# Recycling the undesired enantiomer of naproxen

**A context/problem-based learning (C/PBL) resource**

**Module booklet**

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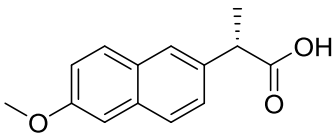
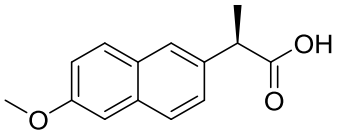
## The project

You and your colleagues are a team of research and development chemists who work for the process development section of a pharmaceutical company. Your teacher will be your line manager.

The company you work for produces and sells (*S*)-naproxen, a non-steroidal anti-inflammatory drug (NSAID). The company's current method to produce naproxen is racemic. Whilst (*S*)-naproxen is highly potent, the (*R)*-enantiomer is inactive. The company may only sell naproxen as the active enantiomer, meaning a lot of time and money is spent to separate the two stereoisomers. Disposing the undesired enantiomer also comes at a considerable cost to your company.




**(*S*)-naproxen**
anti-inflammatory




**(*R*)-naproxen**
inactive

**Figure 1: (S) and (R)-naproxen**

To overcome these problems, your company have decided to invest resources to develop a method that will recycle the undesired (*R*)-enantiomer of naproxen into the (*S*)-enantiomer. It is also important that this method can be performed in their pilot plant.

The management team have designed a strategy outlined in figure 2 on the next page. You and your team will work together to find the optimal conditions and test this out on a 20 g scale.

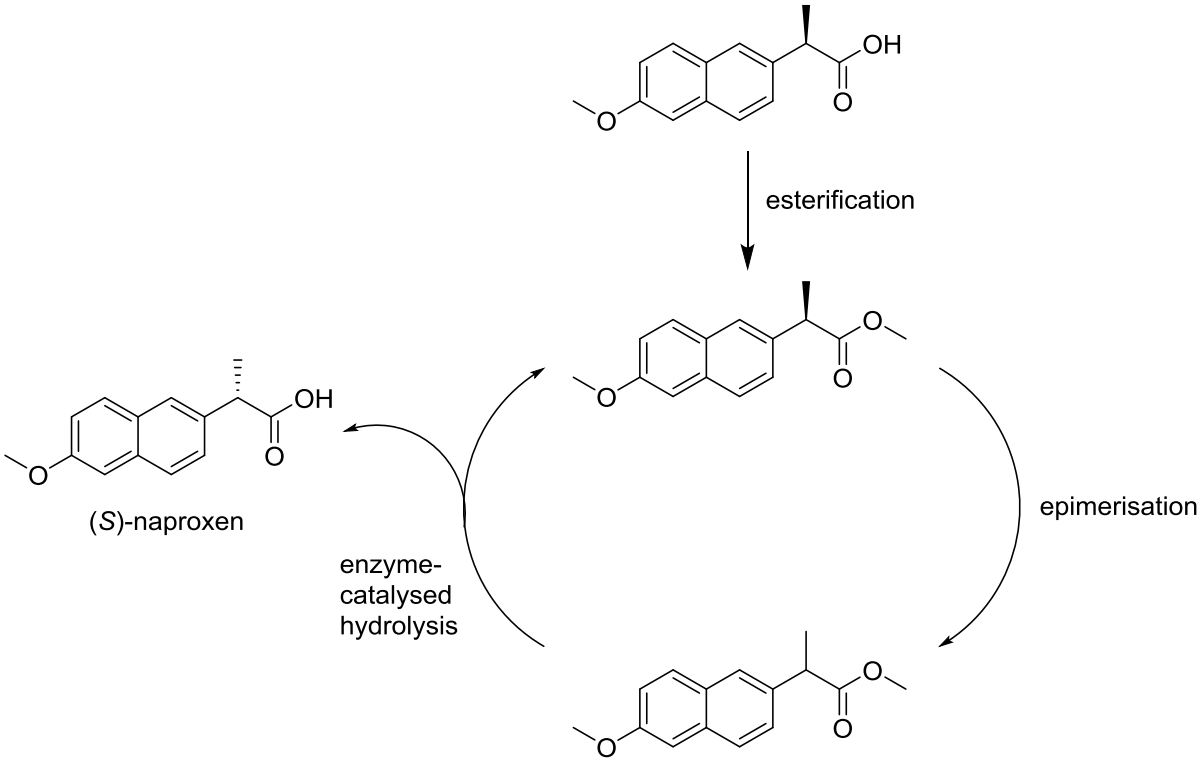



**Figure 2: Strategy to convert (*R*)-naproxen to the (*S*)-enantiomer**

The aims of the project are as follows.

