mentioned above, strong odor, etc.)? (20 pts)	High	No	0
5)	Is pressure between 1.0 and 10 atm or less than 20 mm of Hg used in this process (other than process steps for which Q1 may be true)? (10 pts)	Moderate	No	0
6)	Are temperatures ranging from 150º to 199º C. or -50º to -78º C. used in this process (other than process steps for which Q1 may be true)? (10 pts)	Moderate	No	0
7)	Is the reaction mixture flammable? (10 pts)	Moderate	Yes	10
8)	Are any of the process mixtures pyrophoric or hypergolic? (10 pts)	Moderate	No	0
9)	Do any of the process mixtures react violently with water? (5 pts)	Mild	No	0
10)	Is a gas generated in any part of this process? (5 pts)	Mild	No	0
11)	Are any of the process mixtures corrosive (pH ≤ 2 or ≥12)? (5 pts)	Mild	Yes	5
12)	Are any of the process mixtures irritants or lachrymators? (5 pts)	Mild	Yes	5

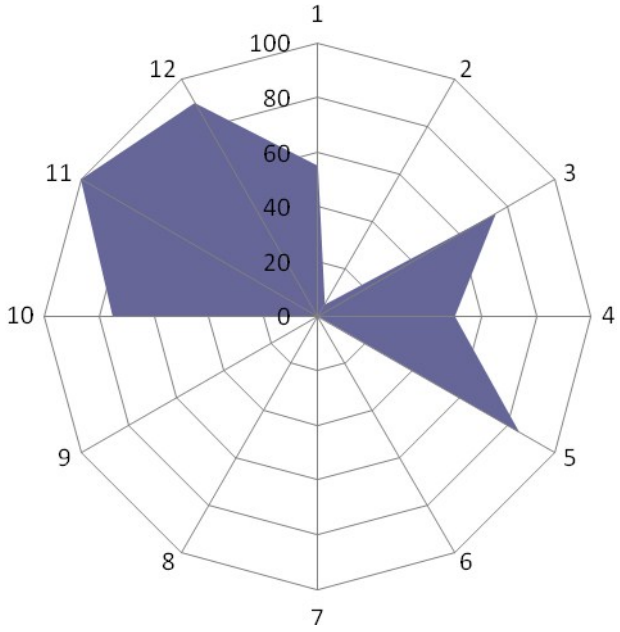
Total Yes Points = ... 20

Metric 12) Inherently Safer Chemistry: Process Safety = ... 80

Scenario: **Synthesis of Tacn.3HCl (5)**
Description: Ts_3Tacn **(4)** was not present in the database so 1,4,7,10-tetrakis(p-toluensulfonyl)-1,4,7,10-tetraazacyclododecane was used.

iSUSTAIN 2

1. Waste Prevention	55
2. Atom Economy	5
3. Safe Raw Materials	75
4. Safe Product	50
5. Safe Solvents	85
6. Energy Efficiency	0
7. Renewables	0
8. Process Complexity	40
9. Catalysis	0
10. Biodegradability	75
11. Process Control	100
12. Safe Process	90



Bill of Materials In	Type of Material	Wt/ Batch	Est. % Recycle	% Renew.	Catalyst Mole %	Usage Wt/ Wt	Safety	Health	Envir Impact	Regul Status	Matl mp	Contrib to Proc Tot
Sulfuric Acid	**Raw**	**450**	**0**	**0**	**0**	**10.022**	**100**	**35**	**100**	**100**	**78**	**30%**
Ethanol	Auxiliary	1,500	80	80	0	6.682	55	100	100	100	85	**20%**
Diethyl ether	Auxiliary	900	80	80	0	4.009	15	80	100	100	65	**12%**
Water	Auxiliary	1,000	80	80	0	4.454	100	100	100	100	100	**13%**
Celite 512 medium	Auxiliary	50	0	0	0	1.114	100	55	100	100	85	**3%**
Hydrochloric acid	**Raw**	**200**	**0**	**0**	**0**	**4.454**	**100**	**55**	**100**	**100**	**85**	**13%**
1,4,7,10-Tetrakis(p-toluensulfonyl)-1,4,7,10-tetraazacyclododecane	**Raw**	**136**	**0**	**0**	**0**	**3.029**	**100**	**55**	**0**	**100**	**51**	**9%**

Metric 2) Atom Economy: Reaction Mass Efficiency = ... 5
Metric 3) Safe Raw Materials: Total Process Material Impact = ... 75
Metric 5) Safe Solvents: Total Process Auxiliary Material Impact = ... v 85
Metric 7) Renewables: Total % Process Renewable Feedstock (as-sold basis) = ... 0
Metric 7) Renewables: Total % Process Renewable Feedstock (neat basis) = 0
Metric 9) Minimum Catalyst Mole % = ... 0
Metric 9) Normalized Catalyst Score % = ... 0

Bill of Materials Out	Type of Material	Wt/ Batch	% Diluents	Severity Multiplier	Wt times Severity	Human Tox. Concern	Aq. Tox. Concern	Ultimate Biodeg.
Tacn.3HCl	**Product**	45	0			Moderate	Moderate	4
Tosic Acid	Waste Class 4	100		0.5	50			
Sulphuric Acid	Waste Class 4	400		0.5	200			

Metric 1) Environmental factor (E+-factor) = ... 5.68
Metric 1) Waste Prevention: Normalized E+-Factor = ... 55
Metric 4) Safe Product: DSfC = ... 50
Metric 10) Biodegradability: Normalized Biodegradation = ... 75

Process Steps		Reactors, etc.	Asset Count	In-Process Add/Remove
Heating & Stirring			3	1
Drip into Ice			2	1
Filter			1	1
Dissolve in H_2O			1	1
Filter			1	1
Rotavap			1	1
Add HCl + Filter Salt			1	2

Temp. (º C.)	Time (Hrs)	Pressure (Atm)	Total Weight	Ave. Heat Capacity	Step EE
120	72	1	500	4.2	**6061.5**
	0	1	0	0.0	**0.0**
	0	1	0	0.0	**0.0**
	0	1	0	0.0	**0.0**
	0	1	0	0.0	**0.0**
	0	1	0	0.0	**0.0**
	0	1	0	0.0	**0.0**

Metric 6) Total Energy Efficiency = ... 6061
Metric 6) Energy Efficency: Normalized EE = ... 0
Metric 8) Process Complexity (PComplex) = ... 10 + 8 = 18
Metric 8) Process Complexity: Nomalized PComplex = ... 40

Question			Answer	Points
1)	Does the potential exist in this process for the formation of hazardous side-products? (30 pts)		No	30
2)	Are adequate monitoring and control apparatus in place to quickly detect excursions in reactors and storage vessels? (0-50 pts)		Yes	50
3)	Is the process common practice and/or in the scale-up or commercialization stages of production? (20 pts)		Yes	**0**
	a)	Is there a regularly scheduled audit or check of this equipment? (10 pts)	Yes	10
	b)	Do formal (written) catastrophe plans and emergency measures exist? (10 pts)	Yes	10

Metric 11) Real-Time Analysis: Total RTA = ... 100

Question		Risk	Answer	Points
1)	Are any extreme conditions (pressure ≥ 10 atm., temperature ≥ 200º C. or ≤ -78º C.) used in the process? (20 pts)	High	No	0
2)	Does the potential exist for a runaway exotherm under the process or upset conditions (including violent polymerization)? (20 pts)	High	No	0
3)	Do any of the process materials or mixtures present an explosion hazard (contact, dust and/or peroxide-forming)? (20 pts)	High	No	0
4)	Are there any process materials present initially or formed during this process that might restrict or exclude its use in the intended production facility (other high hazards than mentioned above, strong odor, etc.)? (20 pts)	High	No	0
5)	Is pressure between 1.0 and 10 atm or less than 20 mm of Hg used in this process (other than process steps for which Q1 may be true)? (10 pts)	Moderate	No	0
6)	Are temperatures ranging from 150º to 199º C. or -50º to -78º C. used in this process (other than process steps for which Q1 may be true)? (10 pts)	Moderate	No	0
7)	Is the reaction mixture flammable? (10 pts)	Moderate	No	0
8)	Are any of the process mixtures pyrophoric or hypergolic? (10 pts)	Moderate	No	0
9)	Do any of the process mixtures react violently with water? (5 pts)	Mild	No	0
10)	Is a gas generated in any part of this process? (5 pts)	Mild	No	0
11)	Are any of the process mixtures corrosive (pH ≤ 2 or ≥12)? (5 pts)	Mild	Yes	5
12)	Are any of the process mixtures irritants or lachrymators? (5 pts)	Mild	Yes	5

