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Synchronous enantiomeric enrichment of both reactant and product by absolute asymmetric synthesis using circularly polarized light. Part 2.[1] Verification of the validity of assuming first-order kinetics upon deriving the equation for the relationship between conversion and enantiomeric excess

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Kagan *et al.* (G, Balavoine, A. Moradpour and H. B. Kagan, *J. Am. Chem. Soc.*, 1974, **96**, 5152) derived an equation showing the relationship between the enantiomeric excess (ee) and the conversion for the irradiation of racemic reactants with circularly polarized light (CPL). The equation was derived based on the assumption of first-order kinetics for the reaction. However, the same equation can be derived from the general expression of the photochemical rate equations without assuming first-order kinetics. The only assumption that is necessary for deriving Kagan's equation is Lambert–Beer's law for the absorbance of the solutions. The relationship between ee and the conversion does not depend on the initial absorbance of the solution, but depends only on the *g* factor. Kagan's equation proved to be applicable to asymmetric photodestruction and also asymmetric one-way photoisomerization reactions. Numerical simulation is also a powerful method, particularly if the analytical solution of the differential equations is not available. In such a case, by expressing the ee as a function of the conversion, a relationship that does not depend on the initial absorbance is obtained.

In the preceding paper of this series,[1] we described a new absolute asymmetric synthesis (NAAS), the photoisomerization of a racemic reactant into the chiral product. In the theoretical formulation of the evolution of enantiomeric excess (ee) of the product and reactant by the irradiation of circularly polarized light (CPL) we have followed the procedure provided by Kagan *et al.*[2] Kagan's equation for the ee of the reactant, which was applied originally for the photodestruction of racemic mixtures, has been shown to be valid also for the photoisomerization of racemic mixtures. Our study has further provided a method that could be used for the analysis of the ee of the product.

In Kagan's procedure of the formulation he assumed that the rate constant of the photodecomposition obeys first-order kinetics. The rate constants of the photodecomposition were assumed to be proportional to the molar extinction coefficients of each enantiomer. We have also assumed in the preceding paper first-order kinetics for the photoisomerization. However, Bonner *et al.*[3] reported a discrepancy between the observed ee and the one predicted by Kagan's equation for the asymmetric photodestruction of leucine. They claimed that the discrepancy might arise from the over-simplified kinetic model.

In the present paper we have examined the applicability of Kagan's equations, which are based on first-order kinetics, for an actual reaction system in which the photochemical reaction does not often follow a first-order rate equation. We also propose the use of numerical simulation for predicting the results of asymmetric synthesis. Curiously, numerical simulation has scarcely been employed for the analysis of the rate of photochemical reactions. However, if the reaction scheme is complicated one cannot solve the rate equation analytically. In this case the numerical method will be helpful for understanding how each parameter in the rate equation affects the course of the reaction.

Results and discussion

Absorbance dependence of the rate of the photochemical reactions

The rate expression [eqn. (1)] for a simple photochemical

$$\frac{\mathrm{d}c}{\mathrm{d}t} = -I_{\mathrm{ex}}\frac{S}{V}(1 - 10^{-A})\frac{\varepsilon c l}{\mathrm{A}}\Phi \qquad (1)$$

reaction was given by Rau *et al.*[4] If S is the same as the cross section of the cuvette, the factor Sl/V is equal to 10^3, where c is the reactant concentration, I_{ex} is the incident photonic flux expressed as einstein $\mathrm{cm}^{-2}\ \mathrm{s}^{-1}$, S is the area of the cross section of the incident light (cm^2), V is the volume of the solution (dm^3), A is the absorbance of the reaction mixture in the reaction cuvette at the wavelength of excitation, ε is the molar absorption coefficient for the reactant, l is the path length of the reaction cuvette (cm), Φ is the quantum yield of the reaction. This equation is obtained by applying Lambert–Beer's law when calculating the amount of photons absorbed by the reactant.

The rate of photochemical reaction is often expressed in the form of first-order kinetics using the rate constant k. This can be justified if the absorbance of the reaction mixture is less than 0.01, because, by approximation, eqn. (1) is reduced to eqn. (2).

$$\frac{\mathrm{d}c}{\mathrm{d}t} = -(\ln 10)I_{\mathrm{ex}}\frac{S}{V}\varepsilon c l\Phi = -kc \qquad (2)$$

In the case of the absorbance of 0.01–0.1 the first-order approximation is not strictly, but is practically, applicable (Fig. 1). In the figures in the present paper the reduced reaction time, $t^* = tI_{\mathrm{ex}}\varepsilon(Sl/V)\Phi(\ln 10)$, is used as a measure of the progress of the reaction.

