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ANTISEPTIC COMPOSITION CONTAINING A QUATERNARY AMMONIUM COMPOUND A CHELATING AGENT AND A POLYOL

5 The invention relates to antiseptic compositions, and in particular to ready to use antiseptic compositions.

10 Many compounds suitable for killing or inhibiting the growth of microorganisms are known. Compositions containing such compounds and suitable for application to the human, or animal, body are generally referred to as antiseptics.

15 Traditionally, antiseptic compositions have been produced, and provided to the public, in concentrated form to be diluted at the time of use. This has a number of drawbacks, including the unavailability of water when antiseptics is required, unclean or
20 contaminated water used for dilution, or inaccurate dilution by the user.

To overcome the above problems the trend has been to produce dilute (or ready to use) antiseptics.

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Many of the recent ready-to-use antiseptics are fairly complex, comprising mixtures of antimicrobial compounds, surfactants, solvents etc. However, many of these extra ingredients may be irritating to the
30 skin (eg. alcohols or surfactants) or may interfere

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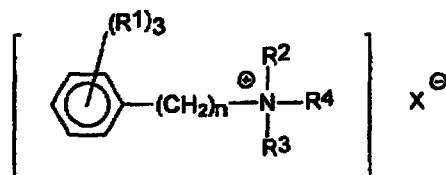
with the antiseptic activity of the active agents (eg surfactants).

We have now found that an effective ready to use
 5 antiseptic composition may be produced by the combination of a relatively small number of ingredients.

According to the invention, there is therefore
 10 provided an aqueous, topical, ready to use, antiseptic composition comprising

a) 0.05 to 1% w/v of a biocidal compound of formula I

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20 wherein

each R^1 is independently selected from hydrogen, a C_{1-4} alkyl group, a C_{1-4} alkoxy group, a halogen or a hydroxy group;

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n is 0 to 3;

R^2 and R^3 are independently selected from C_{1-4} alkyl groups;

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R^4 is a C_{6-22} alkyl chain (or a mixture thereof), and

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X is an anion;

b) 0.005 to 0.2% w/v of a chelating agent, and

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c) 1 to 5% w/v of a polyhydric alcohol;

the composition further comprising substantially no monohydric alcohols.

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The monohydric alcohols to be excluded from the compositions of the invention include ethanol and methanol.

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Preferably in the compounds of formula I R^1 is hydrogen, n is 1 or 2 (most preferably 1), R^2 and R^3 are each methyl, R^4 is an alkyl chain of C_{6-18} length (or a mixture thereof) and X is a halogen.

20

Most preferably, the compound of formula I is a mixture of alkyldimethylbenzyl ammonium chlorides (commercially available as "benzalkonium chloride").

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Preferably in the compositions of the invention the concentration of the compound of formula I is from 0.1 to 0.5 % w/v, more preferably 0.15 to 0.3% w/v.

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Preferably the chelating agents are selected from ethylenediamine tetraacetic acid (EDTA) or a derivative or a salt thereof, or ethylene glycol bis

[β -aminoethyl ether] -N,N,N', N'-tetraacetic acid (EGTA) or a derivative or salt thereof.

5 More preferably the chelating agent is EDTA or a sodium or potassium salt thereof, or EGTA or a sodium or potassium salt thereof; most preferably it is a sodium salt of EDTA.

10 Preferably in the compositions of the invention the concentration of the chelating agent is from 0.005 to 0.1% w/v, more preferably 0.01 to 0.05% w/v (expressed as the free acid where appropriate)

15 Preferably the polyhydric alcohol is selected from polyethylene glycols of average molecular weight 200 to 1000 (particularly 200 to 600), propylene glycol, ethylene glycol or mixtures thereof. Most preferably the polyhydric alcohol is propylene glycol.

20 Preferably the amount of polyhydric alcohol in a composition of the invention is from 2 to 4% w/v, more preferably 2 to 3% w/v.

25 By topical, ready to use, antiseptic compositions it is meant that the compositions of the invention are suitable (and are intended) to be used directly on the skin of humans or animals without further dilution.

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Therefore preferably the compositions of the invention are substantially free of any compound which may cause irritation to the skin.

5 Preferably the compositions of the invention contain substantially no biocidal phenolic compounds (other than compounds of formula I, where appropriate). More preferably the compositions of the invention are substantially free of any biocidal compounds other
10 than compounds of formula I. For the avoidance of doubt, we do not consider EDTA or EGTA (or salts thereof) to be biocidal compounds.