Total Yes Points = ... 10

Metric 12) Inherently Safer Chemistry: Process Safety = ... 90

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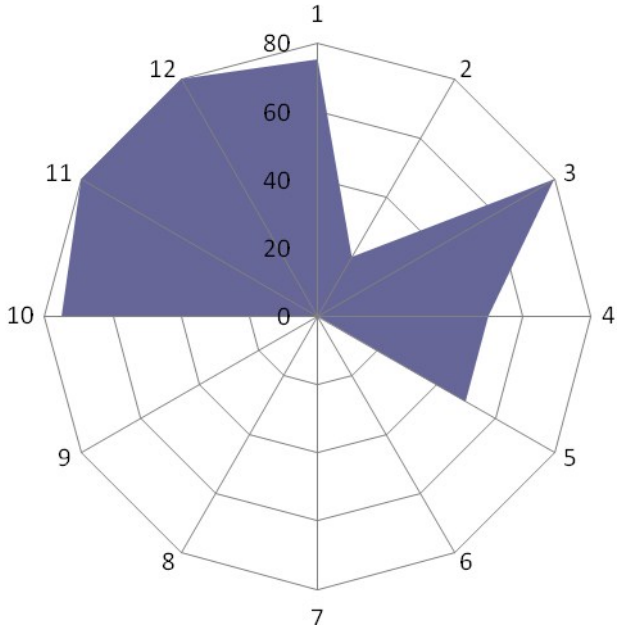
Scenario: **Synthesis of Free Tacn (1)**
Description: Tacn.3HCl was not present in the database. Instead the product was used as a raw material for the safety data.

iSUSTAIN 3

1. Waste Prevention	75
2. Atom Economy	20
3. Safe Raw Materials	80
4. Safe Product	50
5. Safe Solvents	50
6. Energy Efficiency	0
7. Renewables	0
8. Process Complexity	70
9. Catalysis	0
10. Biodegradability	75
11. Process Control	80
12. Safe Process	80



Bill of Materials In	Type of Material	Wt/ Batch	Est. % Recycle	% Renew.	Catalyst Mole %	Usage Wt/ Wt	Safety	Health	Envir Impact	Regul Status	Matl mp	Contrib to Proc Tot
1,4,7-triazacyclononane	**Raw**	**44**	**0**	**0**	**0**	**2.544**	**100**	**55**	**100**	**100**	**85**	**9%**
Water	Solvent	500	80	80	0	5.718	100	100	100	100	100	**21%**
Caustic soda [sodium hydroxide]	**Raw**	**36**	**0**	**0**	**0**	**2.030**	**100**	**35**	**100**	**100**	**78**	**7%**
Toluene	Solvent	1,500	80	80	0	17.153	55	55	100	50	35	**63%**

Metric 2) Atom Economy: Reaction Mass Efficiency = ... 20
Metric 3) Safe Raw Materials: Total Process Material Impact = ... 80
Metric 5) Safe Solvents: Total Process Auxiliary Material Impact = ... 50
Metric 7) Renewables: Total % Process Renewable Feedstock (as-sold basis) = ... 0
Metric 7) Renewables: Total % Process Renewable Feedstock (neat basis) = 0
Metric 9) Minimum Catalyst Mole % = ... 0
Metric 9) Normalized Catalyst Score % = ... 0

Bill of Materials Out	Type of Material	Wt/ Batch	% Diluents	Severity Multiplier	Wt times Severity	Human Tox. Concern	Aq. Tox. Concern	Ultimate Biodeg.
1,4,7-Triazacyclononane	**Product**	17	0			Moderate	Moderate	4
NaCl	Waste Class 3	20		2	40			

Metric 1) Environmental factor (E+-factor) = ... 2.35
Metric 1) Waste Prevention: Normalized E+-Factor = ... 75
Metric 4) Safe Product: DSfC = ... 50
Metric 10) Biodegradability: Normalized Biodegradation = ... 75

Process Steps		Reactors, etc.	Asset Count	In-Process Add/Remove
Rotavap Water			1	1
Dean Stark			3	3
Rotavap			1	1
Step 4			0	0
Step 5			0	0

Temp. (º C.)	Time (Hrs)	Pressure (Atm)	Total Weight	Ave. Heat Capacity	Step EE
	0	1	0	0.0	**0.0**
120	48	1	500	4.2	**10373.9**
	0	1	0	0.0	**0.0**
	0	1	0	0.0	**0.0**
	0	1	0	0.0	**0.0**

Metric 6) Total Energy Efficiency = ... 10374
Metric 6) Energy Efficency: Normalized EE = ... 0
Metric 8) Process Complexity (PComplex) = ... 5 + 5 = 10
Metric 8) Process Complexity: Nomalized PComplex = ... 70

Question			Answer	Points
1)	Does the potential exist in this process for the formation of hazardous side-products? (30 pts)		No	30
2)	Are adequate monitoring and control apparatus in place to quickly detect excursions in reactors and storage vessels? (0-50 pts)		Yes	50
3)	Is the process common practice and/or in the scale-up or commercialization stages of production? (20 pts)		Yes	**0**
	a)	Is there a regularly scheduled audit or check of this equipment? (10 pts)		
	b)	Do formal (written) catastrophe plans and emergency measures exist? (10 pts)		

Metric 11) Real-Time Analysis: Total RTA = ... 80

Question		Risk	Answer	Points
1)	Are any extreme conditions (pressure ≥ 10 atm., temperature ≥ 200º C. or ≤ -78º C.) used in the process? (20 pts)	High	No	0
2)	Does the potential exist for a runaway exotherm under the process or upset conditions (including violent polymerization)? (20 pts)	High	No	0
3)	Do any of the process materials or mixtures present an explosion hazard (contact, dust and/or peroxide-forming)? (20 pts)	High	No	0
4)	Are there any process materials present initially or formed during this process that might restrict or exclude its use in the intended production facility (other high hazards than mentioned above, strong odor, etc.)? (20 pts)	High	No	0
5)	Is pressure between 1.0 and 10 atm or less than 20 mm of Hg used in this process (other than process steps for which Q1 may be true)? (10 pts)	Moderate	No	0
6)	Are temperatures ranging from 150º to 199º C. or -50º to -78º C. used in this process (other than process steps for which Q1 may be true)? (10 pts)	Moderate	No	0
7)	Is the reaction mixture flammable? (10 pts)	Moderate	Yes	10
8)	Are any of the process mixtures pyrophoric or hypergolic? (10 pts)	Moderate	No	0
9)	Do any of the process mixtures react violently with water? (5 pts)	Mild	No	0
10)	Is a gas generated in any part of this process? (5 pts)	Mild	No	0
11)	Are any of the process mixtures corrosive (pH ≤ 2 or ≥12)? (5 pts)	Mild	Yes	5
12)	Are any of the process mixtures irritants or lachrymators? (5 pts)	Mild	Yes	5

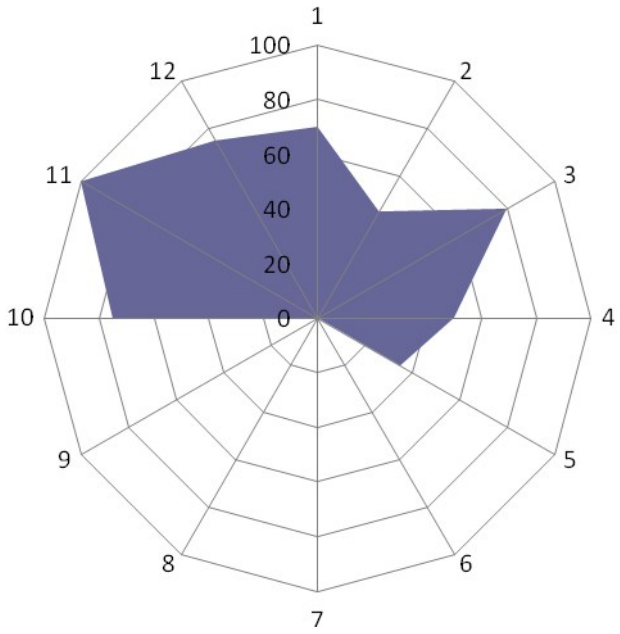
Total Yes Points = ... 20

Metric 12) Inherently Safer Chemistry: Process Safety = ... 80

Scenario: **Synthesis of Tacn Orthoamide (10)**
Description:

iSUSTAIN 4

1. Waste Prevention	70
2. Atom Economy	45
3. Safe Raw Materials	80
4. Safe Product	50
5. Safe Solvents	35
6. Energy Efficiency	0
7. Renewables	0
8. Process Complexity	75
9. Catalysis	0
10. Biodegradability	75
11. Process Control	100
12. Safe Process	75



Bill of Materials In	Type of Material	Wt/ Batch	Est. % Recycle	% Renew.	Catalyst Mole %	Usage Wt/ Wt	Safety	Health	Envir Impact	Regul Status	Matl mp	Contrib to Proc Tot
1,4,7-Triazacyclononane	**Raw**	**17**	**0**	**0**	**0**	**1.164**	**100**	**55**	**100**	**100**	**85**	**21%**
Toluene	Solvent	250	80	80	0	3.329	55	55	100	50	35	**60%**
N,N-Dimethylformamide dimethyl acetal	**Raw**	**16**	**0**	**0**	**0**	**1.071**	**55**	**65**	**100**	**100**	**73**	**19%**

Metric 2) Atom Economy: Reaction Mass Efficiency = ... 45
Metric 3) Safe Raw Materials: Total Process Material Impact = ... 80
Metric 5) Safe Solvents: Total Process Auxiliary Material Impact = ... v 35
Metric 7) Renewables: Total % Process Renewable Feedstock (as-sold basis) = ... 0
Metric 7) Renewables: Total % Process Renewable Feedstock (neat basis) = 0
Metric 9) Minimum Catalyst Mole % = ... 0
Metric 9) Normalized Catalyst Score % = ... 0