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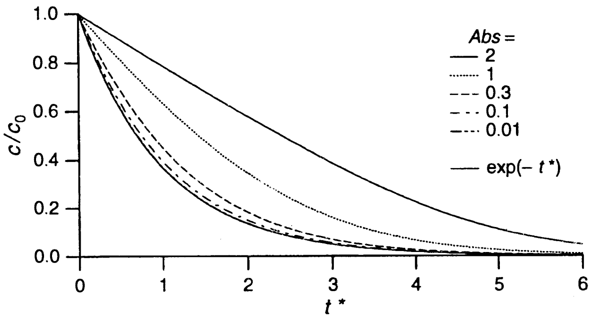

Fig. 1 The time profiles of the decrease of a reactant by a photochemical reaction in solutions of various values of initial absorbance. Only the reactant is assumed to absorb the light for excitation. The reduced reaction time, $t^* = tI_{ex}\varepsilon(Sl/V)\Phi(\ln 10)$, is used as a measure of the reaction time.

Kagan *et al.* started from this first-order approximation when he derived the relationship between the ee and conversion for CPL irradiation of a racemic mixture. However, in the actual reaction system, the absorbance of the reaction mixture often exceeds 0.1.[13] Therefore, it is essential to examine the effect of the value of the absorbance on the relationship between the ee and the conversion of the product for the CPL irradiation of a racemic mixture.

Derivation of Kagan's equation starting from the general expression of the rate equation

For the photodestruction or photoisomerization of racemic sample **A** ($\mathbf{A}_R$ and $\mathbf{A}_S$), the rate of the decrease in the concentration of the reactant enantiomers, c_{AR} and c_{AS}, is given by eqns. (3) and (4), where eqn. (5) holds and Φ_A is the quantum

$$\frac{dc_{AR}}{dt} = -I_{ex}\frac{S}{V}(1 - 10^{-A})\frac{\varepsilon_{AR}c_{AR}l}{A}\Phi_A \qquad (3)$$

$$\frac{dc_{AS}}{dt} = -I_{ex}\frac{S}{V}(1 - 10^{-A})\frac{\varepsilon_{AS}c_{AS}l}{A}\Phi_A \qquad (4)$$

$$A = (\varepsilon_{AR}c_{AR} + \varepsilon_{AS}c_{AS})l \qquad (5)$$

yield, ε_{AR} and ε_{AS} are the molar absorption coefficients for $\mathbf{A}_R$ and $\mathbf{A}_S$. Here we assume that only the (*R*)- and (*S*)-isomers of **A** absorb the incident light and the reaction proceeds in one way.

By dividing each side of eqn. (3) by the corresponding sides of eqn. (4) we get a differential equation, eqn. (6) or eqn. (7).

$$\frac{dc_{AR}}{dc_{AS}} = \frac{\varepsilon_{AR}c_{AR}}{\varepsilon_{AS}c_{AS}} \qquad (6)$$

$$\frac{dc_{AR}}{c_{AR}} = \frac{\varepsilon_{AS}}{\varepsilon_{AR}}\frac{dc_{AS}}{c_{AS}} \qquad (7)$$

By integrating this equation we obtain eqn. (8) from which eqn. (9) follows.

$$\int_{c_{AR0}}^{c_{AR}}\frac{dc_{AR}}{c_{AR}} = \frac{\varepsilon_{AS}}{\varepsilon_{AR}}\int_{c_{AS0}}^{c_{AS}}\frac{dc_{AS}}{c_{AS}} \qquad (8)$$

$$\ln\frac{c_{AS}}{c_{AS0}} = \frac{\varepsilon_{AS}}{\varepsilon_{AR}}\ln\frac{c_{AR}}{c_{AR0}} \qquad (9)$$

By using the definition of the conversion x and the ee (y) we obtain eqns. (10) and eqns.(11). We can rewrite eqn. (9) in terms of x and y (see Appendix for details), eqn. (12). This expression is equivalent to what has been presented by Kagan *et al* [eqn. (13)].[2]

$$x = 1 - \frac{c_{AR} + c_{AS}}{c_{AR0} + c_{AS0}} \qquad (10)$$

$$y = \frac{c_{AR} - c_{AS}}{c_{AR} + c_{AS}} \qquad (11)$$

$$x = 1 - \frac{1}{1+y}\left(\frac{1+y}{1-y}\right)^{\frac{1}{g}+\frac{1}{2}} \qquad (12)$$

$$x = 1 - \frac{1}{2}\left\{\left(\frac{1+y}{1-y}\right)^{\frac{1}{2}+\frac{1}{g}} + \left(\frac{1+y}{1-y}\right)^{-\frac{1}{2}+\frac{1}{g}}\right\} \qquad (13)$$