 The compositions of the invention may further
15 contain conventional ingredients of antiseptic compositions, as appropriate. However, it is preferred that the compositions of the invention contain substantially no nonionic surfactants and most preferably they contain substantially no surfactants
20 at all (other than quaternary ammonium biocides of Formula I)

 A preferred extra component in the compositions of the invention is a topical anaesthetic. Most
25 preferably the topical anaesthetic is lignocaine or the hydrochloride salt thereof.

 When present, the lignocaine will be present at an amount of from 1 to 5% w/v, more preferably from 2 to
30 3.5% w/v.

Further according to the invention there is provided an aqueous, topical, ready to use, antiseptic composition comprising

- 5 a) 0.1 to 0.5 w/v benzalkonium chloride;
b) 0.005 to 0.1% w/w EDTA, or a sodium salt thereof;
c) 1 to 5% w/v propylene glycol; and
d) 0 to 5% w/v (preferably 1 to 5% w/v, more preferably 2 to 3.5% w/v) lignocaine hydrochloride;

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the composition further containing substantially no biocidal phenolic compounds (and preferably no further biocides);

15

and substantially no monohydric alcohols.

Further conventional components include buffering and pH control agents (for example sodium acid phosphate and sodium phosphate), perfumes and
20 colouring agents.

The balance of the compositions of the invention will be water. Preferably the water is softened, distilled or deionised water, most preferably it is
25 softened water.

The compositions of the invention may be produced by any conventional manufacturing process; for example by simply mixing all of the ingredients at room
30 temperature, or whilst heating the mixture, until a solution is formed. The compositions may be produced

directly in dilute form or as concentrates to be diluted before packaging.

5 The compositions of the invention may be packaged in any conventional form. Examples include in sprayable form such as aerosols (also comprising a propellant) or so called pump packs; dispersed onto cloths as antiseptic wipes; in ampoules as single use packs or in conventional (multiple dose) bottles.

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The advantages of the compositions of the invention are that they are in a ready to use form, are simple to produce, none irritant and have effective antiseptic properties on the skin.

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The invention will now be illustrated by the following examples.

5 Example 1

A composition was made up at 25°C by mixing the following components together

	% w/v
10 Benzalkonium chloride 50%	0.395
Disodium EDTA	0.015
Propylene glycol	2.080
Sodium acid phosphate	0.718
Sodium phosphate	0.143
15 Perfume	0.050 (ml)
Softened Water	to 100 ml

Example 2

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A composition was made up at 25°C by mixing the following components together

	% w/v
Benzalkonium chloride 50%	0.395
25 Disodium EDTA	0.015
Propylene glycol	2.080
Lignocaine HCl	2.200
Sodium acid phosphate	0.718
Sodium phosphate	0.143
30 Perfume	0.050 (ml)
Softened water	to 100 ml

The compositions of Examples 1 and 2 can be applied to the skin "neat" and have good antiseptic properties.

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Example 3

A composition was made up at 25°C by mixing the following components together.

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	%w/v
Cetrimide (available as	
Cetavlon from ICI)	0.15
Tetrasodium EDTA	0.02
15 Polyethylene glycol 400	2.5
Sodium acid phosphate	0.718
Sodium phosphate	0.143
Perfume	0.05 (ml)
Softened water	to 100 ml

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Example 4

The microbiological activity of the composition of Example 2 was tested using the Proposed Suspension

25 Test for the Evaluation of Antimicrobial Efficacy of Antiseptic and Disinfectant products for Medical Usage (WG1 phase 2 step 1) of the Committee for European Normalisation TC 216 (1995).

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Activity after a 5 minute contact time against *Staphylococcus aureus* ATCC 6538, Methicillin Resistant

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S. aureus (MRSA), *Enterococcus hirae* ATCC 10541, *Escherichia coli* ATCC 10536, *Citrobacter freundii* ATCC 8090, *Klebsiella pneumoniae* ATCC 13883, *Proteus mirabilis* ATCC 14153 and *Pseudomonas aeruginosa* ATCC 15442 was assessed in the presence of 1% combined albumin/yeast extract (CAY). Under the test conditions the maximum concentration of product that can be tested is 80% v/v.