Bill of Materials Out	Type of Material	Wt/ Batch	% Diluents	Severity Multiplier	Wt times Severity	Human Tox. Concern	Aq. Tox. Concern	Ultimate Biodeg.
Tacn Orthoamide	**Product**	15	0			Moderate	Moderate	4
MeOH	Waste Class 2	10		4	40			
Dimethylamine	Waste Class 2	2		4	8			

Metric 1) Environmental factor (E+-factor) = ... 3.20
Metric 1) Waste Prevention: Normalized E+-Factor = ... 70
Metric 4) Safe Product: DSfC = ... 50
Metric 10) Biodegradability: Normalized Biodegradation = ... 75

Process Steps		Reactors, etc.	Asset Count	In-Process Add/Remove
Dean Stark		2	3	1
Rotavap		2	2	1
Kugelrohr		2	1	1
Step 4			0	0

Temp. (º C.)	Time (Hrs)	Pressure (Atm)	Total Weight	Ave. Heat Capacity	Step EE
120	24	1	500	4.2	**6039.9**
40	1	0.2	500	4.2	**139.8**
80	0	0.1	50	4.2	**0.0**
	0	1	0	0.0	**0.0**

Metric 6) Total Energy Efficiency = ... 6180
Metric 6) Energy Efficency: Normalized EE = ... 0
Metric 8) Process Complexity (PComplex) = ... 6 + 3 = 9
Metric 8) Process Complexity: Nomalized PComplex = ... 75

Question			Answer	Points
1)	Does the potential exist in this process for the formation of hazardous side-products? (30 pts)		No	30
2)	Are adequate monitoring and control apparatus in place to quickly detect excursions in reactors and storage vessels? (0-50 pts)		Yes	50
3)	Is the process common practice and/or in the scale-up or commercialization stages of production? (20 pts)		Yes	**0**
	a)	Is there a regularly scheduled audit or check of this equipment? (10 pts)	Yes	10
	b)	Do formal (written) catastrophe plans and emergency measures exist? (10 pts)	Yes	10

Metric 11) Real-Time Analysis: Total RTA = ... 100

Question		Risk	Answer	Points
1)	Are any extreme conditions (pressure ≥ 10 atm., temperature ≥ 200º C. or ≤ -78º C.) used in the process? (20 pts)	High	No	0
2)	Does the potential exist for a runaway exotherm under the process or upset conditions (including violent polymerization)? (20 pts)	High	No	0
3)	Do any of the process materials or mixtures present an explosion hazard (contact, dust and/or peroxide-forming)? (20 pts)	High	No	0
4)	Are there any process materials present initially or formed during this process that might restrict or exclude its use in the intended production facility (other high hazards than mentioned above, strong odor, etc.)? (20 pts)	High	No	0
5)	Is pressure between 1.0 and 10 atm or less than 20 mm of Hg used in this process (other than process steps for which Q1 may be true)? (10 pts)	Moderate	Yes	10
6)	Are temperatures ranging from 150º to 199º C. or -50º to -78º C. used in this process (other than process steps for which Q1 may be true)? (10 pts)	Moderate	No	0
7)	Is the reaction mixture flammable? (10 pts)	Moderate	Yes	10
8)	Are any of the process mixtures pyrophoric or hypergolic? (10 pts)	Moderate	No	0
9)	Do any of the process mixtures react violently with water? (5 pts)	Mild	No	0
10)	Is a gas generated in any part of this process? (5 pts)	Mild	No	0
11)	Are any of the process mixtures corrosive (pH ≤ 2 or ≥12)? (5 pts)	Mild	No	0
12)	Are any of the process mixtures irritants or lachrymators? (5 pts)	Mild	Yes	5

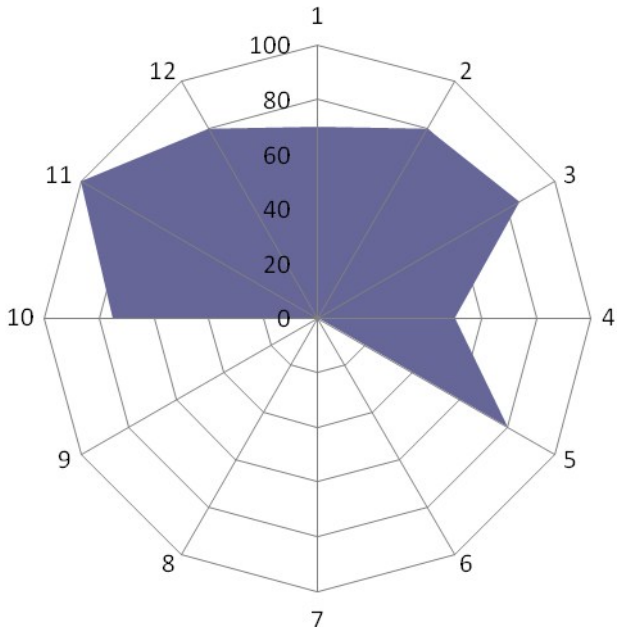
Total Yes Points = ... 25

Metric 12) Inherently Safer Chemistry: Process Safety = ... 75

Scenario: **Synthesis of Bis(tacn) Salt (2)**
Description: Tacn orthoamide **(10)** was not present it the database and tacn **(1)** was used for the safety data.

iSUSTAIN 5

1. Waste Prevention	70
2. Atom Economy	80
3. Safe Raw Materials	85
4. Safe Product	50
5. Safe Solvents	80
6. Energy Efficiency	0
7. Renewables	0
8. Process Complexity	40
9. Catalysis	0
10. Biodegradability	75
11. Process Control	100
12. Safe Process	80



Bill of Materials In	Type of Material	Wt/ Batch	Est. % Recycle	% Renew.	Catalyst Mole %	Usage Wt/Wt	Safety	Health	Envir Impact	Regul Status	MatImp	Contrib to Proc Tot
α,α′-Dibromo-m-xylene	**Raw**	**3**	**0**	**0**	**0**	**0.693**	**100**	**55**	**100**	**100**	**85**	**4%**
1,4,7-Triazacyclononane	**Raw**	**3**	**0**	**0**	**0**	**0.569**	**100**	**55**	**100**	**100**	**85**	**3%**
Acetonitrile	Solvent	120	80	80	0	4.878	55	65	100	100	73	**25%**
Hydrochloric acid	Diluent	50	0	0	0	10.163	100	55	100	100	85	**53%**
Ethanol	Auxiliary	50	80	80	0	2.033	55	100	100	100	85	**11%**
Diethyl ether	Auxiliary	25	80	80	0	1.016	15	80	100	100	65	**5%**

Metric 2) Atom Economy: Reaction Mass Efficiency = ... 80
Metric 3) Safe Raw Materials: Total Process Material Impact = ... 85
Metric 5) Safe Solvents: Total Process Auxiliary Material Impact = ... 80
Metric 7) Renewables: Total % Process Renewable Feedstock (as-sold basis) = ... 0
Metric 7) Renewables: Total % Process Renewable Feedstock (neat basis) = 0
Metric 9) Minimum Catalyst Mole % = ... 0
Metric 9) Normalized Catalyst Score % = ... 0

Bill of Materials Out	Type of Material	Wt/ Batch	% Diluents	Severity Multiplier	Wt times Severity	Human Tox. Concern	Aq. Tox. Concern	Ultimate Biodeg.
Bis(tacn)	**Product**	5	0			Moderate	Moderate	4
HBr	Waste Class 4	2		0.5	0			
HCl	Waste Class 4	20		0.5	10			

Metric 1) Environmental factor (E+-factor) = ... 2.70
Metric 1) Waste Prevention: Normalized E+-Factor = ... 70
Metric 4) Safe Product: DSfC = ... 50
Metric 10) Biodegradability: Normalized Biodegradation = ... 75

Process Steps		Reactors, etc.	Asset Count	In-Process Add/Remove
Dropwise addition			3	1
Stirring			2	0
Filtration			3	1
Reflux			3	1
Rotavap			2	1

Temp. (º C.)	Time (Hrs)	Pressure (Atm)	Total Weight	Ave. Heat Capacity	Step EE
25	1	1	0	4.2	**0.0**
25	48	1	0	4.2	**0.0**
25	1	1	0	4.2	**0.0**
120	14	1	100	4.2	**2151.2**
25	1	1	0	0.0	**0.0**

Metric 6) Total Energy Efficiency = ... 2151
Metric 6) Energy Efficency: Normalized EE = ... 0
Metric 8) Process Complexity (PComplex) = ... 13 + 4 = 17
Metric 8) Process Complexity: Nomalized PComplex = ... 40

Question			Answer	Points
1)	Does the potential exist in this process for the formation of hazardous side-products? (30 pts)		No	30
2)	Are adequate monitoring and control apparatus in place to quickly detect excursions in reactors and storage vessels? (0-50 pts)		Yes	50
3)	Is the process common practice and/or in the scale-up or commercialization stages of production? (20 pts)		Yes	**0**
	a)	Is there a regularly scheduled audit or check of this equipment? (10 pts)	Yes	10
	b)	Do formal (written) catastrophe plans and emergency measures exist? (10 pts)	Yes	10