By the above procedure it has been proven that Kagan's equation can be derived from the general expression of the photochemical rate equations without assuming first-order kinetics. The only assumption that is necessary for deriving Kagan's equation is Lambert–Beer's law for the absorbance of the solutions.

The key equation in this derivation is eqn. (7), which indicates that the ratio of the change (the decrease) in the concentrations of (*R*)- and (*S*)-isomers depends only on the ratio of the ε's and the concentrations of themselves. It does not depend on the initial absorbance of the solution. This is the crucial reason why the relationship between y and x does not depend on the initial absorbance of the solution.

Effect of the initial absorbance on the developing pattern of enantiomeric excess for reactant and product in a one-way photoisomerization of a racemic mixture

In the preceding paper of this series we have presented a one-way photoisomerization of a racemic mixture as an example of NAAS (Class (b)). In the reaction the product was also chiral, and each enantiomer of the product does not convert into the other. The product did not absorb the incident light, therefore the back reaction did not occur.

$$\mathbf{A}_R \xrightarrow{h\nu} \mathbf{B}_R$$

$$\mathbf{A}_S \xrightarrow{h\nu} \mathbf{B}_S$$

We have proven that, in this type of NAAS, the ee of the reactant y follows Kagan's equation and the ee of the product y' is given by the eqn. (14).[1]

$$y' = -\frac{y(1 - x)}{x} \qquad (14)$$

Kagan's equation is valid in any photodestruction of racemic compounds, if the dependence of the absorbance on the concentration follows Lambert–Beer's law. Therefore eqn. (14) is also valid, if the dependence of the absorbance on the concentration follows Lambert–Beer's law.

In order to visualize the difference in the time course of the development of the ee by the difference in the initial absorbance, we have simulated the reaction numerically by using the Runge–Kutta method for the case, $g = 1$ as an example. If the initial absorbance of the solution differs, the time course of

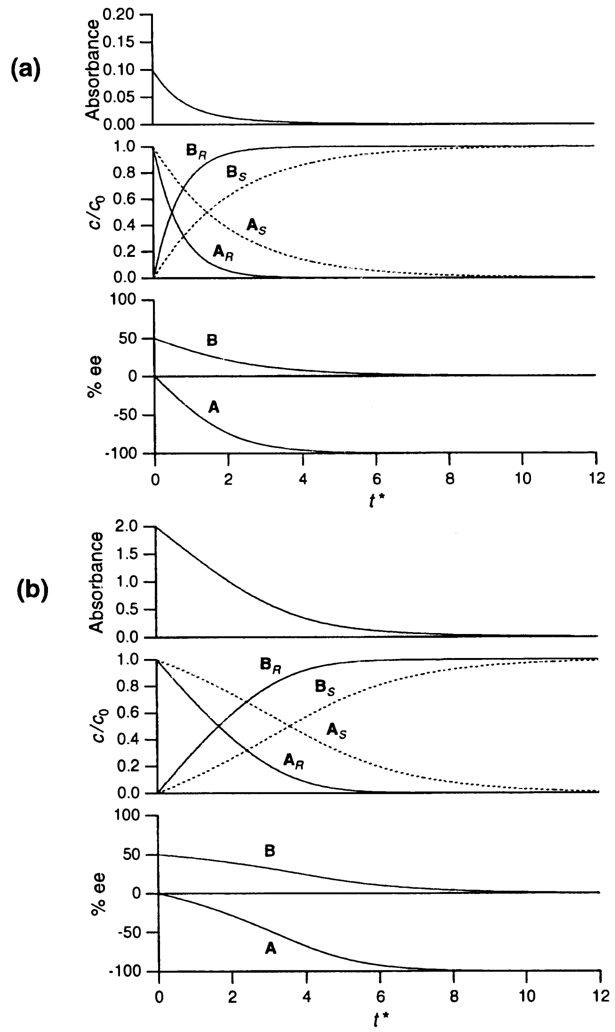

Fig. 2 Variation with time of the concentration of the enantiomers of the reactant and product, the absorbance of the reaction mixture, and the ee of the reactant and product, for the one-way photoisomerization of the racemic mixture of **A** into **B** by CPL irradiation. The Kuhn's anisotropy factor (*g*) is assumed to be 1.0. The initial absorbance is (a) 0.1 or (b) 2.0. The reduced reaction time, $t^* = t\,I_{\mathrm{ex}}\{(\varepsilon_{\mathrm{A}R} + \varepsilon_{\mathrm{A}S})/2\} \times (Sl/V)\Phi_{\mathrm{A}}(\ln 10)$, is used as a measure of the reaction time.

