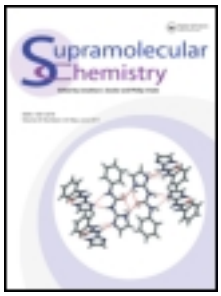

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The influence of stereochemistry on anion binding and transport

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The influence of stereochemistry on anion binding and transport

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Bis(thio)urea receptors (**1**–**4**) based on 1,2-bisaminocyclohexane are shown to function as transmembrane anion antiporters. The results show that *cis*-receptors have a greater propensity for anion transport than analogous *trans*-receptors. Stability constants using ^{1}H NMR techniques highlight the significance of stereoisomerism on anion binding in solution, as *cis*-receptors bind anions more strongly than *trans*-receptors.

Keywords: anion; urea; thiourea; hydrogen bond; stereochemistry

Introduction

The transport of anions across lipid bilayers is important to many biological processes (*1*), and is often mediated by proteins embedded within the lipid bilayer of cells, which form ion channels. Genetic mutation of these proteins can cause them to malfunction, leading to various diseases, including cystic fibrosis (*2*), cardiac disorders, epilepsy and Bartter syndrome (*3*). For this reason, there is an ever-growing interest in the development of synthetic small molecules, which can bind or encapsulate ions for transport across lipid bilayers. These 'carriers' have potential to be developed as therapeutic replacements for the malfunctioning proteins that form ion channels (*1*). Previous work within the Gale group has developed structurally simple transmembrane anion receptors based on the *ortho*-phenylenediamine bis-urea scaffold, which exhibit transport activity across 1-palmitoyl-2-oleoylphosphatidylcholine (POPC) bilayers at receptor to lipid ratios as low as 1:1,000,000 (*4*). These receptors have shown to bind chloride anions with stability constants of $\sim$10–80 M^{-1} and bicarbonate anions with stability constants of roughly 800–4000 M^{-1} (in DMSO-d_6/0.5% water at 298 K). The addition of an electron-withdrawing group to the central core or peripheral phenyl groups of such receptors results in increased anion affinity due to the increased acidity of the H-bond donor N—H groups. We postulated that the halogenation of the central core phenyl group in such receptors also increases the acidity of the phenylene C—H groups, resulting in strengthened intramolecular H-bonds and pre-organisation of the receptors for binding anions (*5*).

Fabbrizzi and co-workers investigated the binding of enantiomeric forms *R*,*R* and *S*,*S* of an *ortho*-cyclohexanediamine-based bis-urea receptor with *para*-nitrophenyl side groups to a variety of anions (*6*). They demonstrated that a chiral discriminating effect does exist between enantiomeric receptors when binding chiral guests, yet no such effect is observed on binding achiral anions. In fact, Odago et al. reported the use of a racemic mix of the thiourea equivalent of this receptor for the optical sensing of cyanide anions (*7*).

To investigate the effect of stereochemistry on anion binding and transport, a series of *cis*- and *trans*-*ortho*-cyclohexanediamine-based bis-(thio)ureas with bis-trifluoromethylphenyl side groups were synthesised (Figure 1). These four receptors were investigated for their ability to transport chloride and bicarbonate anions across bilayers of POPC, as well as their binding affinity with a variety of different anions. U-tube experiments were carried out to help determine the mode of anion transport.

Nagasawa and co-workers have previously reported urea **3** as a catalyst for the hetero-Michael addition reaction between pyrrolidine and γ-crotonolactone, in which **3** exhibits a low chiral induction effect on the final product (*8*). In addition, thiourea **4** was shown to catalyse the aza-Henry reaction of a Boc-protected imine, again with a slight asymmetric induction (*9*). Receptor **2** has also been previously reported (*10*).