Metric 11) Real-Time Analysis: Total RTA = ... 100

Question		Risk	Answer	Points
1)	Are any extreme conditions (pressure ≥ 10 atm., temperature ≥ 200º C. or ≤ -78º C.) used in the process? (20 pts)	High	No	0
2)	Does the potential exist for a runaway exotherm under the process or upset conditions (including violent polymerization)? (20 pts)	High	No	0
3)	Do any of the process materials or mixtures present an explosion hazard (contact, dust and/or peroxide-forming)? (20 pts)	High	No	0
4)	Are there any process materials present initially or formed during this process that might restrict or exclude its use in the intended production facility (other high hazards than mentioned above, strong odor, etc.)? (20 pts)	High	No	0
5)	Is pressure between 1.0 and 10 atm or less than 20 mm of Hg used in this process (other than process steps for which Q1 may be true)? (10 pts)	Moderate	No	0
6)	Are temperatures ranging from 150º to 199º C. or -50º to -78º C. used in this process (other than process steps for which Q1 may be true)? (10 pts)	Moderate	No	0
7)	Is the reaction mixture flammable? (10 pts)	Moderate	Yes	10
8)	Are any of the process mixtures pyrophoric or hypergolic? (10 pts)	Moderate	No	0
9)	Do any of the process mixtures react violently with water? (5 pts)	Mild	No	0
10)	Is a gas generated in any part of this process? (5 pts)	Mild	No	0
11)	Are any of the process mixtures corrosive (pH ≤ 2 or ≥12)? (5 pts)	Mild	Yes	5
12)	Are any of the process mixtures irritants or lachrymators? (5 pts)	Mild	Yes	5

Total Yes Points = ... 20

Metric 12) Inherently Safer Chemistry: Process Safety = ... 80

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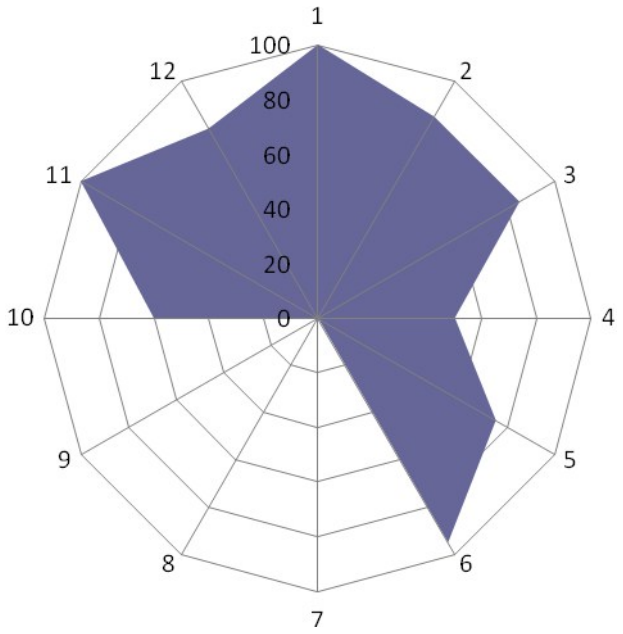
Scenario: **Synthesis of DiBoc Tacn (12)**
Description:

iSUSTAIN 6

1. Waste Prevention	100
2. Atom Economy	85
3. Safe Raw Materials	85
4. Safe Product	50
5. Safe Solvents	75
6. Energy Efficiency	95
7. Renewables	0
8. Process Complexity	40
9. Catalysis	0
10. Biodegradability	60
11. Process Control	100
12. Safe Process	80



Bill of Materials In	Type of Material	Wt/ Batch	Est. % Recycle	% Renew.	Catalyst Mole %	Usage Wt/Wt	Safety	Health	Envir Impact	Regul Status	MatImp	Contrib to Proc Tot
Triethylamine	Auxiliary	25	0	0	0	0.249	55	35	100	100	63	**1%**
1,4,7-Triazacyclononane	**Raw**	**25**	**0**	**0**	**0**	**0.249**	**100**	**55**	**100**	**100**	**85**	**1%**
2-(Boc-oxyimino)-2-phenylacetonitrile	**Raw**	**96**	**0**	**0**	**0**	**0.946**	**100**	**65**	**100**	**100**	**88**	**5%**
Chloroform	Solvent	500	80	80	0	0.980	100	35	100	0	0	**5%**
Ethyl acetate	Auxiliary	750	80	80	0	1.471	55	80	100	100	78	**7%**
Sodium bicarbonate	Auxiliary	30	0	0	0	0.294	100	100	100	100	100	**1%**
Sodium chloride	Auxiliary	300	0	0	0	2.941	100	65	100	100	88	**14%**
Sodium hydroxide [caustic soda]	Auxiliary	20	0	0	0	0.196	100	35	100	100	78	**1%**
Chloroform	Auxiliary	1,500	80	80	0	2.941	100	35	100	0	0	**14%**
Sodium sulfate	Auxiliary	5	0	0	0	0.049	100	65	100	100	88	**0%**
Citric acid	Auxiliary	225	0	0	0	2.206	100	55	100	100	85	**11%**
Water	Auxiliary	4,000	80	80	0	7.843	100	100	100	100	100	**39%**

Metric 2) Atom Economy: Reaction Mass Efficiency = ... 85
Metric 3) Safe Raw Materials: Total Process Material Impact = ... 85
Metric 5) Safe Solvents: Total Process Auxiliary Material Impact = ...v 75
Metric 7) Renewables: Total % Process Renewable Feedstock (as-sold basis) = ... 0
Metric 7) Renewables: Total % Process Renewable Feedstock (neat basis) = 0
Metric 9) Minimum Catalyst Mole % = ... 0
Metric 9) Normalized Catalyst Score % = ... 0

Bill of Materials Out	Type of Material	Wt/ Batch	% Diluents	Severity Multiplier	Wt times Severity	Human Tox. Concern	Aq. Tox. Concern	Ultimate Biodeg.
Diboc Tacn	**Product**	54	0			Moderate	Moderate	4
Boc3Tacn	**Product**	9	0			Moderate	Moderate	4
BOC-ON side product	**Product**	40	0			Moderate	Moderate	2.5

Metric 1) Environmental factor (E+-factor) = ... 0.00
Metric 1) Waste Prevention: Normalized E+-Factor = ... 100
Metric 4) Safe Product: DSfC = ... 50
Metric 10) Biodegradability: Normalized Biodegradation = ... 60

Process Steps		Reactors, etc.	Asset Count	In-Process Add/Remove
Stirring			2	1
Rotavap			1	1
washing			4	9
Step 4			0	0

Temp. (º C.)	Time (Hrs)	Pressure (Atm)	Total Weight	Ave. Heat Capacity	Step EE
25	1	1	800	4.2	**0.0**
40	1	1	800	4.2	**6.6**
	0	1	0	0.0	**0.0**
	0	1	0	0.0	**0.0**

Metric 6) Total Energy Efficiency = ... 7
Metric 6) Energy Efficency: Normalized EE = ... 95
Metric 8) Process Complexity (PComplex) = ... 7 + 11 = 18
Metric 8) Process Complexity: Nomalized PComplex = ... 40

Question			Answer	Points
1)	Does the potential exist in this process for the formation of hazardous side-products? (30 pts)		No	30
2)	Are adequate monitoring and control apparatus in place to quickly detect excursions in reactors and storage vessels? (0-50 pts)		Yes	50
3)	Is the process common practice and/or in the scale-up or commercialization stages of production? (20 pts)		Yes	**0**
	a)	Is there a regularly scheduled audit or check of this equipment? (10 pts)	Yes	10
	b)	Do formal (written) catastrophe plans and emergency measures exist? (10 pts)	Yes	10

Metric 11) Real-Time Analysis: Total RTA = ... 100

Question		Risk	Answer	Points
1)	Are any extreme conditions (pressure ≥ 10 atm., temperature ≥ 200º C. or ≤ -78º C.) used in the process? (20 pts)	High	No	0
2)	Does the potential exist for a runaway exotherm under the process or upset conditions (including violent polymerization)? (20 pts)	High	No	0
3)	Do any of the process materials or mixtures present an explosion hazard (contact, dust and/or peroxide-forming)? (20 pts)	High	No	0
4)	Are there any process materials present initially or formed during this process that might restrict or exclude its use in the intended production facility (other high hazards than mentioned above, strong odor, etc.)? (20 pts)	High	No	0
5)	Is pressure between 1.0 and 10 atm or less than 20 mm of Hg used in this process (other than process steps for which Q1 may be true)? (10 pts)	Moderate	No	0
6)	Are temperatures ranging from 150º to 199º C. or -50º to -78º C. used in this process (other than process steps for which Q1 may be true)? (10 pts)	Moderate	No	0
7)	Is the reaction mixture flammable? (10 pts)	Moderate	Yes	10
8)	Are any of the process mixtures pyrophoric or hypergolic? (10 pts)	Moderate	No	0
9)	Do any of the process mixtures react violently with water? (5 pts)	Mild	No	0
10)	Is a gas generated in any part of this process? (5 pts)	Mild	No	0
11)	Are any of the process mixtures corrosive (pH ≤ 2 or ≥12)? (5 pts)	Mild	Yes	5
12)	Are any of the process mixtures irritants or lachrymators? (5 pts)	Mild	Yes	5