the reaction is different (Fig. 2). For example, the ee of the reactant grows more slowly if the initial absorbance is larger. However, in spite of this difference, the relationship between the ee and the conversion is exactly the same for the two conditions. In Fig. 3 the ee's are plotted against the conversion, for any value of the initial absorbance we get the same relationship between the ee's and the conversion.

The relationship between the ee of the reactant and product and the conversion does not depend on the initial absorbance of the solution, it also does not depend on the incident light flux or the quantum yield of the reaction, it depends solely on the *g* factor.

Comparison of the methods for obtaining the relationship between the ee and conversion

The theoretical background for the first-order kinetics approximation has already been implied, though not explicitly, by Blume *et al.*[4] They showed that the rate equation became first order if one uses the parameter τ as a measure of the progress of the reaction eqn. (15).

$$\tau = \int_0^t \frac{1 - 10^{-A(t)}}{A(t)}\,\mathrm{d}t \qquad (15)$$

If the expressions for the reactions are first order in terms of τ, we can apply the procedure of Kagan for deriving the relationship between ee and conversion. During the process the parameter τ is canceled out, thus we obtain an equation for the relationship which does not contain any term for absorbance.

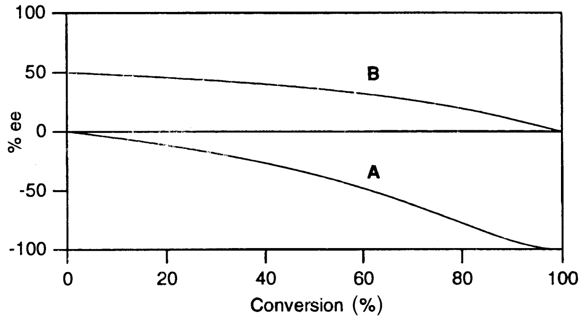

Fig. 3 Plots of ee against conversion for the one-way photoisomerization by CPL irradiation. The Kuhn's anisotropy factor is assumed to be 1.0.

However, for a more complicated system like reversible photoisomerization (Class (a) NAAS),[1] even by applying the first-order-kinetics approximation we cannot get any simple analytical equation for the relationship between the ee and the conversion. In such a case, after obtaining a numerical solution for the time course of the reaction, by plotting ee as a function of the conversion we obtain a relationship which does not depend on the initial absorbance or absolute quantum yield of the reaction. This procedure may be practically of much more value.

Effect of the initial absorbance of the solution on the other types of absolute asymmetric synthesis

In the above discussions we have verified the validity of Kagan's equation in asymmetrical photodestruction and in asymmetrical one-way photoisomerization reactions (Class (b) NAAS). In these asymmetrical photoreactions the same relationship between the ee and the conversion was applicable to the system without regard to whether first-order kinetics was met or not.

We will show, in the following paper of this series,[1] for asymmetric reversible photoisomerization (Class (a) NAAS), that the relationship between the ee and the conversion does not depend on the initial absorbance of the solution. For a complicated system like the reversible photoisomerization the numerical method was much more useful than the analytical one.

We predict that, for any kind of absolute asymmetric synthesis, the relationship between the ee and the conversion does not depend on the initial absorbance of the reactant. The only factors which are crucial for determining the relationship are the *g* factors, the ratios of ε's and Φ's. If the reaction is reversible, we need the ratios of ε's and Φ's in addition to the *g* factors in order to estimate the contribution of the back reaction that leads to a photostationary state.