- Find the optimal conditions to convert (*R*)-naproxen into (*S*)-naproxen by the deadline of the project.
- Present your findings to your manager (teacher) in the form of a group presentation and laboratory report.

## Suggested reading

Pharmaceutical Process Chemistry for Synthesis: Rethinking Routes to Scale-Up, P. J. Harrington, Wiley, 2011.

## Module structure

### Table 1: Module structure

| Week | Session | Length | Descriptions |
|---|---|---|---|
| 1 | Lecture 1 | 1 h | Introduction to the project.<br>An introduction to the process chemistry, pilot plant vessels, heating and cooling on large scale, addition of reagents, work-up, transfer and purification |
| 1 | Workshop 1 | 1 h | Adapting laboratory scale reactions to pilot plant scale using the principles from lecture 1. |
| 2 | Lecture 2 | 1 h | Health and safety. Green chemistry considerations. Time and cost in process chemistry. |
| 2 | Workshop 2 | 1 h | Adapting laboratory scale reactions to pilot plant scale using the principles from lectures 1 and 2. |
| 3 – 6 | Laboratory work | Timetabled | Laboratory investigations to find the optimum conditions to recycle (*R*)-naproxen. |
| 7 | Group presentation | 20 – 30 min | A group presentation to the manager and pilot plant team. |
| 9 –10 | Written report due | | Deadline for written report describing the project work and giving full experimental details for the lab work you carried out. |

## Learning outcomes

LO1 – Introduce chemical contexts from industrial chemistry
LO2 – Familiarise yourself with the practical aspects of synthetic chemistry associated with process/pilot plant scale chemistry
LO3 – Develop synthetic practical skills
LO4 – Develop problem-solving and investigative skills
LO5 – Develop team working skills in a synthetic chemistry scenario
LO6 – Develop scientific literacy
LO7 – Develop presentation skills

## Assessment

## Table 2: Project assessment

| Type | Contribution | Assessment of learning outcomes |
|---|---|---|
| Project results | 30% | LO1, LO2, LO3, LO4 |
| Laboratory report | 40% | LO1, LO2, LO4, LO6 |
| Group presentation | 20% Instructor assessment | LO1, LO2, LO4, LO5, LO7 |
| Peer mark for contribution | 10% | LO5 |

### Project results

Your supervisor will award a mark worth 30% based upon your team's progress and results. You will be assessed as a group by the following criteria.

- **Quantity of results** – Did you and your team generate enough results to drive the project forwards?
- **Quality of results** – Were you able to successfully find appropriate conditions to recycle (*R*)-naproxen? Were your results reliable?
- **Practical Skills** – Did you demonstrate good practical skills throughout the project? Did you and your team comply with health and safety requirements?
- **Independence** – Were you and your team able to work independently from your supervisor to achieve the aims of the project? Were you able to generate your own ideas?
- **Teamwork** – Were you and your group able to work effectively together so that progress was being made throughout the project. Did you communicate and delegate responsibilities effectively?
- **Problem solving** – Were you able to overcome any difficulties, large or small that were either theoretical or practical in nature to ensure the project continuously moved forwards?
- **Chemical understanding and application** – Were you able to apply your knowledge and understanding of chemistry to design experiments, interpret results and solve any problems you may have encountered?

### Laboratory report

A final report should be submitted at the end of the project. The report should discuss the outcome of the project. Results and data should be shared with every member of the group so that each individual can produce a report of depth and brevity. However, within the report, you should highlight your own contribution. The report should be divided into the following sections.

**Table of Contents**

### Introduction
An overview of the project which discusses the background before you started work. The aims and objectives should be included.

### Results and discussion
Discuss the results that you and your colleagues achieved. Explain the reasoning behind the experiments that were conducted and discuss your interpretation of results including which conditions were chosen for scale up and why. Discuss how the reaction can be adapted for pilot plant scale. Also include a costing of your optimised conditions if it were to be conducted in a pilot plant.