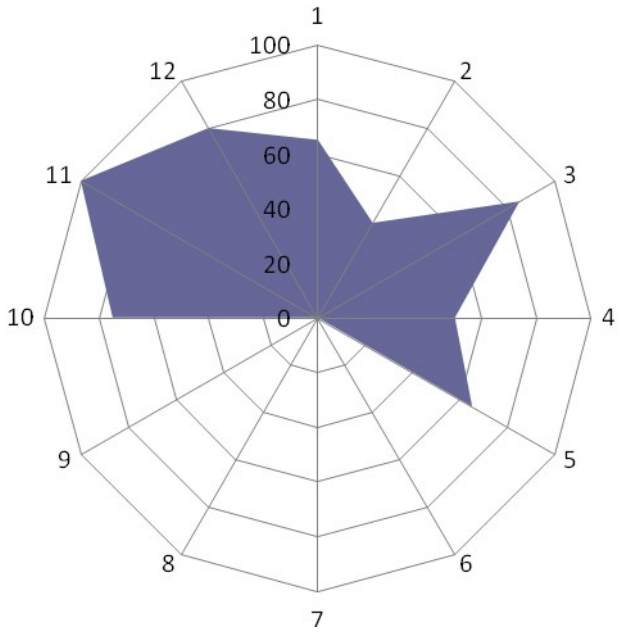
Total Yes Points = ... 20

Metric 12) Inherently Safer Chemistry: Process Safety = ... 80

Scenario: **Synthesis of Bis-Tacn Salt (2)**
Description: Diboc Tacn **(12)** was not present in the database so tacn **(1)** was used

iSUSTAIN 7

1. Waste Prevention	65
2. Atom Economy	40
3. Safe Raw Materials	85
4. Safe Product	50
5. Safe Solvents	65
6. Energy Efficiency	0
7. Renewables	0
8. Process Complexity	15
9. Catalysis	0
10. Biodegradability	75
11. Process Control	100
12. Safe Process	80



Bill of Materials In	Type of Material	Wt/ Batch	Est. % Recycle	% Renew.	Catalyst Mole %	Usage Wt/ Wt	Safety	Health	Envir Impact	Regul Status	MatImp	Contrib to Proc Tot
α,α′-Dibromo-m-xylene	**Raw**	**4**	**0**	**0**	**0**	**0.761**	**100**	**55**	**100**	**100**	**85**	**1%**
1,4,7-Triazacyclononane	**Raw**	**8**	**0**	**0**	**0**	**1.722**	**100**	**55**	**100**	**100**	**85**	**1%**
Triethylamine	Auxiliary	1	0	0	0	0.217	55	35	100	100	63	**0%**
Acetonitrile	Solvent	100	80	80	0	4.348	55	65	100	100	73	**4%**
Sodium hydroxide [caustic soda]	Auxiliary	100	0	0	0	21.739	100	35	100	100	78	**19%**
Water	Auxiliary	50	0	0	0	10.870	100	100	100	100	100	**9%**
Sodium chloride	Auxiliary	50	0	0	0	10.870	100	65	100	100	88	**9%**
Dichloromethane	Auxiliary	40	80	80	0	1.739	100	55	100	0	0	**1%**
Ethyl acetate	Auxiliary	500	80	80	0	21.739	55	80	100	100	78	**19%**
Hexane, n-	Auxiliary	500	80	80	0	21.739	55	55	35	50	24	**19%**
Silica, crystalline, cristobalite	Auxiliary	50	0	0	0	10.870	100	35	100	50	39	**9%**
Hydrochloric acid	Diluent	50	0	0	0	10.870	100	55	100	100	85	**9%**

Metric 2) Atom Economy: Reaction Mass Efficiency = ... 40
Metric 3) Safe Raw Materials: Total Process Material Impact = ... 75
Metric 5) Safe Solvents: Total Process Auxiliary Material Impact = ... 65
Metric 7) Renewables: Total % Process Renewable Feedstock (as-sold basis) = ... 0
Metric 7) Renewables: Total % Process Renewable Feedstock (neat basis) = 0
Metric 9) Minimum Catalyst Mole % = ... 0
Metric 9) Normalized Catalyst Score % = ... 0

Bill of Materials Out	Type of Material	Wt/ Batch	% Diluents	Severity Multiplier	Wt times Severity	Human Tox. Concern	Aq. Tox. Concern	Ultimate Biodeg.
Bis(tacn)	**Product**	5	0			Moderate	Moderate	4
tert-Butanol	Waste Class 2	3		4	10			
Triethylamine HBr	Waste Class 3	2		2	4			

Metric 1) Environmental factor (E+-factor) = ... 3.50
Metric 1) Waste Prevention: Normalized E+-Factor = ... 65
Metric 4) Safe Product: DSfC = ... 50
Metric 10) Biodegradability: Normalized Biodegradation = ... 75

Process Steps		Reactors, etc.	Asset Count	In-Process Add/Remove	Temp. (º C.)	Time (Hrs)	Pressure (Atm)	Total Weight	Ave. Heat Capacity	Step EE
Heating & Stirring			3	1	85	72	1	200	4.2	**14462.6**
Washes			3	6		1	1	0	0.0	**0.0**
Column			3	4		0	1	0	0.0	**0.0**
Treatment with HCl			0	0		0	1	0	0.0	**0.0**
Rotavap x 2			4	2		0	1	0	0.0	**0.0**

Metric 6) Total Energy Efficiency = ... 14463
Metric 6) Energy Efficency: Normalized EE = ... 0
Metric 8) Process Complexity (PComplex) = ... 13 + 13 = 26
Metric 8) Process Complexity: Nomalized PComplex = ... 15

Question			Answer	Points
1)	Does the potential exist in this process for the formation of hazardous side-products? (30 pts)		No	30
2)	Are adequate monitoring and control apparatus in place to quickly detect excursions in reactors and storage vessels? (0-50 pts)		Yes	50
3)	Is the process common practice and/or in the scale-up or commercialization stages of production? (20 pts)		Yes	**0**
	a)	Is there a regularly scheduled audit or check of this equipment? (10 pts)	Yes	10
	b)	Do formal (written) catastrophe plans and emergency measures exist? (10 pts)	Yes	10

Metric 11) Real-Time Analysis: Total RTA = ... 100

Question		Risk	Answer	Points
1)	Are any extreme conditions (pressure ≥ 10 atm., temperature ≥ 200º C. or ≤ -78º C.) used in the process? (20 pts)	High	No	0
2)	Does the potential exist for a runaway exotherm under the process or upset conditions (including violent polymerization)? (20 pts)	High	No	0
3)	Do any of the process materials or mixtures present an explosion hazard (contact, dust and/or peroxide-forming)? (20 pts)	High	No	0
4)	Are there any process materials present initially or formed during this process that might restrict or exclude its use in the intended production facility (other high hazards than mentioned above, strong odor, etc.)? (20 pts)	High	No	0
5)	Is pressure between 1.0 and 10 atm or less than 20 mm of Hg used in this process (other than process steps for which Q1 may be true)? (10 pts)	Moderate	No	0
6)	Are temperatures ranging from 150º to 199º C. or -50º to -78º C. used in this process (other than process steps for which Q1 may be true)? (10 pts)	Moderate	No	0
7)	Is the reaction mixture flammable? (10 pts)	Moderate	Yes	10
8)	Are any of the process mixtures pyrophoric or hypergolic? (10 pts)	Moderate	No	0
9)	Do any of the process mixtures react violently with water? (5 pts)	Mild	No	0
10)	Is a gas generated in any part of this process? (5 pts)	Mild	No	0
11)	Are any of the process mixtures corrosive (pH ≤ 2 or ≥12)? (5 pts)	Mild	Yes	5
12)	Are any of the process mixtures irritants or lachrymators? (5 pts)	Mild	Yes	5

Total Yes Points = ... 20

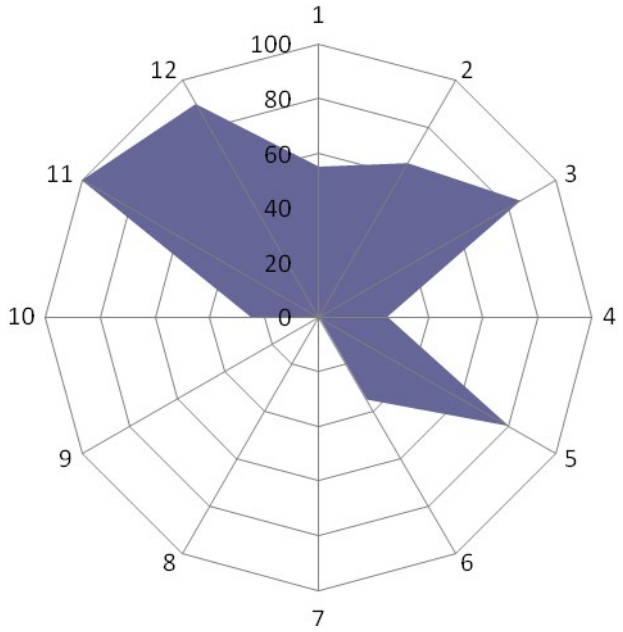
Metric 12) Inherently Safer Chemistry: Process Safety = ... 80

s

Scenario: **Syntheis of 3,6–Di(tosyl)–3,6–diazaoctane–1,8–di(toluene–4–sulfonate) (7)**
Description:

iSUSTAIN 8

1. Waste Prevention	55
2. Atom Economy	65
3. Safe Raw Materials	85
4. Safe Product	25
5. Safe Solvents	80
6. Energy Efficiency	35
7. Renewables	0
8. Process Complexity	30
9. Catalysis	0
10. Biodegradability	25
11. Process Control	100
12. Safe Process	90