Methods

Numerical simulation

For obtaining the numerical solution of differential equations a fourth-order Runge–Kutta method was employed.[1] If we use the reduced reaction time, $t^* = tI_{\mathrm{ex}}\{(\varepsilon_{\mathrm{A}R} + \varepsilon_{\mathrm{A}S})/2\}(Sl/V)\Phi_{\mathrm{A}}(\ln 10)$, as a measure of the reaction time, eqns. (4) and (5) are transformed into eqns. (16)–(18), where $\varepsilon_{\mathrm{A}} = (\varepsilon_{\mathrm{A}R} + \varepsilon_{\mathrm{A}S})/2$.

$$\frac{\mathrm{d}c_{\mathrm{A}R}}{\mathrm{d}t^*} = -\frac{(1 - 10^{-A})}{A\ln 10}\frac{\varepsilon_{\mathrm{A}R}}{\varepsilon_{\mathrm{A}}}c_{\mathrm{A}R} \qquad (16)$$

$$\frac{\mathrm{d}c_{\mathrm{A}S}}{\mathrm{d}t^*} = -\frac{(1-10^{-A})}{A\ln 10}\frac{\varepsilon_{\mathrm{A}S}}{\varepsilon_{\mathrm{A}}}c_{\mathrm{A}S} \tag{17}$$

$$A = (\varepsilon_{\mathrm{A}R}c_{\mathrm{A}R} + \varepsilon_{\mathrm{A}S}c_{\mathrm{A}S})l \tag{18}$$

For the numerical integration we need the values of the three parameters ($\varepsilon_{\mathrm{A}R}$, $\varepsilon_{\mathrm{A}S}$, and l) and the initial values of the concentrations ($c_{\mathrm{A}R0}$ and $c_{\mathrm{A}S0}$). If we know the values of ε_{A}, g_{A}, the initial concentration of the racemic mixture (c_0) and the initial absorbance of the solution (A_0) we can calculate the values we need in the following way.

By definition eqns. (19)–(22) apply.

$$c_0 = c_{\mathrm{A}R0} + c_{\mathrm{A}S0} = 2c_{\mathrm{A}R0} = 2c_{\mathrm{A}S0} \tag{19}$$

$$\varepsilon_{\mathrm{A}} = (\varepsilon_{\mathrm{A}R} + \varepsilon_{\mathrm{A}S})/2 \tag{20}$$

$$g_{\mathrm{A}} = (\varepsilon_{\mathrm{A}R} - \varepsilon_{\mathrm{A}S})/\varepsilon_{\mathrm{A}} \tag{21}$$

$$A_0 = \varepsilon_{\mathrm{A}}c_0 l \tag{22}$$

From eqns. (19)–(22) we obtain eqns. (23)–(26).

$$\varepsilon_{\mathrm{A}R} = (2 + g_{\mathrm{A}})\varepsilon_{\mathrm{A}} \tag{23}$$

$$\varepsilon_{\mathrm{A}S} = (2 - g_{\mathrm{A}})\varepsilon_{\mathrm{A}} \tag{24}$$

$$c_{\mathrm{A}R0} = c_{\mathrm{A}S0} = c_0/2 \tag{25}$$

$$l = A_0/\varepsilon_{\mathrm{A}}c_0 \tag{26}$$

Therefore, by using the values of ε_{A}, g_{A}, c_0, and A_0, we can predict the time-dependent change of the concentrations of the enantiomers. By plotting the ee of the enantiomers against the conversion at each time interval we obtain a relationship between the ee of the enantiomers and the conversion. During this procedure all the parameters except the g factor are canceled out, thus the obtained relationship depends only on the g factor.

Conclusions

Kagan's equation showing the relationship between the ee and the conversion of reactant is also valid for systems in which the approximation of first-order kinetics is not met. There is no limitation of the value of the absorbance for the application of Kagan's equation, if the absorbance of the reaction mixture follows Lambert–Beer's law. The relationship between ee and the conversion does not depend on the initial absorbance of the solution, it depends only on the g factor.

Kagan's equation was proved to be applicable to both asymmetric photodestruction and also asymmetric one-way photoisomerization reactions.

Numerical simulation also proves to be a powerful method, especially if the analytical solution of the differential equations is not available or if it is too complicated. In such a case, by expressing the ee as a function of the conversion, we can obtain a relationship that does not depend on the initial absorbance of the solution.

Appendix

The procedure of the transformation of eqn. (9) into eqn. (12) is as follows. We can rewrite eqn. (9) into the form given in eqn. (27). This expression is transformed to eqn. (28). By definition eqn. (10) holds, thus eqn. (29) holds. We can rewrite this into the form, given in eqn. (30). By substituting the term $c_{\mathbf{AR}}$ in the right side of eqn. (28) by using eqn. (30), we obtain eqn. (31). This can be transformed into eqn. (32), where we used the relationship given in eqn. (33).