### Experimental
Include experimental procedures of all the different experiments that were conducted. This should be written in the style of a scientific journal or thesis. You do not need to write the procedures for similar experiments conducted multiple times, rather provide one procedure as an example followed by a table with individual results. There is also no need to provide compound data for the same compound multiple times, instead just one set of data for each compound is required.

### Conclusion
Summarise the findings from your project and explain why you would recommend your chosen set of conditions for use in the pilot plant. Highlight any further investigations or considerations that would need to be carried out before attempting your synthesis on a larger scale.

### Self-reflection
Include a statement describing your experiences that have helped develop your teamwork, time management, communication and problem-solving skills. Indicate where you started, where you have gone and where you would like to go to in your skills development.

## Group presentation (20 – 30 minutes)
A PowerPoint presentation should be given collectively to your instructor at a time chosen by them. You should present as though you and your team are briefing colleagues at the pilot plant who are about to carry out your chemistry on scale for the first time, ie a technology transfer report. Each person from the group should collectively take part in preparing and delivering the presentation. You do should all aim to speak for approximately the same length of time. You do not have to only present on the aspects of the project that you did yourself.

Your presentation should contain the following.

- **A reaction flow scheme**.
- **Details of each synthetic step** - Include critical process details, eg, strictly anhydrous conditions. Summarize data using tables of yields, quality and impurities. Describe procedures to neutralize by-product & waste streams.

- **Discussion of results** - Provide a description of how you developed the current process. Explain what is known and not known in current process. Describe what worked and what did not work.
- **Considerations for pilot plant scale** - Provide a safety assessment and safety considerations for scale-up.

## Peer evaluation

You will contribute towards the assessment of your fellow team members. You will assess each member on.

- Level of enthusiasm/participation
- Suggesting ideas
- Helping drive the group function as a team
- Performing tasks efficiently

The evaluation forms can be found in appendix D and should be submitted with your laboratory report. For each student the marks from each of their colleagues will be added together then divided by the number of students in the group. This average mark will be used for the Peer Evaluation section of the assessment for each student.

## Background chemistry

The (*R*)-enantiomer is first converted into methyl ester (Figure 3). The conditions to form the methyl ester have been developed so it can be used on a pilot plant scale. You will see in the workshop why this is the case.

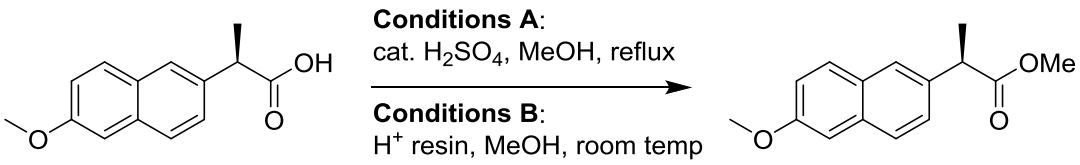



**Figure 3: Esterification of (*R*)-naproxen**

In the next step, the proton next to the carbonyl group of the methyl ester can be deprotonated to form an enolate (Figure 4). The carbon of the enolate is now $sp^2$ hybridised meaning the stereocentre has been eroded.