Bill of Materials In	Type of Material	Wt/ Batch	Est. % Recycle	% Renew.	Catalyst Mole %	Usage Wt/Wt	Safety	Health	Envir Impact	Regul Status	MatImp	Contrib to Proc Tot
N,N'-Bis(2-hydroxyethyl)ethylenediamine	**Raw**	**19**	**0**	**0**	**0**	**0.256**	**100**	**55**	**100**	**100**	**85**	**4%**
Pyridine	Solvent	140	80	80	0	0.368	55	65	100	100	73	**5%**
p-Toluenesulfonyl chloride	**Raw**	**100**	**0**	**0**	**0**	**1.314**	**100**	**55**	**100**	**100**	**85**	**19%**
Hydrochloric acid	Solvent	200	0	0	0	2.628	100	55	100	100	85	**39%**
Water	Solvent	600	80	80	0	1.577	100	100	100	100	100	**23%**
Methanol	Solvent	100	80	80	0	0.263	55	0	100	100	51	**4%**
Dichloromethane	Solvent	100	80	80	0	0.263	100	55	100	0	0	**4%**
Acetonitrile	Solvent	50	80	80	0	0.131	55	65	100	100	73	**2%**

Metric 2) Atom Economy: Reaction Mass Efficiency = ... 65
Metric 3) Safe Raw Materials: Total Process Material Impact = ... 75
Metric 5) Safe Solvents: Total Process Auxiliary Material Impact = ... 80
Metric 7) Renewables: Total % Process Renewable Feedstock (as-sold basis) = ... 0
Metric 7) Renewables: Total % Process Renewable Feedstock (neat basis) = 0
Metric 9) Minimum Catalyst Mole % = ... 0
Metric 9) Normalized Catalyst Score % = ... 0

Bill of Materials Out	Type of Material	Wt/ Batch	% Diluents	Severity Multiplier	Wt times Severity	Human Tox. Concern	Aq. Tox. Concern	Ultimate Biodeg.
3,6–Di(tosyl)–3,6–diazaoctane–1,8–di(toluene–4–sulfonate)	**Product**	76	0			Moderate	High	2
Pyridine HCl	Waste Class 2	100		4	400			

Metric 1) Environmental factor (E+-factor) = ... 5.26
Metric 1) Waste Prevention: Normalized E+-Factor = ... 55
Metric 4) Safe Product: DSfC = ... 25
Metric 10) Biodegradability: Normalized Biodegradation = ... 25

Process Steps		Reactors, etc.	Asset Count	In-Process Add/Remove
Stirring			2	2
Stirring			1	1
Addtion to HCl			3	1
Wash			3	4
Filter			3	1

Temp. (º C.)	Time (Hrs)	Pressure (Atm)	Total Weight	Ave. Heat Capacity	Step EE
0	4	1	500	4.2	**276.0**
25	12	1	500	4.2	**0.0**
	0	1	0	0.0	**0.0**
	0	1	0	0.0	**0.0**
	0	1	0	0.0	**0.0**

Metric 6) Total Energy Efficiency = ... 276
Metric 6) Energy Efficency: Normalized EE = ... 35
Metric 8) Process Complexity (PComplex) = ... 12 + 9 = 21
Metric 8) Process Complexity: Nomalized PComplex = ... 30

Question			Answer	Points
1)	Does the potential exist in this process for the formation of hazardous side-products? (30 pts)		No	30
2)	Are adequate monitoring and control apparatus in place to quickly detect excursions in reactors and storage vessels? (0-50 pts)		Yes	50
3)	Is the process common practice and/or in the scale-up or commercialization stages of production? (20 pts)		No	**20**
	a)	Is there a regularly scheduled audit or check of this equipment? (10 pts)		
	b)	Do formal (written) catastrophe plans and emergency measures exist? (10 pts)		

Metric 11) Real-Time Analysis: Total RTA = ... 100

Question		Risk	Answer	Points
1)	Are any extreme conditions (pressure ≥ 10 atm., temperature ≥ 200º C. or ≤ -78º C.) used in the process? (20 pts)	High	No	0
2)	Does the potential exist for a runaway exotherm under the process or upset conditions (including violent polymerization)? (20 pts)	High	No	0
3)	Do any of the process materials or mixtures present an explosion hazard (contact, dust and/or peroxide-forming)? (20 pts)	High	No	0
4)	Are there any process materials present initially or formed during this process that might restrict or exclude its use in the intended production facility (other high hazards than mentioned above, strong odor, etc.)? (20 pts)	High	No	0
5)	Is pressure between 1.0 and 10 atm or less than 20 mm of Hg used in this process (other than process steps for which Q1 may be true)? (10 pts)	Moderate	Yes	10
6)	Are temperatures ranging from 150º to 199º C. or -50º to -78º C. used in this process (other than process steps for which Q1 may be true)? (10 pts)	Moderate	No	0
7)	Is the reaction mixture flammable? (10 pts)	Moderate	No	0
8)	Are any of the process mixtures pyrophoric or hypergolic? (10 pts)	Moderate	No	0
9)	Do any of the process mixtures react violently with water? (5 pts)	Mild	No	0
10)	Is a gas generated in any part of this process? (5 pts)	Mild	No	0
11)	Are any of the process mixtures corrosive (pH ≤ 2 or ≥12)? (5 pts)	Mild	No	0
12)	Are any of the process mixtures irritants or lachrymators? (5 pts)	Mild	No	0

Total Yes Points = ... 10

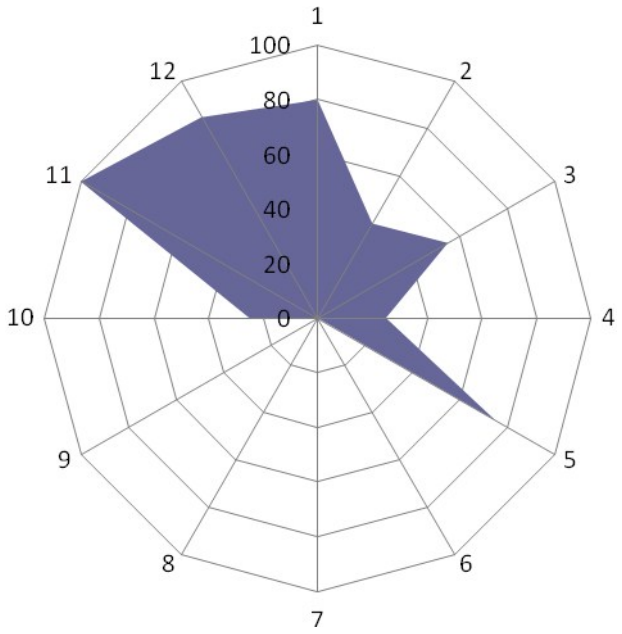
Metric 12) Inherently Safer Chemistry: Process Safety = ... 90

Scenario: **Synthesis of DiTosylBenzyl Tacn (8)**

Description: 3,6–Di(tosyl)–3,6–diazaoctane–1,8–di(toluene–4–sulfonate) **(7)** was not present in the database so 1,4,7,10-tetrakis(p-toluensulfonyl)-1,4,7,10-tetraazacyclododecane was used.

iSUSTAIN 9

1. Waste Prevention	80
2. Atom Economy	40
3. Safe Raw Materials	55
4. Safe Product	25
5. Safe Solvents	75
6. Energy Efficiency	0
7. Renewables	0
8. Process Complexity	75
9. Catalysis	0
10. Biodegradability	25
11. Process Control	100
12. Safe Process	85



Bill of Materials In	Type of Material	Wt/ Batch	Est. % Recycle	% Renew.	Catalyst Mole %	Usage Wt/Wt	Safety	Health	Envir Impact	Regul Status	MatImp	Contrib to Proc Tot
Benzylamine	**Raw**	**8**	**0**	**0**	**0**	**0.345**	**100**	**55**	**100**	**100**	**85**	**4%**
Potassium carbonate	Auxiliary	20	0	0	0	0.905	100	65	100	100	88	**10%**
Acetonitrile	Solvent	600	80	80	0	5.455	55	65	100	100	73	**61%**
1,4,7,10-tetrakis(p-toluensulfonyl)-1,4,7,10-tetraazacyclododecane	**Raw**	**50**	**0**	**0**	**0**	**2.274**	**100**	**55**	**0**	**100**	**51**	**25%**

Metric 2) Atom Economy: Reaction Mass Efficiency = ... 40
Metric 3) Safe Raw Materials: Total Process Material Impact = ... 55
Metric 5) Safe Solvents: Total Process Auxiliary Material Impact = ... 75
Metric 7) Renewables: Total % Process Renewable Feedstock (as-sold basis) = ... 0
Metric 7) Renewables: Total % Process Renewable Feedstock (neat basis) = 0
Metric 9) Minimum Catalyst Mole % = ... 0
Metric 9) Normalized Catalyst Score % = ... 0