Experimental

Synthesis

*1,1′-((1R,2S)-Cyclohexane-1,2-diyl)bis(3-(3,5-bis(trifluoromethyl)phenyl)urea) (**1**)*

3,5-Bis(trifluoromethyl)phenyl isocyanate (0.62 mL, 3.6 mmol) and *cis*-1,2-diaminocyclohexane (0.21 mL, 1.8 mmol) were dissolved in dichloromethane (DCM) (40 mL) and stirred for 6.5 h at rt under a nitrogen atmosphere. A white precipitate was isolated by filtration in a 71% yield after washing with excess DCM. ^{1}H NMR (DMSO-d_6, 300 MHz): $\delta = 1.30–1.75$ (m, 8H), 3.91 (br s,

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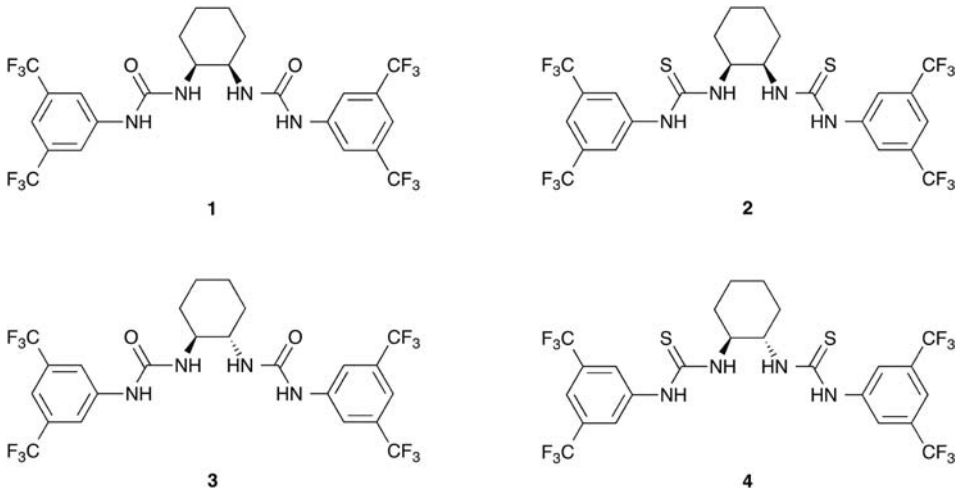


Figure 1. *ortho*-Cyclohexanediamine-based bis-(thio)ureas of **1**–**4**.

2H), 6.40 (d, 2H, $J = 6.0$ Hz), 7.52 (s, 2H), 7.99 (s, 4H), 9.16 (s, 2H). $^{13}C\{^1H\}$ NMR (DMSO-d_6, 100 MHz): $\delta = 21.7$ (CH_2), 28.6 (CH_2), 48.7 (CH), 113.4 (Ar CH), 117.1 (Ar CH), 123.3 (q, CF_3, $J = 270.9$ Hz), 130.6 (q, Ar C—CF_3, $J = 32.2$ Hz), 142.3 (Ar C), 154.4 (C═O). $^{19}F\{^1H\}$ NMR (DMSO-d_6, 282 MHz): $\delta = 61.86$. LR-MS ES$^-$ (*m/z*): 623 $[M - H]^-$. HR-MS ES$^+$ (*m/z*): Act. 647.1293 $[M + Na]^+$. Calcd 647.1287 $[M + Na]^+$, err. (ppm) −0.9 m.p. (°C): 275.7–275.9.

*1,1′-((1R,2S)-Cyclohexane-1,2-diyl)bis(3-(3,5-bis(trifluoromethyl)phenyl)thiourea) (**2**)*