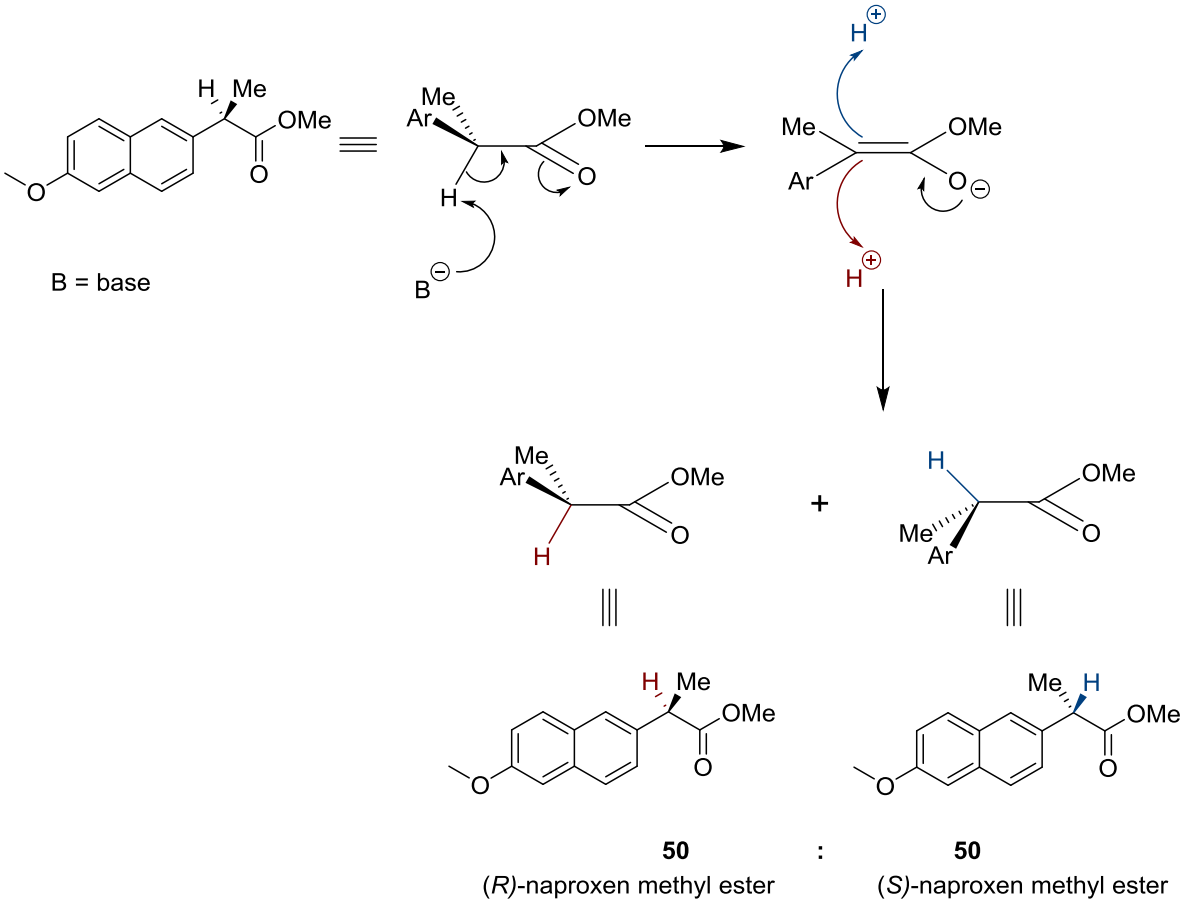



**Figure 4: Racemisation of (*R*-naproxen methyl ester)**

The enolate can tautomerise back to the ester however the protonation can occur both above and below the enolate. This means the (*R*)-ester is racemised (also known as epimerised) to give a 50:50 mixture of (*R*) and (*S*) enantiomers. LDA is a commonly used method to form enolates however it is not safe to use LDA on a large scale. The company would like you to investigate using milder conditions such as a weak base in conjuction with an additive known as a 'soft' enolisation.

The ester can be hydrolysed into naproxen (scheme 4). Enzymes such as lipases and hydrolases can selectively hydrolyse one enantiomer of an ester. The company would like you to find the best conditions to do this. Ideally only the (*S*)-enantiomer would be hydrolysed which can be separated from the (*R*)-ester. The (*R*)-ester is not wasted as it can be recycled in the racemisation/hydrolysis pathway. Any (*R*)-naproxen is not wasted either as it can be converted to the methyl ester. Of course, this would add time and cost to the recycling pathway.