Bill of Materials Out	Type of Material	Wt/ Batch	% Diluents	Severity Multiplier	Wt times Severity	Human Tox. Concern	Aq. Tox. Concern	Ultimate Biodeg.
DiTosylBenzyl Tacn	**Product**	22	0			Moderate	High	2
Tosic Acid	Waste Class 3	20		2	40			

Metric 1) Environmental factor (E+-factor) = ... 1.82
Metric 1) Waste Prevention: Normalized E+-Factor = ... 80
Metric 4) Safe Product: DSfC = ... 25
Metric 10) Biodegradability: Normalized Biodegradation = ... 25

Process Steps		Reactors, etc.	Asset Count	In-Process Add/Remove
Heated 6 days			3	1
Filtration			2	1
Recryst			1	1
Step 4			0	0

Temp. (º C.)	Time (Hrs)	Pressure (Atm)	Total Weight	Ave. Heat Capacity	Step EE
90	148	1	500	4.2	**16952.7**
	0	1	0	0.0	**0.0**
	0	1	0	0.0	**0.0**
	0	1	0	0.0	**0.0**

Metric 6) Total Energy Efficiency = ... 16953
Metric 6) Energy Efficency: Normalized EE = ... 0
Metric 8) Process Complexity (PComplex) = ... 6 + 3 = 9
Metric 8) Process Complexity: Nomalized PComplex = ... 75

Question			Answer	Points
1)	Does the potential exist in this process for the formation of hazardous side-products? (30 pts)		No	30
2)	Are adequate monitoring and control apparatus in place to quickly detect excursions in reactors and storage vessels? (0-50 pts)		Yes	50
3)	Is the process common practice and/or in the scale-up or commercialization stages of production? (20 pts)		Yes	**0**
	a)	Is there a regularly scheduled audit or check of this equipment? (10 pts)	Yes	10
	b)	Do formal (written) catastrophe plans and emergency measures exist? (10 pts)	Yes	10

Metric 11) Real-Time Analysis: Total RTA = ... 100

Question		Risk	Answer	Points
1)	Are any extreme conditions (pressure ≥ 10 atm., temperature ≥ 200º C. or ≤ -78º C.) used in the process? (20 pts)	High	No	0
2)	Does the potential exist for a runaway exotherm under the process or upset conditions (including violent polymerization)? (20 pts)	High	No	0
3)	Do any of the process materials or mixtures present an explosion hazard (contact, dust and/or peroxide-forming)? (20 pts)	High	No	0
4)	Are there any process materials present initially or formed during this process that might restrict or exclude its use in the intended production facility (other high hazards than mentioned above, strong odor, etc.)? (20 pts)	High	No	0
5)	Is pressure between 1.0 and 10 atm or less than 20 mm of Hg used in this process (other than process steps for which Q1 may be true)? (10 pts)	Moderate	No	0
6)	Are temperatures ranging from 150º to 199º C. or -50º to -78º C. used in this process (other than process steps for which Q1 may be true)? (10 pts)	Moderate	No	0
7)	Is the reaction mixture flammable? (10 pts)	Moderate	Yes	10
8)	Are any of the process mixtures pyrophoric or hypergolic? (10 pts)	Moderate	No	0
9)	Do any of the process mixtures react violently with water? (5 pts)	Mild	No	0
10)	Is a gas generated in any part of this process? (5 pts)	Mild	No	0
11)	Are any of the process mixtures corrosive (pH ≤ 2 or ≥12)? (5 pts)	Mild	No	0
12)	Are any of the process mixtures irritants or lachrymators? (5 pts)	Mild	Yes	5

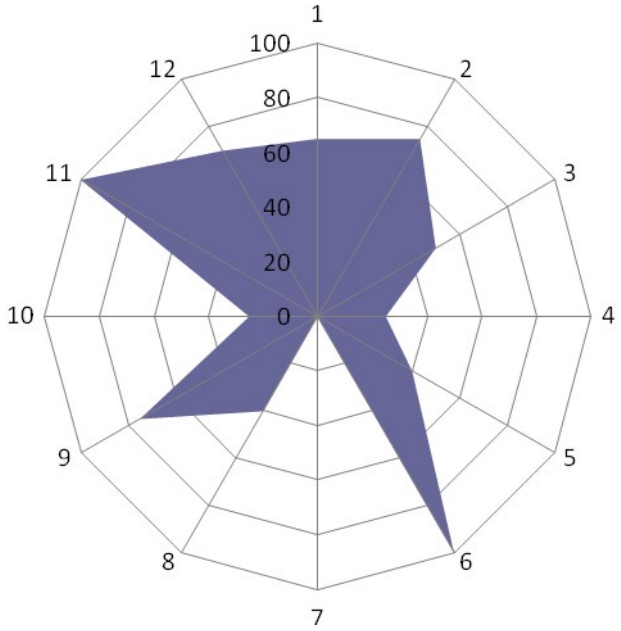
Total Yes Points = ... 15

Metric 12) Inherently Safer Chemistry: Process Safety = ... 75

Scenario: **Synthesis of Ditosyl Tacn (9)**
Description: DiTosylBenzyl Tacn **(8)** was not present in the database so 1,4,7,10-tetrakis(p-toluensulfonyl)-1,4,7,10-tetraazacyclododecane was used.

iSUSTAIN 10

1. Waste Prevention	65
2. Atom Economy	75
3. Safe Raw Materials	50
4. Safe Product	25
5. Safe Solvents	40
6. Energy Efficiency	100
7. Renewables	0
8. Process Complexity	40
9. Catalysis	75
10. Biodegradability	25
11. Process Control	100
12. Safe Process	70



Bill of Materials In	Type of Material	Wt/ Batch	Est. % Recycle	% Renew.	Catalyst Mole %	Usage Wt/Wt	Safety	Health	Envir Impact	Regul Status	MatImp	Contrib to Proc Tot
Palladium on carbon	Auxiliary	1	0	0	15	0.533	100	55	100	100	85	**0%**
Acetic acid	Solvent	50	0	0	0	33.333	100	35	100	100	78	**12%**
Hydrogen	Auxiliary	0	0	0	0	0.000	45	100	100	100	81	**0%**
Celite 512 medium	Auxiliary	20	0	0	0	13.333	100	55	100	100	85	**5%**
Methanol	Diluent	50	0	0	0	33.333	55	0	100	100	51	**12%**
Ethyl acetate	Diluent	50	0	0	0	33.333	55	80	100	100	78	**12%**
Chloroform	Solvent	200	0	0	0	133.333	100	35	100	0	0	**47%**
Caustic soda [sodium hydroxide]	Auxiliary	50	0	0	0	33.333	100	35	100	100	78	**12%**
Magnesium sulfate	Auxiliary	2	0	0	0	1.000	100	100	100	100	100	**0%**
1,4,7,10-Tetrakis(p-toluensulfonyl)-1,4,7,10-tetraazacyclododecane	**Raw**	**2**	**0**	**0**	**0**	**1.333**	**100**	**55**	**0**	**100**	**51**	**0%**

Metric 2) Atom Economy: Reaction Mass Efficiency = ... 75
Metric 3) Safe Raw Materials: Total Process Material Impact = ... 50
Metric 5) Safe Solvents: Total Process Auxiliary Material Impact = ... 40
Metric 7) Renewables: Total % Process Renewable Feedstock (as-sold basis) = ... 0
Metric 7) Renewables: Total % Process Renewable Feedstock (neat basis) = 0
Metric 9) Minimum Catalyst Mole % = ... 15
Metric 9) Normalized Catalyst Score % = ... 75

Bill of Materials Out	Type of Material	Wt/ Batch	% Diluents	Severity Multiplier	Wt times Severity	Human Tox. Concern	Aq. Tox. Concern	Ultimate Biodeg.
Ditosyl Tacn	**Product**	2	0			Moderate	High	2
Toluene	Waste Class 2	1		4	4			
		0						

Metric 1) Environmental factor (E+-factor) = ... 4.00
Metric 1) Waste Prevention: Normalized E+-Factor = ... 65
Metric 4) Safe Product: DSfC = ... 25
Metric 10) Biodegradability: Normalized Biodegradation = ... 25

Process Steps		Reactors, etc.	Asset Count	In-Process Add/Remove
Stirring			3	1
Stirring			2	1
Filtration			2	1
Wash			2	6

Temp. (º C.)	Time (Hrs)	Pressure (Atm)	Total Weight	Ave. Heat Capacity	Step EE
25	24	1	100	4.2	**0.0**
25	1	1	100	4.2	**0.0**
	0	1	0	0.0	**0.0**
	0	1	0	0.0	**0.0**

Metric 6) Total Energy Efficiency = ... 0
Metric 6) Energy Efficency: Normalized EE = ... 100
Metric 8) Process Complexity (PComplex) = ...
. 9 + 9 = 18
Metric 8) Process Complexity: Nomalized PComplex = ...
. 40