3,5-Bis(trifluoromethyl)phenyl isothiocyanate (0.66 mL, 3.6 mmol) and *cis*-1,2-diaminocyclohexane (0.21 mL, 1.8 mmol) were dissolved in DCM (40 mL) and stirred for 6.5 h at rt under a nitrogen atmosphere. A white precipitate was isolated by filtration in 78% yield after washing with excess DCM. ^1H NMR (DMSO-d_6, 300 MHz): $\delta = 1.40$–1.85 (m, 8H), 4.69 (br s, 2H), 7.73 (br s, 2H), 7.99 (d, 2H, $J = 6.0$ Hz), 8.29 (br s, 4H), 10.13 (br s, 2H). $^{13}C\{^1H\}$ NMR (DMSO-d_6, 100 MHz): $\delta = 21.9$ (CH_2), 27.8 (CH_2), 52.5 (CH), 116.2 (Ar CH), 121.7 (Ar CH), 125.0 (q, CF_3, $J = 272.49$ Hz), 129.9 (q, Ar C—CF_3, $J = 31.2$ Hz), 141.7 (Ar C), 180.3 (C═O). $^{19}F\{^1H\}$ NMR (DMSO-d_6, 282 MHz): $\delta = 61.45$. LR-MS ES$^-$ (*m/z*): 655 $[M - H]^-$. HR-MS ES$^+$ (*m/z*): Act. 679.0832 $[M + Na]^+$. Calcd 679.0830 $[M + Na]^+$, err. (ppm) −0.3 m.p. (°C): 189.8–189.9.

*1,1′-((1S,2S)-Cyclohexane-1,2-diyl)bis(3-(3,5-bis(trifluoromethyl)phenyl)urea) (**3**)*

3,5-Bis(trifluoromethyl)phenyl isocyanate (0.62 mL, 3.6 mmol) and (±)-*trans*-1,2-diaminocyclohexane (0.21 mL, 1.8 mmol) were dissolved in DCM (40 mL) and stirred for 72 h at rt under a nitrogen atmosphere. A white precipitate was isolated by filtration in a 96% yield after washing with excess DCM. ^1H NMR (DMSO-d_6, 300 MHz): $\delta = 1.30$ (br s, 4H), 1.70 (br s, 2H), 1.87 (br s, 2H), 3.48 (br s, 2H), 6.24 (d, 2H, $J = 8.29$ Hz), 7.37 (s, 2H), 7.90 (s, 4H), 9.211 (s, 2H). $^{13}C\{^1H\}$ NMR (DMSO-d_6, 75 MHz): $\delta = 24.6$ (CH_2), 32.2 (CH_2), 53.7 (CH), 113.2 (Ar CH), 116.8 (Ar CH), 123.2 (q, CF_3, $J = 271.3$ Hz), 130.4 (q, Ar C—CF_3, $J = 31.9$), 142.3 (Ar C), 155.0 (C═O). $^{19}F\{^1H\}$ NMR (DMSO-d_6, 282 MHz): $\delta = 61.72$. LR-MS ES$^+$ (*m/z*): 625 $[M + H]^+$. HR-MS ES$^+$ (*m/z*): Act. 647.1289 $[M + Na]^+$. Calcd 647.1287 $[M + Na]^+$, err. (ppm) −0.3 m.p. (°C): 305.3–305.5.

*1,1′-((1S,2S)-Cyclohexane-1,2-diyl)bis(3-(3,5-bis(trifluoromethyl)phenyl)thiourea) (**4**)*

3,5-Bis(trifluoromethyl)phenyl isothiocyanate (0.66 mL, 3.6 mmol) and (±)-*trans*-1,2-diaminocyclohexane (0.21 mL, 1.8 mmol) were dissolved in DCM (40 mL) and stirred for 72 h at rt under a nitrogen atmosphere. A white solid was collected and triturated in DCM (40 mL) at 40°C for 2 h. The precipitate was isolated by filtration in a 98% yield after washing with excess DCM. ^1H NMR (DMSO-d_6, 300 MHz): $\delta = 1.30$ (br s, 4H), 1.71 (br s, 2H), 2.18 (br s, 2H), 4.33 (br s, 2H), 7.70 (s, 2H), 8.17 (s, 6H), 10.14 (br s, 2H). $^{13}C\{^1H\}$ NMR (DMSO-d_6, 75 MHz): $\delta = 24.2$ (CH_2), 31.2 (CH_2), 56.8 (CH), 116.2 (Ar CH), 122.0 (Ar CH), 123.2 (q, CF_3, $J = 271.4$ Hz), 130.0 (q, Ar C—CF_3, $J = 33.0$ Hz), 141.6 (Ar C), 180.1 (C═O). $^{19}F\{^1H\}$ NMR (DMSO-d_6, 282 MHz): $\delta = 61.48$. LR-MS ES$^+$ (*m/z*): 657 $[M + H]^+$. HR-MS ES$^+$ (*m/z*): Act. 679.0825 $[M + Na]^+$. Calcd 679.0830 $[M + Na]^+$, err. (ppm) +0.8 m.p. (°C): 199.9–200.1.