By definition eqn. (11) holds and based on this equation we obtain eqn. (34) and also eqn. (35).

By definition eqn. (36) holds from which we obtain eqn. (37) and thus eqn. (38).

By using eqns. (34), (35), and (38), eqn. (32) can be transformed into eqn. (12).

We can easily show that this is equivalent to Kagan's equation in its original form [eqn. (13)].

$$\frac{c_{\mathrm{A}S}}{c_{\mathrm{A}S0}} = \left(\frac{c_{\mathrm{A}R}}{c_{\mathrm{A}R0}}\right)^{\frac{\varepsilon_{\mathrm{A}S}}{\varepsilon_{\mathrm{A}R}}} \tag{27}$$

$$\frac{c_{\mathrm{A}R}}{c_{\mathrm{A}S}} = \left(\frac{c_{\mathrm{A}R}}{c_{\mathrm{A}R0}}\right)^{1-\frac{\varepsilon_{\mathrm{A}S}}{\varepsilon_{\mathrm{A}R}}} \tag{28}$$

$$x = 1 - \frac{c_{\mathrm{A}R} + c_{\mathrm{A}S}}{c_{\mathrm{A}R0} + c_{\mathrm{A}S0}} \tag{10}$$

$$1 - x = \frac{c_{\mathrm{A}R} + c_{\mathrm{A}S}}{c_{\mathrm{A}R0} + c_{\mathrm{A}S0}} \tag{29}$$

$$c_{\mathrm{A}R} = \frac{(1-x)(c_{\mathrm{A}R0} + c_{\mathrm{A}S0})}{1 + c_{\mathrm{A}S}/c_{\mathrm{A}R}} \tag{30}$$

$$\frac{c_{\mathrm{A}R}}{c_{\mathrm{A}S}} = \left\{\frac{(1-x)(c_{\mathrm{A}R0} + c_{\mathrm{A}S0})}{(1 + c_{\mathrm{A}S}/c_{\mathrm{A}R})c_{\mathrm{A}R0}}\right\}^{1-\frac{\varepsilon_{\mathrm{A}S}}{\varepsilon_{\mathrm{A}R}}} \tag{31}$$

$$\begin{aligned} 1 - x &= \frac{c_{\mathrm{A}R0}}{c_{\mathrm{A}R0} + c_{\mathrm{A}S0}}\left(1 + \frac{c_{\mathrm{A}S}}{c_{\mathrm{A}R}}\right)\left(\frac{c_{\mathrm{A}S}}{c_{\mathrm{A}R}}\right)^{\frac{1}{(\varepsilon_{\mathrm{A}S})/(\varepsilon_{\mathrm{A}R})-1}} \\ &= \frac{1}{2}\left(1 + \frac{c_{\mathrm{A}S}}{c_{\mathrm{A}R}}\right)\left(\frac{c_{\mathrm{A}S}}{c_{\mathrm{A}R}}\right)^{\frac{1}{(\varepsilon_{\mathrm{A}S})/(\varepsilon_{\mathrm{A}R})-1}} \end{aligned} \tag{32}$$

$$c_{\mathrm{A}R0} = c_{\mathrm{A}S0} \tag{33}$$

$$y = \frac{c_{\mathrm{A}R} - c_{\mathrm{A}S}}{c_{\mathrm{A}R} + c_{\mathrm{A}S}} \tag{11}$$

$$1 + \frac{c_{\mathrm{A}S}}{c_{\mathrm{A}R}} = \frac{2}{1 + y} \tag{34}$$

$$\frac{c_{\mathrm{AS}}}{c_{\mathrm{A}R}} = \frac{1 - y}{1 + y} \tag{35}$$

$$g = 2\,\frac{\varepsilon_{\mathrm{A}R} - \varepsilon_{\mathrm{AS}}}{\varepsilon_{\mathrm{A}R} + \varepsilon_{\mathrm{AS}}} \tag{36}$$

$$\frac{\varepsilon_{\mathrm{AS}}}{\varepsilon_{\mathrm{AR}}} = \frac{2 - g}{2 + g} \tag{37}$$

$$\frac{1}{(\varepsilon_{\mathrm{A}S})/(\varepsilon_{\mathrm{A}S}) - 1} = -\left(\frac{1}{g} + \frac{1}{2}\right) \tag{38}$$

$$x = 1 - \frac{1}{1 + y}\left(\frac{1 + y}{1 - y}\right)^{\frac{1}{g} + \frac{1}{2}} \tag{12}$$

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