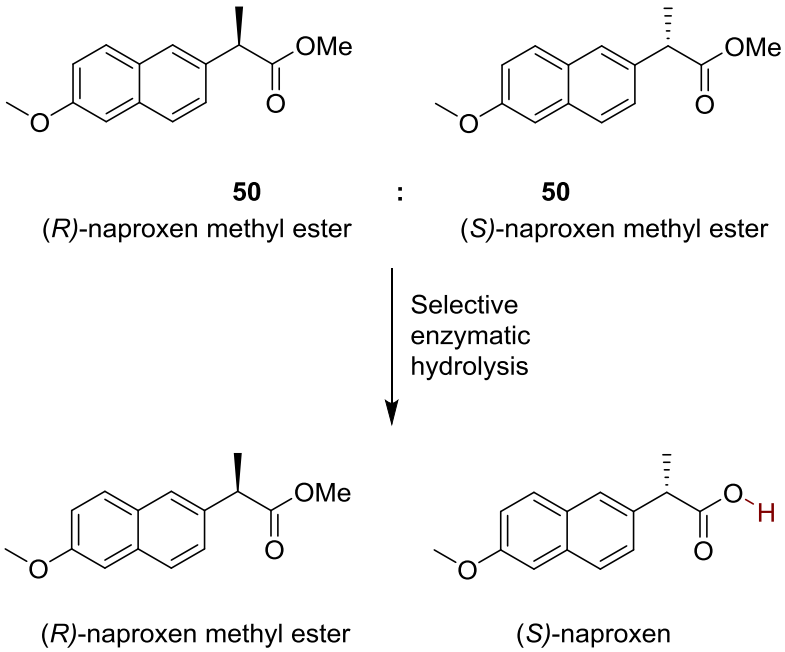



**Figure 5: Selective hydrolysis of (*S*)-naproxen methyl ester**

## Appendix A: Project assessment sheet

Group number:

Supervisor(s):

### Descriptor guidelines for levels of achievement

## Table 3: Descriptor guidelines for levels of achievement

| Mark | Descriptor | Attributes |
|---|---|---|
| 10 | Outstanding | An exceptional level of knowledge, originality and independence throughout the project that goes significantly beyond the typical level. |
| 9 | | |
| 8 | Excellent | A high level of originality and independence throughout the project with some evidence of extension beyond the standard level. A good capacity for self-direction. |
| 7 | | |
| 6 | Good | A degree of autonomy in planning and carrying out a substantial research project; a good ability for self-direction, teamwork and a good level of knowledge. |
| 5 | OK | The ability to perform the project with competency but guidance was required. Limited evidence of independent thought and originality. |
| 4 | Poor | A reasonable effort but only rudimentary skills displayed. No ability or demonstration of originality or independence. |
| 3 | Fail | Little or no engagement or contribution to the project. Little or no results to show. |
| 2 | | |
| 1 | | |
| 0 | | |

| **Quantity of results** | |
|---|---|
| Competency descriptors | The group were able to<br><br>Generate experimental results quickly and efficiently<br>Overcome practical obstacles to carry out experiments |
| Comments | |
| | |
| | |
| Mark | / 15 |

| **Quality of results** | |
|---|---|
| Competency descriptors | The group were able to<br><br>Undertake experiments that address the aim of the project<br>Generate results whose significance (positive or negative) drive the project forward<br>Produce results with high accuracy and precision<br>Avoid having to repeat experiments due to mistake or foreseeable errors |
| Comments | |
| | |
| | |
| Mark | / 15 |

| **Practical skills** | |
|---|---|
| Competency descriptors | The group were able to<br><br>Follow experimental and operating procedures accurately and confidently<br>Adapt practical techniques to the need of the project<br>Be aware of safety issues and comply with risk assessments |
| Comments | |
| | |
| | |
| Mark | / 10 |

| **Commitment** | |
|---|---|
| Competency descriptors | The group were able to<br><br>Demonstrate commitment to achieving the aims of the project work |
| Comments | |
| | |
| | |
| Mark | / 10 |

| **Independence** | |
|---|---|
| Competency descriptors | The group were able to<br><br>Take the lead in managing activities<br>Propose and execute original experiments<br>work increasingly independently as the project develops |
| Comments | |
| | |
| | |
| Mark | / 10 |

| **Teamwork** | |
|---|---|
| Competency descriptors | The group were able to<br><br>Delegate responsibilities in the team<br>Communicate effectively with each other<br>Collectively drive the project forward |
| Comments | |
| | |
| | |
| Mark | / 15 |

| **Problem solving** | |
|---|---|
| Competency descriptors | The group were able to<br><br>Overcome difficulties encountered during the project<br>Propose original approaches and solutions to solve project problems |
| Comments | |
| | |
| | |
| Mark | / 15 |

| **Chemical understanding and application** | |
|---|---|
| Competency descriptors | The group were able to<br><br>Apply chemical principles to the advancement of the project<br>Discuss rigorously the limitations of data from the project<br>Interpret results and discuss conclusions of the project |
| Comments | |
| | |
| | |
| Mark | / 10 |

**Total mark** **/ 100**

## Appendix B: Laboratory report assessment sheet

Group number:

Student:

Assessor:

### Descriptor guidelines for levels of achievement

## Table 4: Descriptor guidelines for levels of achievement

| Mark | Descriptor | Attributes |
|---|---|---|
| 10 | Outstanding | An exceptional level of knowledge, originality and independence throughout the project that goes significantly beyond the typical level. |
| 9 | | |
| 8 | Excellent | A high level of originality and independence throughout the project with some evidence of extension beyond the standard level. A good capacity for self-direction. |
| 7 | | |
| 6 | Good | A degree of autonomy in planning and carrying out a substantial research project; a good ability for self-direction, teamwork and a good level of knowledge. |
| 5 | OK | The ability to perform the project with competency but guidance was required. Limited evidence of independent thought and originality. |
| 4 | Poor | A reasonable effort but only rudimentary skills displayed. No ability or demonstration of originality or independence. |
| 3 | Fail | Little or no engagement or contribution to the project. Little or no results to show. |
| 2 | | |
| 1 | | |
| 0 | | |

| **Presentation** | |
|---|---|
| Competency descriptors | The student was able to<br><br>Present their work in an attractive and well laid out way<br>Demonstrate the use of diagrams to illustrate results<br>Describe their work using correct English, free from spelling mistakes<br>Present references in the correct fashion |
| Comments | |
| | |
| | |
| Mark | / 15 |

| **Introduction** | |
|---|---|
| Competency descriptors | The student was able to<br><br>Display a good understanding of the background to the project<br>Display a good understanding of the aims of the project |
| Comments | |
| | |
| | |
| Mark | / 15 |

| **Results and discussion** | |
|---|---|
| Competency descriptors | The student was able to<br><br>Present the results of their project clearly<br>Write a logical and well-argued discussion of their results<br>Make this discussion truly critical<br>Place the results in the context of the project |
| Comments | |
| | |
| | |
| Mark | / 30 |

| **Experimental** | |
|---|---|
| Competency descriptors | The student was able to<br><br>Write a clear and comprehensive experimental in the manner appropriate of a scientific report in synthetic chemistry<br>Use correct nomenclature, style and units<br>Provide comprehensive analytical data for experiments that were performed |
| Comments | |
| | |
| | |
| Mark | / 10 |

| **Conclusion** | |
|---|---|
| Competency descriptors | The student was able to<br><br>Write a well-argued conclusion that is clear, informative and concise<br>Write a conclusion that describes the major findings of the project<br>Write a conclusion that puts these results in the context of the aims |
| Comments | |
| | |
| | |
| Mark | / 15 |

| **Self-reflective statement** | |
|---|---|
| Competency descriptors | The student was able to<br><br>Reflect upon their own abilities against the learning objectives at the start of the project<br>Discuss their own progress in the areas of practical chemistry, teamwork, communication and problem solving as a result of the project<br>Suggest strategies to further develop skills in these areas in the future |
| Comments | |
| | |
| | |
| Mark | / 15 |

**Total mark** **/ 100**

## Appendix C: Presentation assessment sheet

Group number

Members

## Table 5: Presentation assessment guidelines

| | Fail | Poor | OK | Good | Excellent | Outstanding |
|---|---|---|---|---|---|---|
| **Structure**<br>A clear structure with introduction, logical presentation and conclusion | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| **Timing**<br>The speakers kept to the allocated time | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| **Content**<br>A good balance between presenting all the relevant material but not overwhelming the audience | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| **Quality of visual material**<br>The presentation slides are clear and easy to follow | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| **Delivery style**<br>The speakers are easy to understand and follow. They spoke to the audience and not the screen | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| **Questions**<br>The speakers dealt with the questions that were posed to them | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |

**Overall mark** **/ 100**

Comments

## Appendix D: Peer evaluation (student sheet)

Please complete the table below, assigning a value for each criterion for each person .Use the guidance below. The figures you give will be used to calculate the peer evaluation mark for each group member.

## Table 6: Peer evaluation scores

| **Write the names of the other group members in the blank boxes provided** | **You** | | | | |
|---|---|---|---|---|---|
| Level of enthusiasm/participation | | | | | |
| Suggesting ideas | | | | | |
| Helping to drive the project forwards | | | | | |
| Helping the group to function as a team | | | | | |
| Performing task efficiently | | | | | |
| **Total mark** | | | | | |

For each criterion, marks are awarded as follows.

- 3 for better than most of the group in this respect
- 2 for average compared to most of the group in this respect
- 1 for not as good as most of the group in this respect
- 0 for no help at all in this respect
- -1 for hindrance to the group in this respect