Results and discussion

Anion-binding studies were carried out for receptors **1**–**4** to determine their binding affinity and binding stoichiometry on a range of different anions. Stability constants for the interaction of receptors **1**–**4** with a variety of anions were determined by fitting the data obtained from ^{1}H NMR titrations to binding isotherms, using WinEQNMR2 (*11*). The stability constants were determined by following the shift of N—H protons. In many cases, the resonance of the more deshielded N—H protons (i.e. those closest to the aromatic ring systems) was subject to peak broadening upon addition of the guest anion. However, the downfield shift of both N—H resonances at the beginning of the titrations does indicate that all four N—H groups are involved in H-bonding to the anions. Amendola et al. (*6*) showed that an analogous cyclohexane-based bis-urea receptor binds a hydrogen-bonded dihydrogen phosphate dimer in the solid state, whereas Costero et al. (*12*) showed that cyclohexane-based bis-thioureas bind dicarboxylate anions in a 1:2 receptor:anion ratio (by UV–vis in DMSO). The results of the anion-binding studies are shown in Table 1.

Receptor **1** was found to bind all tested anionic guests in a 1:2 receptor:anion stoichiometry. The first stability constant associated with the binding of chloride, acetate and benzoate is high ($>10^4\,M^{-1}$), indicating a strong affinity for the first equivalent on anion. For the remaining anions (bicarbonate, hydrogen sulphate, dihydrogen phosphate and sulphate) the calculated K_1 values were in a lower order of magnitude ($>10^3\,M^{-1}$), but still indicate a strong affinity for the anions. For each of the anions mentioned (excluding sulphate), the second stability constant is significantly lower than the first, showing the decreased affinity of receptor **1** for a second equivalent of anion. This is most likely a result of the charged anions repelling each other as well as steric restraints around the binding site.

The ^{1}H NMR titration data between the same set of anions and receptor **2** were also fitted to a 1:2 receptor:anion-binding isotherm, with the exception of the data for the titration with bicarbonate, which showed only a small downfield shift in N—H resonance position upon addition of anion. This suggested that only a very weak binding event was taking place, hence it was only possible to fit the data to a 1:1 receptor:anion-binding isotherm. The remaining results for **2** show trends similar to those observed for **1** with each of the receptor–anion interactions (excluding that with sulphate) having a K_1 value that is greater than the K_2 value.

For ^{1}H NMR titrations of receptors **3** and **4** with the series of anions, it was not possible to fit all the data-sets using WinEQNMR2. Some of the titrations showed peak broadening and peak slitting of the N—H and aromatic C—H peaks upon addition of the anions, which could be attributed to secondary equilibria processes in solution. Of the results that were fitted to a 1:2 or 1:1 receptor:anion-binding isotherm, trends similar to those of **1** and **2** were observed. For all 1:2 receptor:anion-binding interactions investigated for receptors **3** and **4**, the first stability constant, K_1, is greater than the second stability constant, K_2, indicating a decreased affinity of the receptors to bind a second equivalent of anion.

Receptors **1**–**4** were investigated for anion transport properties using Hill analysis techniques (*13*). Chloride efflux from POPC vesicles was monitored upon addition of varying loadings of receptor, for both Cl^-/NO_3^- and Cl^-/HCO_3^- antiport processes, using a chloride ion selective electrode (ISE). Figure 2 shows the percentage of chloride efflux upon addition of 2 mol% receptor with

Table 1. Stability constants K_1 and K_2 (M^{-1}) for receptors **1**–**4**, measured in DMSO-d_6/H_2O 0.5% at 298 K.