Question			Answer	Points
1)	Does the potential exist in this process for the formation of hazardous side-products? (30 pts)		No	30
2)	Are adequate monitoring and control apparatus in place to quickly detect excursions in reactors and storage vessels? (0-50 pts)		Yes	50
3)	Is the process common practice and/or in the scale-up or commercialization stages of production? (20 pts)		Yes	**0**
	a)	Is there a regularly scheduled audit or check of this equipment? (10 pts)	Yes	10
	b)	Do formal (written) catastrophe plans and emergency measures exist? (10 pts)	Yes	10

Metric 11) Real-Time Analysis: Total RTA = ... 100

Question		Risk	Answer	Points
1)	Are any extreme conditions (pressure ≥ 10 atm., temperature ≥ 200º C. or ≤ -78º C.) used in the process? (20 pts)	High	No	0
2)	Does the potential exist for a runaway exotherm under the process or upset conditions (including violent polymerization)? (20 pts)	High	No	0
3)	Do any of the process materials or mixtures present an explosion hazard (contact, dust and/or peroxide-forming)? (20 pts)	High	No	0
4)	Are there any process materials present initially or formed during this process that might restrict or exclude its use in the intended production facility (other high hazards than mentioned above, strong odor, etc.)? (20 pts)	High	No	0
5)	Is pressure between 1.0 and 10 atm or less than 20 mm of Hg used in this process (other than process steps for which Q1 may be true)? (10 pts)	Moderate	Yes	10
6)	Are temperatures ranging from 150º to 199º C. or -50º to -78º C. used in this process (other than process steps for which Q1 may be true)? (10 pts)	Moderate	No	0
7)	Is the reaction mixture flammable? (10 pts)	Moderate	Yes	10
8)	Are any of the process mixtures pyrophoric or hypergolic? (10 pts)	Moderate	No	0
9)	Do any of the process mixtures react violently with water? (5 pts)	Mild	No	0
10)	Is a gas generated in any part of this process? (5 pts)	Mild	No	0
11)	Are any of the process mixtures corrosive (pH ≤ 2 or ≥12)? (5 pts)	Mild	Yes	5
12)	Are any of the process mixtures irritants or lachrymators? (5 pts)	Mild	Yes	5

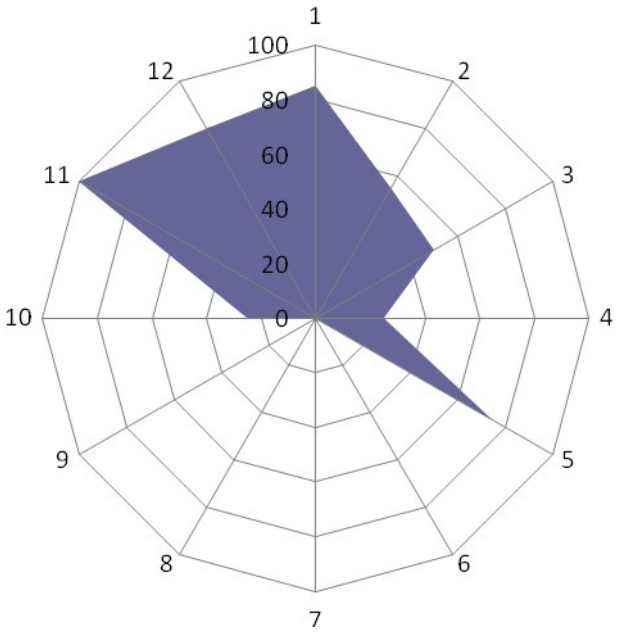
Total Yes Points = ... 30

Metric 12) Inherently Safer Chemistry: Process Safety = ... 70

Scenario: **Syntheis of Tetratosyl bis(tacn) (14)**
Description: 3,6–Di(tosyl)–3,6–diazaoctane–1,8–di(toluene–4–sulfonate) **(7)** was not present in the database so 1,4,7,10-tetrakis(p-toluensulfonyl)-1,4,7,10-tetraazacyclododecane was used.

iSUSTAIN 11

1. Waste Prevention	85
2. Atom Economy	55
3. Safe Raw Materials	50
4. Safe Product	25
5. Safe Solvents	75
6. Energy Efficiency	0
7. Renewables	0
8. Process Complexity	20
9. Catalysis	0
10. Biodegradability	25
11. Process Control	100
12. Safe Process	80



Bill of Materials In	Type of Material	Wt/ Batch	Est. % Recycle	% Renew.	Catalyst Mole %	Usage Wt/Wt	Safety	Health	Envir Impact	Regul Status	MatImp	Contrib to Proc Tot
1-3-Diaminopropane	**Raw**	**0**	**0**	**0**	**0**	**0.081**	**85**	**35**	**100**	**100**	**73**	**0%**
Potassium carbonate	Auxiliary	2	0	0	0	0.623	100	65	100	100	88	**3%**
Acetonitrile	Solvent	60	0	0	0	20.000	55	65	100	100	73	**89%**
1,4,7,10-Tetrakis(p-toluensulfonyl)-1,4,7,10-tetraazacyclododecane	**Raw**	**5**	**0**	**0**	**0**	**1.667**	**100**	**55**	**0**	**100**	**51**	**7%**

Metric 2) Atom Economy: Reaction Mass Efficiency = ... 55
Metric 3) Safe Raw Materials: Total Process Material Impact = ... 50
Metric 5) Safe Solvents: Total Process Auxiliary Material Impact = ... 75
.
Metric 7) Renewables: Total % Process Renewable Feedstock (as-sold basis) = ... 0
. .
Metric 7) Renewables: Total % Process Renewable Feedstock (neat basis) = 0
Metric 9) Minimum Catalyst Mole % = ... 0
. .
Metric 9) Normalized Catalyst Score % = ... 0
. .

Bill of Materials Out	Type of Material	Wt/ Batch	% Diluents	Severity Multiplier	Wt times Severity	Human Tox. Concern	Aq. Tox. Concern	Ultimate Biodeg.
Tetratosyl Bis(tacn)	**Product**	3	0			Moderate	High	2
Tosic Acid	Waste Class 3	2		2	4			

Metric 1) Environmental factor (E+-factor) = ... 1.33
.
Metric 1) Waste Prevention: Normalized E+-Factor = ... 85
Metric 4) Safe Product: DSfC = ... 25
Metric 10) Biodegradability: Normalized Biodegradation = ... 25
.

Process Steps		Reactors, etc.	Asset Count	In-Process Add/Remove
Heating and stirring			3	1
Filtration			3	1
Rotavap x 2			4	2
Column			3	5
Treatment with acid			2	1

Temp. (º C.)	Time (Hrs)	Pressure (Atm)	Total Weight	Ave. Heat Capacity	Step EE
90	240	1	100	4.2	**40320.0**
	0	1	0	0.0	**0.0**
	0	1	0	0.0	**0.0**
	0	1	0	0.0	**0.0**
	0	1	0	0.0	**0.0**

Metric 6) Total Energy Efficiency = ... 40320

Metric 6) Energy Efficency: Normalized EE = ... 0

Metric 8) Process Complexity (PComplex) = ... 15 + 10 = 25

Metric 8) Process Complexity: Nomalized PComplex = ... 20

Question			Answer	Points
1)	Does the potential exist in this process for the formation of hazardous side-products? (30 pts)		No	30
2)	Are adequate monitoring and control apparatus in place to quickly detect excursions in reactors and storage vessels? (0-50 pts)		Yes	50
3)	Is the process common practice and/or in the scale-up or commercialization stages of production? (20 pts)		Yes	**0**
	a)	Is there a regularly scheduled audit or check of this equipment? (10 pts)	Yes	10
	b)	Do formal (written) catastrophe plans and emergency measures exist? (10 pts)	Yes	10

Metric 11) Real-Time Analysis: Total RTA = ... 100

Question		Risk	Answer	Points
1)	Are any extreme conditions (pressure ≥ 10 atm., temperature ≥ 200º C. or ≤ -78º C.) used in the process? (20 pts)	High	No	0
2)	Does the potential exist for a runaway exotherm under the process or upset conditions (including violent polymerization)? (20 pts)	High	No	0
3)	Do any of the process materials or mixtures present an explosion hazard (contact, dust and/or peroxide-forming)? (20 pts)	High	No	0
4)	Are there any process materials present initially or formed during this process that might restrict or exclude its use in the intended production facility (other high hazards than mentioned above, strong odor, etc.)? (20 pts)	High	No	0
5)	Is pressure between 1.0 and 10 atm or less than 20 mm of Hg used in this process (other than process steps for which Q1 may be true)? (10 pts)	Moderate	No	0
6)	Are temperatures ranging from 150º to 199º C. or -50º to -78º C. used in this process (other than process steps for which Q1 may be true)? (10 pts)	Moderate	No	0
7)	Is the reaction mixture flammable? (10 pts)	Moderate	Yes	10
8)	Are any of the process mixtures pyrophoric or hypergolic? (10 pts)	Moderate	No	0
9)	Do any of the process mixtures react violently with water? (5 pts)	Mild	No	0
10)	Is a gas generated in any part of this process? (5 pts)	Mild	No	0
11)	Are any of the process mixtures corrosive (pH ≤ 2 or ≥12)? (5 pts)	Mild	Yes	5
12)	Are any of the process mixtures irritants or lachrymators? (5 pts)	Mild	Yes	5

Total Yes Points = ... 20

Metric 12) Inherently Safer Chemistry: Process Safety = ... 80