10 The composition of Example 2 achieved excellent activity, log reductions in excess of 5, against all the challenge organisms, see Table 1.

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TABLE 1 : Antibacterial Activity in the presence of 1% organic soil

	Organism	ME value (after 5 minute contact time) on three consecutive days:
5	<i>Staphylococcus aureus</i> ATCC 6538	>6.5 >6.5 5.7
10	Methicillin Resistant <i>Staphylococcus aureus</i> clinical isolate	>3.3 >6.3 >6.3
	<i>Enterococcus hirae</i> ATCC 10541	>6.4 >6.5 >6.6
15	<i>Escherichia coli</i> ATCC 10536	>6.5 >6.8 >6.3
20	<i>Citrobacter freundii</i> ATCC 8090	2.0 >6.8 >6.1
	<i>Klebsiella pneumoniae</i> ATCC 13883	>6.8 >6.8 >6.3
25	<i>Proteus mirabilis</i> ATCC 14153	>6.0 4.8 >6.0
30	<i>Pseudomonas aeruginosa</i> ATCC 15442	>5.9 >6.2 >6.2

Example 5

The lack of irritancy of the composition of Example
5 2 was tested by the following procedure.

Twenty-six human volunteers of either sex aged
between 18 and 65 took part in the trial. The
composition of Example 2 was applied to the skin
10 undiluted. Deionised water and a blank untreated site
were included as controls. Each sample was applied to
the upper outer arm via an occlusive aluminium Finn
chamber which provided a test area of 50 mm² and a
volume of 25 µl. Patches were applied for an initial
15 period of 6 hours, then removed and assessed using a
numerical scoring system.

After assessment an identical fresh patch was
applied to the same site for a further 17 hours and
20 test sites were examined for irritation 1 hour later.
A third identical fresh patch was applied to the same
skin site for a further 23 hours and test sites were
examined 1 hour later. Twenty-four out of 26 subjects
completed the study. No adverse events were observed.

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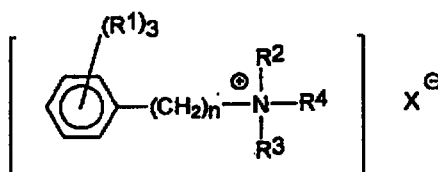


Claims

- 5 1. An aqueous, topical, ready to use, antiseptic composition comprising

a) 0.05 to 1% w/v of a biocidal compound of formula I

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15 wherein

each R^1 is independently selected from hydrogen, a C_{1-4} alkyl group, a C_{1-4} alkoxy group, a halogen or a hydroxy group;

20

n is 0 to 3;

R^2 and R^3 are independently selected from C_{1-4} alkyl groups;

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R^4 is a C_{6-22} alkyl chain (or a mixture thereof), and

X is an anion;

- 30 b) 0.005 to 0.2% w/v of a chelating agent, and





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c) 1 to 5% w/v of a polyhydric alcohol;

the composition further comprising substantially no monohydric alcohols.

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2. An aqueous, topical, ready to use, antiseptic composition as claimed in Claim 1 wherein in the compounds of formula I R^1 is hydrogen, n is 1 or 2 (most preferably 1), R^2 and R^3 are each methyl, R^4 is an alkyl chain of C_{8-18} length (or a mixture thereof) and X is a halogen.

3. An aqueous, topical, ready to use, antiseptic composition as claimed in claim 2 wherein the compound of formula I is a mixture of alkyldimethylbenzyl ammonium chlorides.

4. An aqueous, topical, ready to use, antiseptic composition as claimed in any preceding claim wherein the concentration of the compound of formula I is from 0.1 to 0.5 % w/v.

5. An aqueous, topical, ready to use, antiseptic composition as claimed in any preceding claim wherein the chelating agent is selected from ethylenediamine tetraacetic acid (EDTA) or a derivative or a salt thereof, or ethylene glycol bis [β -aminoethyl ether] -N,N,N', N'-tetraacetic acid (EGTA) or a derivative or salt thereof.