	Receptor **1**[a]		Receptor **2**[a]		Receptor **3**[a]		Receptor **4**[a]	
Anion	K_1	K_2	K_1	K_2	K_1	K_2	K_1	K_2
Cl^-	$>10^4$	70	3970	70	<10	<10	[e]	[e]
HCO_3^-[b]	5490	200	$<10^4$[d]	N/A	1080[c]	40[c]	[f]	[f]
HSO_4^-	6090	20	$>10^4$	60	<10	<10	$<10^4$[d]	N/A
CH_3COO^-	$>10^4$	40	$>10^4$	10[c]	$>10^4$	50	[f,g]	[f,g]
$C_6H_5COO^-$	$>10^4$	160	$>10^4$	70	$>10^4$	50	$>10^4$	100
$H_2PO_4^-$	2930	330	7130	110	[e]	[e]	[f,h]	[f,h]
SO_4^{2-}	5280	$>10^4$	$>10^4$	$>10^4$	$>10^4$	10	[g,h]	[g,h]

Notes: Guest anions were added as tetrabutylammonium salts, unless otherwise stated, and the stability constants were determined by ^{1}H NMR titrations following the N—H resonance found closest to the aromatic region of the spectra. All data-sets were fitted to a 1:2 receptor:anion-binding isotherm using WinEQNMR2, unless otherwise indicated.

[a] Errors within 15% unless otherwise stated.

[b] Added as the tetraethylammonium salt.

[c] Error > 15%.

[d] Data fitted to a 1:1 binding isotherm.

[e] Titration curves slightly plateau at 1 equiv. of anion, so data cannot be fitted to a binding isotherm.

[f] Peak broadening upon addition of anionic guest.

[g] Peak hidden by aromatic C—H peaks.

[h] Peak splitting upon addition of anionic guest.

respect to lipid for the Cl^-/NO_3^- antiport test. It can be seen that thioureas **2** and **4** have an increased transport activity relative to the analogous ureas **1** and **3** (*14*) and that interestingly the *cis*-receptors outperform the *trans*-receptors.

The same trends are present in the Cl^-/HCO_3^- antiport results, with receptors **1** and **4** showing almost identical transport activity (Figure 3).

Results of the Hill analyses are shown in Table 2.

The EC_{50} values for the Cl^-/NO_3^- and Cl^-/HCO_3^- tests show similar trends, indicating the thiourea receptors to be more efficient antiporters than the analogous ureas (*14*), and show the most active transporter to be receptor **2**, with an EC_{50} of 0.61 mol% for Cl^-/NO_3^- antiport and 1.47 mol% for Cl^-/HCO_3^- antiport. The Hill coefficient values support a mobile carrier transport mechanism for all receptors.

This trend in transport efficiency may be explained by considering the spatial arrangements of the *cis*- versus *trans*-receptors. The hydrogen bond donor N—H groups of the *cis*-receptors (**1** and **2**) are more favourably orientated in an axial–equatorial arrangement, to bind to a guest molecule (Figure 4). They are closer together and in better spatial agreement to direct four hydrogen bonds towards the guest species than analogous *trans*-receptors (**3** and **4**). This is especially true when compared with the axial–axial conformer of the *trans*-receptor, where the two arms of the receptor point in opposite directions. The difference in spatial arrangement likely makes it more difficult for the

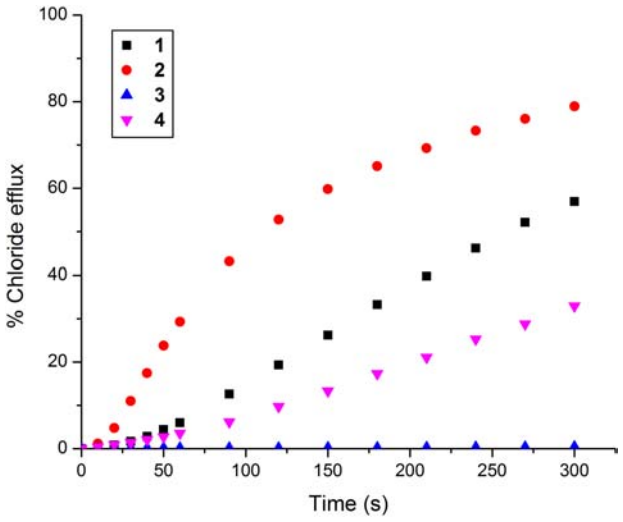


Figure 2. Chloride efflux as a function of time, promoted by the addition of receptors **1**–**4** (2 mol% with respect to lipid) from unilamellar POPC vesicles containing 489 mM NaCl buffered to pH 7.2 with 5 mM sodium phosphate salts. The vesicles were dispersed in 489 mM $NaNO_3$ buffered to pH 7.2 with 5 mM sodium phosphate salts. The receptor was loaded as a DMSO solution at 0 s. At the end of the experiment, the vesicles were lysed to calibrate the ISE to 100% chloride efflux. Each point represents the average of three repeats.

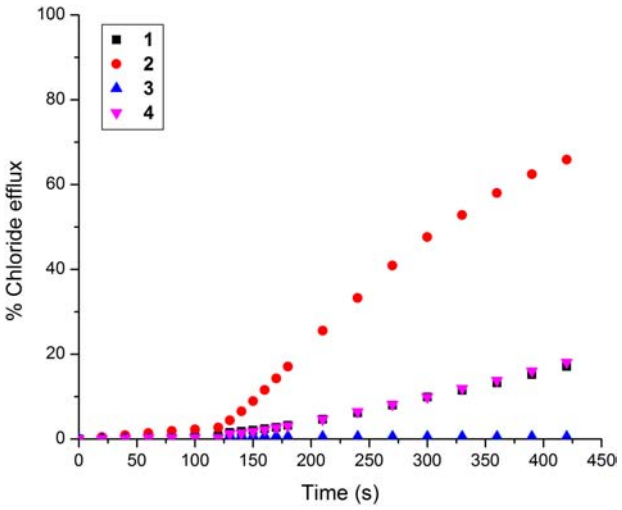


Figure 3. Chloride efflux as a function of time, promoted by the addition of receptors **1** and **2** (2 mol% with respect to lipid) from unilamellar POPC vesicles containing 451 mM NaCl buffered to pH 7.2 with 20 mM sodium phosphate salts. The vesicles were dispersed in the external solution containing 150 mM Na_2SO_4 buffered to pH 7.2 with 20 mM sodium phosphate salts. The receptor was loaded as a DMSO solution at 0 s, and a spike of $NaHCO_3$ (33 mM) added at 120 s. At the end of the experiment, the vesicles were lysed to calibrate the ISE to 100% chloride efflux. Each point represents the average of three repeats.

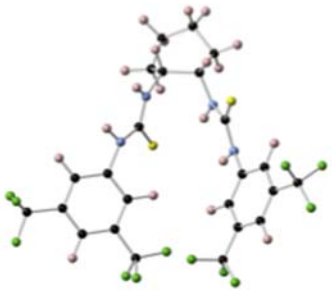
trans-receptors to shield the charged guest from the lipophilic interior of the POPC bilayer. This makes it more difficult for the *trans*-receptors to partition into the phospholipid bilayer, resulting in decreased transport efficiency with respect to that of the *cis*-receptors.

U-tube experiments, as described in the electronic supplementary information (ESI), were used to probe the mode of anion transport. The results of the U-tube experiment show an increase in the chloride concentration of the sodium nitrate receiver solutions over time, indicating that all the receptors function as mobile carriers. The large volume, and hence distance separation, of the two aqueous

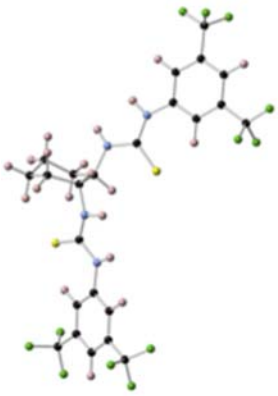
Table 2. EC_{50} values of **1**–**4** for the release of chloride from POPC vesicles in Cl^-/NO_3^- and Cl^-/HCO_3^- antiport systems at 270 and 390 s, respectively.