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6. An aqueous, topical, ready to use, antiseptic composition as claimed in claim 5 wherein the chelating agent is EDTA or a sodium or potassium salt thereof, or EGTA or a sodium or potassium salt thereof.
7. An aqueous, topical, ready to use, antiseptic composition as claimed in any preceding claim wherein the concentration of chelating agent is from 0.005 to 0.1% w/v (expressed as the free acid where appropriate).
8. An aqueous, topical, ready to use, antiseptic composition as claimed in any preceding claim wherein the polyhydric alcohol is selected from polyethylene glycols of average molecular weight 200 to 1000 (particularly 200 to 600), propylene glycol, ethylene glycol or mixtures thereof.
9. An aqueous, topical, ready to use, antiseptic composition as claimed in any preceding claim wherein the concentration of polyhydric alcohol is from 2 to 4% w/v, more preferably 2 to 3% w/v.
10. An aqueous, topical, ready to use, antiseptic composition as claimed in any preceding claim containing substantially no nonionic surfactants.
11. An aqueous, topical, ready to use, antiseptic composition as claimed in claim 10 containing

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substantially no surfactants (other than quaternary ammonium biocides of Formula I).

12. An aqueous, topical, ready to use, antiseptic
5 composition as claimed in any preceding claim further comprising a topical anaesthetic.

13. An aqueous, topical, ready to use, antiseptic
composition as claimed in claim 12 wherein the topical
10 anaesthetic is lignocaine or the hydrochloride salt thereof.

14. An aqueous, topical, ready to use, antiseptic
composition as claimed in claim 13 wherein the
15 concentration of lignocaine is from 1 to 5% w/v.

15. An aqueous, topical, ready to use, antiseptic
composition comprising

- 20 a) 0.1 to 0.5 w/v benzalkonium chloride;
b) 0.005 to 0.1% w/w EDTA, or a sodium salt thereof;
c) 1 to 5% w/v propylene glycol; and
d) 1 to 5% w/v lignocaine hydrochloride;

25 the composition further containing substantially no biocidal phenolic compounds;

and substantially no monohydric alcohols.

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16. An aqueous, topical, ready to use, antiseptic composition as claimed in any preceding claim substantially as described in any of Examples 1 to 3.

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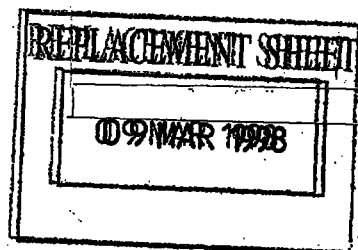
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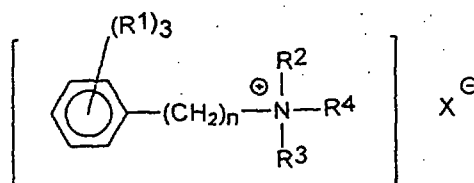
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Claims

1. An aqueous topical, ready to use, antiseptic composition suitable for application to the skin comprising

a) 0.05 to 1% w/v of a biocidal compound of formula I



wherein

each R^1 is independently selected from hydrogen, a C_{1-4} alkyl group, a C_{1-4} alkoxy group, a halogen or a hydroxy group;

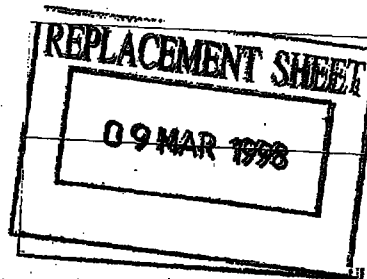
n is 0 to 3;

R^2 and R^3 are independently selected from C_{1-4} alkyl groups;

and X is an anion;

b) 0.005 to 0.2% w/v of a chelating agent, and

c) 1 to 5% w/v of a polyhydric alcohol, selected from polyethylene glycols of average molecular weight 200 to 1000 (particularly 200 to 600), propylene glycol, ethylene glycol or mixtures thereof, the composition further comprising



substantially no monohydric alcohols.

2. An aqueous, topical, ready to use, antiseptic composition as claimed in Claim 1 wherein in the compounds of formula I R^1 is hydrogen, n is 1 or 2 (most preferably 1), R^2 and R^3 are each methyl, R^4 is an alkyl chain of C_{8-18} length (or a mixture thereof) and X is a halogen.
3. An aqueous, topical, ready to use, antiseptic composition as claimed in Claim 2 wherein the compound of formula I is a mixture of alkyl dimethylbenzyl ammonium chlorides.
4. An aqueous, topical, ready to use, antiseptic composition as claimed in any preceding claim wherein the concentration of the compound of formula I is from 0.1 to 0.5% w/v.
5. An aqueous, topical, ready to use, antiseptic composition as claimed in any preceding claim wherein the chelating agent is selected from ethylenediamine tetraacetic acid (EDTA) or a derivative or a salt thereof, or ethylene glycol bis [β-aminoethyl ether] -N,N,N', N'-tetraacetic acid (EGTA) or a derivative or salt thereof.
6. An aqueous, topical, ready to use, antiseptic composition as claim in claim 5 wherein the chelating agent is EDTA or a sodium or potassium salt thereof, or EGTA or a sodium or potassium salt thereof.

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7. An aqueous, topical, ready to use antiseptic composition as claimed in any preceding claim wherein the concentration of chelating agent is from 0.005 to 0.1% w/v (expressed as the free acid where appropriate).

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8. An aqueous, topical, ready to use, antiseptic composition as claimed in any preceding claim wherein the concentration of polyhydric alcohol is from 2 to 4% w/v, more preferably 2 to 3% w/v.

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9. An aqueous, topical, ready to use, antiseptic composition as claimed in any preceding claim containing substantially no nonionic surfactants.

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10. An aqueous, topical, ready to use, antiseptic composition as claimed in claim 9 containing substantially no surfactants (other than quaternary ammonium biocides of Formula I).

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11. an aqueous topical, ready to use antiseptic composition as claimed in any preceding claim further comprising a topical anaesthetic.

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12. An aqueous topical, ready to use antiseptic composition as claimed in Claim 11 wherein the topical anaesthetic is lignocaine or the hydrochloride salt thereof.

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13. An aqueous, topical, ready to use, antiseptic composition as claimed in claim 12 wherein the concentration of lignocaine is from 1 to 5% w/v.

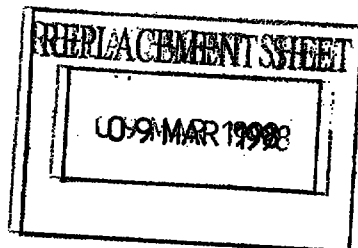


14. An aqueous, topical, ready to use, antiseptic composition according to claim 1 comprising

- a) 0.1 to 0.5% w/v benzalkonium chloride;
- b) 0.005 to 0.1% w/w EDTA, or a sodium salt thereof;
- c) 1 to 5% w/v propylene glycol; and
- d) 1 to 5% w/v lignocaine hydrochloride;

the composition further containing substantially no biocidal phenolic compounds;

and substantially no monohydric alcohols.



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(21) International Application Number: PCT/GB96/03037 ✓ (22) International Filing Date: 11 December 1996 (11.12.96) ✓ (30) Priority Data: 9600140.9 5 January 1996 (05.01.96) ✓ GB (71) Applicant: RECKITT & COLMAN PRODUCTS LIMITED [GB/GB]; One Burlington Lane, London W4 2RW (GB). (72) Inventor: TYERS, Gerald, David; 26 Wold View, Brough, East Yorkshire HU15 1DB (GB). (74) Agents: SANDERSON, Nigel, Paul et al.; Reckitt & Colman plc, Group Patents Dept., Dansom Lane, Hull HU8 7DS (GB).		(81) Designated States: AU, CN, LK, NZ, SG, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published With international search report.
(54) Title: ANTISEPTIC COMPOSITION CONTAINING A QUATERNARY AMMONIUM COMPOUND A CHELATING AGENT AND A POLYOL (57) Abstract Aqueous, topical, ready to use, antiseptic compositions comprising: a) 0.05 to 1 % w/v of a biocidal compound of formula (I) wherein each R¹ is independently selected from hydrogen, a C₁₋₄ alkyl group, a C₁₋₄ alkoxy group, a halogen or a hydroxy group; n is 0 to 3; R² and R³ are independently selected from C₁₋₄ alkyl groups; R⁴ is a C₆₋₂₂ alkyl chain (or a mixture thereof), and X is an anion; b) 0.005 to 0.2 % w/v of a chelating agent; and c) 1 to 5 % w/v of a polyhydric alcohol; the composition further comprising substantially no monohydric alcohols. $\left[\text{C}_6\text{H}_3(\text{R}^1)_3 - (\text{CH}_2)_n - \text{N}^+(\text{R}^2)(\text{R}^3)\text{R}^4 \right] \text{X}^- \quad (\text{I})$		