Receptor	EC_{50}[a], 270 s (Cl^-/NO_3^-)	n[b] (Cl^-/NO_3^-)	EC_{50}[a], 390 s (Cl^-/HCO_3^-)	n[b] (Cl^-/HCO_3^-)
1	1.74	1.20	7.04	1.75
2	0.61	1.18	1.47	1.43
3	[c]	[c]	[c]	[c]
4	3.48	1.90	9.24	1.08

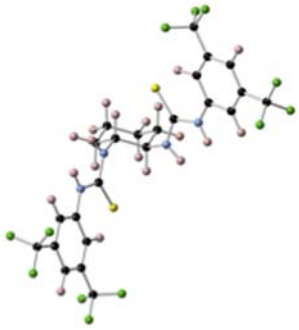
[a] EC_{50}, defined as the concentration (mol% carrier to lipid) required to obtain 50% chloride efflux from inside the vesicles.
[b] Hill coefficient.
[c] Receptor **3** was virtually inactive and at 20 mol% receptor loading, with respect to lipid, showed only 5.20% chloride efflux at 270 s for Cl^-/NO_3^- antiport and 3.99% chloride efflux at 390 s for Cl^-/HCO_3^-. Consequently the data obtained for this receptor was not fitted to the Hill equation.



Axial-equatorial conformation of **2**.



Axial-axial conformation of **4**.



Equatorial-equatorial conformation of **4**.

Figure 4. Axial–equatorial conformation of **2**, axial–axial conformation of **4** and equatorial–equatorial conformation of **4**. Structure was generated using Spartan'10 for Macintosh (PM3 molecular dynamics energy minimisation) (*15*). Spheres have been resized for clarity.

phases of the U-tube experiment ensures that channel formation across the span of the organic phase is not possible, hence a channel mechanism of transport is not conceivable.

Conclusions

The *cis*-receptors **1** and **2** have a greater activity as anion antiporters than the corresponding *trans*-receptors **3** and **4**. The evidence presented supports our previous findings that thioureas are more effective functional group motifs than ureas for promoting anion antiport across lipid bilayers, possibly due to the increased lipophilicity of sulphur atoms as compared with oxygen atoms (*16*). In addition, the difference in transport efficiency between *cis*- and *trans*-stereoisomers can be rationalised with respect to their differing ability to shield hydrophilic receptor regions and anionic guests from the lipophilic interior of phospholipid membranes. Anion-binding investigations were able to highlight the significance of stereoisomerism on anion binding in solution, as the *cis*-receptors interact with anions more favourably than the *trans*-receptors, and show how a lack of conformational isomers in *cis*-receptors allows for less complex binding equilibria.

Supplementary Information

Please see ESI for additional information on anion transport studies using vesicles, mobility assays, anion binding studies and for general experimental procedures.

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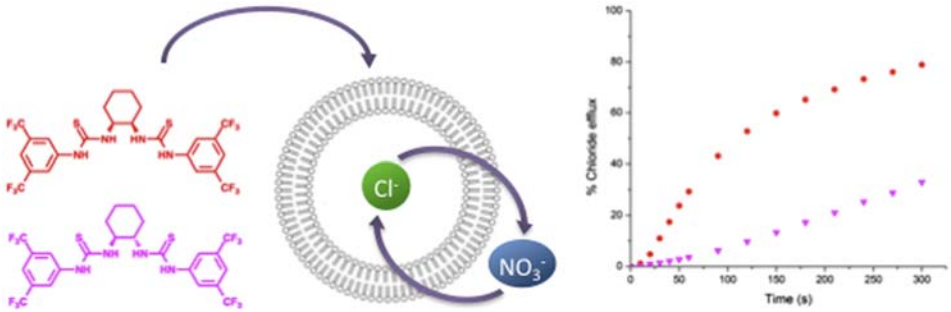

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